Additions of water, hydroxide ions, alcohols and alkoxide ions to carbonyl and azomethine bonds

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Abstract

In this review are discussed equilibria involved in nucleophilic additions of H_2O, HO^-, ROH, and RO^- (where R is an alkyl) to compounds containing carbonyl and azomethine bonds. These reactions result in a formation of covalent bonds between the heteroatom of the nucleophile and the carbon of the carbonyl double bond. After a brief summary of reactions resulting in additions to aliphatic carbonyl compounds, attention is paid to additions to benzaldehydes and formyl aromatic heterocycles. Equilibria involving additions to pyridoxal and some related compounds are dealt with in some detail. Discussion of additions of stated nucleophiles to azomethine bonds is practically restricted to additions to C=N bonds in heterocyclic rings. The reactivity of nucleophiles in such additions depends on the number of heteroatoms (in particular nitrogen) in the attacked ring, as well as on the number and position of substituents in such rings. In polynuclear compounds the reactivity depends on the number and kind of annelled rings, on the number and mutual position of heteroatoms and on the kind, number and position of substituents. In particular additions to pyrimidines, quinazolines, 1,2,4- and 1,3,5-triazines, pteridines and other heterocycles with four nitrogens, as well as 8-azapurines are mentioned.

Keywords: Carbonyl, azomethine, hydroxide ion, alkoxide ion, water, alcohols

Contents

1. Introduction

Interactions of water with inorganic or organic species are termed hydration. Such interactions are a result of a wide variety of processes, consisting of solvent-solute and solute-solute interactions. Such interactions can have different origins and can be a manifest of polar, van der Waals, hydrophilic-hydrophilic or hydrophobic-hydrophobic forces, charge-transfer phenomena as well as of formation of hydrogen bonds. All these types of interactions play an important role in numerous biologically important processes, involving for example DNA[1] and its constituents[2].

An extreme case of interactions of organic compounds with water is formation of a covalent bond. Investigations of such reactions in aqueous solutions are limited by the impossibility to vary the concentrations of water as the reagent. It is sometimes possible to use an aprotic solvent, like acetonitrile, add water gradually and to follow a characteristic property of the substrate as a function of the composition of the mixed solvent. Equilibrium constants obtained in this way, nevertheless,

characterize the addition of water in the organic solvent used, where both the substrate and water molecules maybe solvated in a different way than in aqueous solutions. To prove the nature of the addition of water in aqueous solutions, therefore, a use is sometimes made of analogous reactions with alcohols. Similarly, additions of hydroxide ions can be compared with reactions with alkoxide ions. In such reactions covalent bond is formed between an electrophilic carbon of the substrate and the oxygen in H_2O, HO^-, ROH and RO^-, acting as a nucleophile. The resulting C-O bond is much stronger than the hydrogen bond, formed in the interaction of the organic compound (usually involving an O, N, or S atom) with the hydrogen of H_2O or ROH. We will restrict our attention to reactions where the carbon with an excess of the positive charge is a part of a carbonyl (C=O) or azomethine (C=N) grouping. Such processes will be in this review termed covalent hydration (when the reactant is water), all other types of interaction between solutes and solvents will be called solvation.

Nucleophilic attacks on heterocycles result in either a nucleophilic substitution or an addition of the nucleophile. The addition, which is the subject of this review, is often a reversible process. It can involve C=O or C=N bonds which are either a part of the heterocyclic ring, or located in the side-chain. In numerous cases a reversible establishment of the equilibrium between the unhydrated species and the hydrate has been followed. In some instances such adducts are reactive intermediates of a limited lifetime and their presence has been deduced from investigation of kinetics and from the products formed.

Some of the aspects of covalent addition to carbonyl groups has already been extensively reviewed[3-7] with stress on reactions of aliphatic compounds. Therefore this aspect is in the present review treated only briefly. Previous reviews also covered additions of hydroxide ion to electron deficient nitrogen containing heterocyclic compounds (pseudobase formation[8]) and addition of water to pteridines[9-11].

In this review attempt has been made to consider additions of hydroxide ions, alcohols and alkoxide ions, in addition to the covalent addition of water. Such covalent additions were particularly dealt with, which involve addition to benzaldehydes and formyl heterocycles among the carbonyl compounds. Furthermore were discussed additions to azomethine bonds, particularly in heterocycles bearing from one to five heteroatoms. Whereas previously discussed data were obtained predominantly by spectrophotometric and NMR methods, the information obtained by electroanalytical methods is also included in this review.

The application of individual methods depends on the solubility of the solute and on the rate of establishment of the equilibrium between the solute and the nucleophile. Limited solubility prevents in many instances the use of NMR methods. For sufficiently soluble species where equilibria are slowly established (with $\vartheta_{1/2}$ of the order of seconds or slower) any of the available techniques, including potentiometry, is suitable. As in NMR and UV-visible spectrophotometry the equilibrium is not perturbed by the measurement, their application offers direct information about the concentration of the parent solute and the product of the covalent addition. On the other hand, the use of separation methods, like HPLC, cannot be recommended, as during the separation perturbation of the equilibrium is possible. Polarography and linear sweep or cyclic voltammetry are

dynamic methods and their use depends on the rate of establishment of the equilibrium relative to the time window in which the actual measurement is carried out. For reactions with $\vartheta_{1/2}$ of the order of second, dc or normal pulse polarography yield limiting currents, which are directly proportional to the concentration of the reacting solute in the bulk of the solution. Such systems are rarely encountered among nucleophilic additions discussed in this review. Majority of the equilibria discussed here are more rapidly established. In such systems the limiting currents are governed not only by diffusion of the unhydrated species, but also by its generation from the hydrated form in the vicinity of the electrode. The measured current is thus higher than would correspond to the concentration of the unhydrated form and only the lower limit of the equilibrium constant can be determined. Measurement at a lower temperature - e.g., 0^oC would minimize or even eliminate the kinetic contribution and limiting currents would be possible to use for at least approximate measurement of equilibrium concentrations, but this is rarely, if ever, done. In linear sweep and cyclic voltammetry the rate of the increase of applied voltage can be changed. At a sufficiently high scan rate the actual time of the measurement is sufficiently short and the rate of perturbation of the equilibrium becomes negligibly slow when compared with that of the diffusion. In this range of sufficiently high scan rates, measured peak currents are a linear function of the concentration of the unhydrated species. As the diffusion layer formed in the vicinity of the electrode is at least one, usually two or more orders of the magnitude broader than that of the double layer, the measured concentrations and the resulting equilibrium constants are not affected by the electrical field in the vicinity of the electrode surface. Thus linear sweep or cyclic voltammetry are the preferred electrochemical methods for determination of covalent hydration constants, whenever they can be used. In some instances their use is prevented by strong adsorption of the oxidized and/or the reduced form. In such instances methods enabling determination of limiting currents, such as dc or normal pulse methods using mercury dropping electrode or rotating disk electrode using solid electrodes enable only determination of the lower limit of the value of the covalent hydration constant. Such limiting value is often useful when it is necessary to choose the most reliable value among several, obtained by different authors and/or by different techniques.

The use of UV-visible spectra is not affected by the rate of the establishment of the hydration-dehydration equilibrium, but has other limitations. As the molar absorptivity of compounds, where the C=O or C=N bond is not conjugated with another unsaturated grouping, is usually very low, practically the spectrophotometric techniques are limited to investigation of compounds bearing either a carbonyl or azomethine bond in the side chain of an aromatic benzenoid ring or of some, mainly aromatic, heterocycles. As for benzene or pyridine derivatives bearing the reactive center in the side chain, the absorption depends strongly on the aromatic system involved, the differences between spectra of the covalently hydrated and unhydrated forms are often small. Furthermore, the molar absorptivities of products formed are often not known. This is reflected in a lower accuracy of the obtained value of the equilibrium constant. Nevertheless, in numerous cases reported in this review, the value of equilibrium constants obtained by electrochemical and spectrophotometric methods agree reasonably well.

On the other hand, values of equilibrium constants obtained by NMR for sufficiently soluble substances are in numerous cases significantly higher than values obtained by electrochemical or spectrophotometrical methods. The NMR data are typically obtained in 0.1 M or more concentrated solutions, whereas in electrochemical or spectrophotometric measurements the solute is present in typically 1 to 2 x 10^{-4} M concentrations. One possible explanation of observed differences is that in more concentrated solution additional solute-solute interactions take place.

2. Covalent additions to a carbonyl group

The addition to water to carbonyl compounds follows an overall process (1), characterized by an equilibrium constant of hydration K_h = [>C(OH)$_2$]/[C=O]:

$$>C=O + H_2O \equiv >C(OH)_2 \quad (1)$$

2.1. Covalent additions to aliphatic carbonyl compounds

2.1.1. Covalent additions of water

Equilibrium constants for addition of water to aliphatic aldehydes and ketones have been tabulated and extensively discussed[3-7]. Only some structural effects will be therefore briefly discussed here. The position of the hydration equilibrium (1) depends for aliphatic aldehydes and ketones strongly on the presence and nature of groups adjacent to the carbonyl group.

The effects of alkyl groups R in the aldehydes R-CHO on values of log K_h can be expressed by a correlation with Taft=s σ substituent constants. For halogenated acetones of the type CH_3COY (where Y=CH_3, CH_2Cl, $CHCl_2$, CH_2F and CF_3) the values of log K_h show a good correlation with inductive substituent constants σ^I.

To demonstrate the role of the adjacent group it is possible to compare the hydration of formaldehyde in aqueous solutions (99.5%) with that of acetaldehyde (about 50% hydrated) and acetone (only about 0.15% hydrated). Introduction of three α-halogens into acetaldehyde leads to almost complete (99.997%) hydration in chloral (CCl_3CHO). Similarly, substitution of CH_3 group in acetone by a CF_3 group results in about 97% hydration.

Substitution of hydrogen by a hydroxyl in glycolaldehyde ***1*** results[12-14] in at least 90%, in lactaldehyde ***2*** in 96% hydration. For protonated forms of α-aminoisobutyraldehyde ***3*** with varying substituents on the α-amino nitrogen, hydration varying between 50 and 90% was reported[4,15].

R-CHO **1** R = CH_2OH
2 R = $CH(OH)CH_3$
3 R = $CH(NH_2)CH(CH_3)_2$

Probably the most frequently investigated - next to that of formaldehyde - is the hydration of a carbonyl group adjacent to a carboxyl or carbalkoxy group. In some α-ketoacids and their esters the situation is further complicated by keto-enol equilibria of the unhydrated form. Most reliable values of K_h have been tabulated[16,17]. Introduction of a halogen in β-fluoropyruvic acid ***4*** results[18] in

predominant formation of the hydrated, geminal diol form. Replacement of the methyl group in pyruvic acid ***5*** by a hydrogen in glyoxalic acid ***6*** increases the K_h-value by two decades of magnitude, whereas extension of the alkyl chain has only a minor effect.

R-COCOOH **4** R = FCH_2
5 R = CH_3
6 R = H

Presence of an α-carbonyl group in α-diketones[19-23], α-ketoaldehydes and 1,2-dialdehydes increase hydration, similarly as observed for the role of COOR. Polarographic limiting currents enable an estimate of the lowest value of K_h, as such currents are often increased by a regeneration of some 1,2-dicarbonyl compound from hydrated forms. Thus for biacetyl polarography indicated $K_h > 3.1$, in agreement with the value 3.3, obtained by spectroscopy[20] and values 3.3 and 3.7 obtained by cyclic voltammetry[21]. Hence estimate based on polarographic limiting currents indicates caution when using some data obtained by UV-spectra (2.7[22] and 2.1[19]) and NMR (2.0[23] and 2.1[24]). For 2,3-pentadione ***7*** polarography indicated[21] $K_h > 1.9$ in agreement with values $K_h = 2.5$ to 3.2 obtained by CV. Value $K_h = 1.7$ obtained by UV-spectra might be thus doubtful. Protonated forms of biacetyl ***8*** ($K_h = 0.19$) and 2,3-pentadione ***7*** ($K_h = 0.16$) are considerably less strongly hydrated[21] than their conjugate bases. For glyoxal ***9*** the mutual interaction of the two formyl groups results in very strong hydration ($K_h > 100$)[25]. The central carbonyl group in 1,2,3-triketones is also strongly hydrated.

R^1COCOR^2 **7** $R^1 = CH_3$, $R^2 = CH_2CH_3$
8 $R^1 = R^2 = CH_3$
9 $R^1 = R^2 = H$

2.1.2. Additions of hydroxide ions

In strongly alkaline solutions, typically at pH > 12, it has been suggested[26] that a nucleophilic addition of hydroxide ions to the carbonyl group competes with the addition of water molecules in reaction (2) (in the absence of hydrogen on ∀-carbon):

$$H_2O + >C=O \rightleftharpoons C(OH)_2 \overset{-H^+}{\rightleftharpoons} C(OH)O^- \rightleftharpoons C=O + OH^- \qquad (2)$$

This has been concluded based on variation of polarographic limiting currents with pH, in particular the decrease of current with increasing pH at pH greater than about 12. Formation of the geminal diol anion in this reaction was confirmed[27], by an increase (with increasing pH) of an anodic wave, corresponding to the oxidation of the geminal diol anion into a carboxylate anion.

2.1.3. Addition of alcohols

Equilibria (3) between aliphatic aldehydes (R^2 = H) and ketones (R^2 = alkyl) yielding hemiacetals

and acetals, or, respectively, hemiketals and ketals, were almost exclusively studied in solutions, where the particular alcohol was present both as a reagent and as a solvent[4,28-30]. Under such conditions the position of equilibrium (3) will be affected not only by structural effects on the carbonyl compound, the alcohol as a nucleophile and the adduct, but also by variations in solvation, in particular of the carbonyl group and of the alcohol.

$$R^1R^2C{=}O + ROH \equiv R^1R^2C(OR)OH \quad (3a)$$

$$R^1R^2C(OR)OH + ROH \equiv R^1R^2C(OR)_2 + H_2O \quad (3b)$$

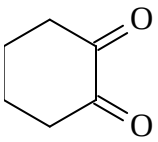
To our best knowledge the only reported equilibrium constants for hemiketal formation (3a) $K_{hemi} = [R^1R^2C(OR)OH]/[R^1R^2CO][ROH]$ in water-alcohol mixtures were those for additions of methanol to fluorinated ketones[30].

In all instances where data were available for comparison[30] the equilibrium constants for acetal or ketal formation were by at least two orders of magnitude larger than the corresponding equilibrium constants for hemiacetal or hemiketal formation. For a given carbonyl compound in reacting alcohol as a solvent, the equilibrium constant in methanol is larger than those in ethanolic solutions. In a given alcohol, effects of structure of the carbonyl compound on the value of K_{hemi} resemble those for hydration.

2.2. Covalent additions to alicyclic ketones

Reported data for values of hydration constants K_h of alicyclic ketones are summarized in Table I. Most of these compounds cannot undergo keto-enol equilibria. For 1,2-cyclohexanedione ***10***, for which polarographic evidence[32] indicates a strong hydration of the diketo form, establishment of keto-enol equilibria prevented quantitative evaluation of the values of K_h in aqueous solutions.

In the other bicyclic compounds studied, the diketo form predominates in the solution, as the ∀-carbons to both carbonyl groups are bridgehead atoms and formation of the enol form would violate Bredt's rule. For such compounds, cyclic 1,2-diketones bearing the keto groups in a five- or six-membered ring are more strongly hydrated (2,3-norbornanedione ***11***, 94%, and the Diels-Alder adduct of 2,3-naphthoquinone and cyclopentadiene ***12***, 93%) than those bearing the dicarbonyl



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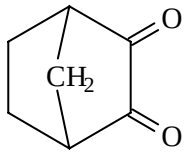
grouping in a seven-membered ring, as for 4,5-homoadamantandione ***13*** (61% hydrate), the behavior of which resembled, more closely, that of the open-chain compounds. On the other hand, in 2,3-camphorquinone ***14*** (bearing the two keto groups in a five- or six-membered ring), the 7-methyl

group that is syn to the dione moiety and possibly also that on carbon 1 exert such a steric hindrance to hydration that the compound is less than about 20% hydrated[32].



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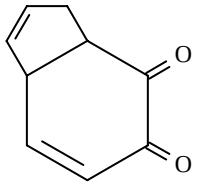

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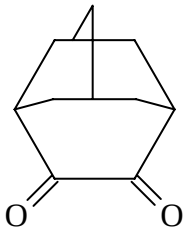

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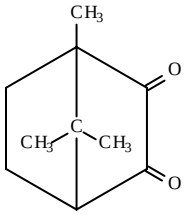

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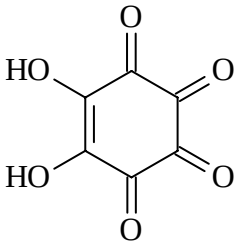
In indantrione (ninhydrin) the central C=O group is strongly hydrated (K_h^1 . 3.10^3), the addition of a second water molecule is much less favored ($K_h^2 = 0.3$)[33].

Similar steric effects of alkyl groups in alicyclic 1,2-diketones have been reported[34] based on spectra. Some of these hydrates have been prepared in crystalline form. ^{13}C-NMR spectra indicated hydration of rhodizonic ***15***, croconic ***16***, squaric ***17*** and deltic ***18*** acids[35], and in the case of rhodizonic acid the dihydrate can be isolated as a crystalline solid.

Hydration of protonated forms of studied 1,2-diketones (Table 1) is stronger than that of the uncharged molecules.



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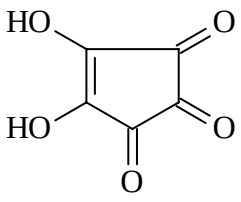

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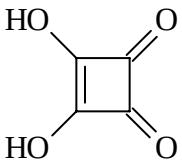

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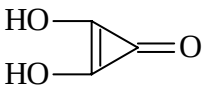

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Table 1. Hydration equilibrium constants (K_h) for some alicyclic ketones

Ketone	K_h^{Coa}	K_h^{COHb}	Ref.
Cyclopentanone	2.9×10^{-4}		6
Cyclohexanone	6.9×10^{-3}		6
1,2-Cyclohexanedione	182[c]		31
2,3-Camphorquinone	3.8	25	32
2,3-Norbornenedione	<0.06	0.92	32
Adduct[d]	0.32		32
4,5-Homoadamantanedione	0.12	0.29	32
Ninhydrin	0.31[e]		33

[a]$K_h^{CO} = [C(OH)_2]/[CO]$; [b]$K_h^{COH} = [C(OH)_2H^+]/[COH^+]$; [c]$K = K_h^{CO}/[H_2O]$ in 99% dioxane 1% water mixture; [d]Diels-Alder adduct of cyclopentadiene and 2,3-naphthoquinone; [e]K_h^{CO} for the addition of second water molecule, K_h^{CO} for addition of the first molecule is about 3×10^3.

2.3. Additions to a carbonyl group in the side-chain of an aromatic ring

This section will deal with addition of water, hydroxide ions, alcohols and alkoxide ions to aromatic aldehydes, aryl and diaryl ketones.

Table 2. Hydration constants ($K_h = [>C(OH)_2]/[>C=O]$) of substituted benzaldehydes

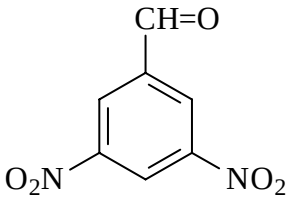
Substituent	K_h	log K_h[a]	Φ
H	0.08	-2.10	0
4-Cl	0.016	-1.79	+0.23
3-Cl	0.022	-1.66	+0.37
3,4-Cl_2	0.045	-1.35	+0.60
4-CF_3	0.056	-1.25	+0.55
3-NO_2	0.110	-0.96	+0.71
4-NO_2	0.170	-0.77	+0.78
4-Cl-3NO_2	0.182	-0.74	+0.94
3,5-$(NO_2)_2$	2.09	0.32	+1.42
2-Cl, 5-NO_2	0.339	-0.47	+0.94

From ref. 6.

2.3.1. Covalent additions of water to benzaldehydes

Most substituted benzaldehydes are in aqueous solutions usually less than 5% hydrated (Table 2), with the exception of nitrobenzaldehydes, where for example 3,5-dinitrobenzaldehyde ***19*** is about 68% hydrated in equilibrium. It was for nitrobenzaldehydes, that the hydration of the formyl group on an aromatic ring was first observed, based on pH-dependence of polarographic limiting currents[36]. The values of log K_h show a good correlation (r = 0.98) with the sum of Hammett

substituent constants, using for the 4-NO_2 group the value of $\Phi_{p\text{-}NO2}$ rather than of $\Phi^-_{p\text{-}NO2}$, showing limited resonance interaction between the formyl and nitro group.



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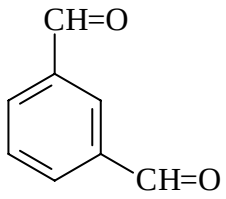
Among the diformylbenzenes the 1,3-derivative (isophthalaldehyde ***20***) does not show marked hydration. In aqueous buffered solutions of 1,2-diformylbenzene (phthalaldehyde ***21***) the concentration of the fully unhydrated form is lower than about 10%. No quantitative data are available for the equilibrium between the hemiacetal and geminal diol form. The terephthalaldehyde ***22*** (1,4-diformylbenzene) is also strongly hydrated, with less than 50% of the unhydrated form present in equilibrium[37].



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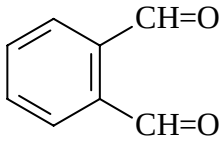

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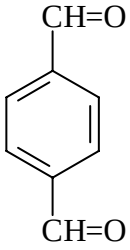

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Table 3. Equilibrium constants for addition of hydroxide ions to 3- and 4-substituted benzaldehydes $K_{OH} = [C(OH)O^-]/[CO][OH^-]$

Substituent	Φ	Φ_p^-	K_{OH}	log K_{OH}[g]
3-O^-	-0.71		0.015[a]; 0.008[f]	-1.96
4-OCH_3	-0.27		0.010[a]; 0.009[f]	-2.0
4-CH_3	-0.17		0.040[a]; 0.033[f]	-1.43
3-CH_3	-0.07		0.10[a]; 0.07[f]	-1.06
4	0.00		0.13[a]; 0.18[c]; 0.09[f]	-0.88
4-F	+0.06		0.081[f]	-1.09
3-OCH_3	+0.11		0.25[a]; 0.17[f]	-0.68
4-COO^-	+0.13	+0.35	0.42[f]	-0.38
4-Cl	+0.23		0.35[a]; 0.47[c]; 0.29[f]	-0.43
3-F	+0.34		0.60[f]	-0.22
3-Cl	+0.37		1.20[a]; 1.13[c]; 0.76[f]; 1.25[d]; 1.26[e]	0.05
3-CHO	+0.38		10[b]	1.0

Table 3. Continued

3-CF_3	+0.41		1.2[f]	0.08
4-CF_3	+0.55		2.1[f]	0.32
3,4-Cl_2	+0.60		2.5[c]; 1.5[f]; 2.33[d]; 2.4[e]	0.34
4-CN	+0.66	+1.00	8.71[a]; 8.9[b]	0.94
4-NMe_3^+	+0.66-1.11		7.6[c]	0.88
3-CN	+0.68		5.5[a]; 4.8[c]; 4.4[f]	0.69
3-NO_2	+0.71		9.1[a]; 8.3[c]; 7.4[d]; 8.0[e]; 6.5[f]	0.90
3,5-Cl_2	+0.74		7.7[c]; 8.1[f]	0.090
4-NO_2	+0.78	+1.04 to 1.27	16.2[a]; 13.3[c]; 15.3[d]; 18.0[e]; 11.3[f]	1.17
3-NO_2; 4-Cl	+0.94		21[a]; 14.8[d]; 17[e]	1.25

[a]Ref. 38; [b]Ref. 39; [c]Ref. 40; [d]Ref. 41, spectroscopy; [e]Ref. 41, kinetics; [f]Ref.42; [g]logarithm of mean value.

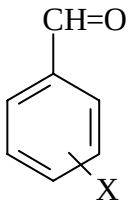
Table 4. Equilibrium constants (K_{OH} = [ArCH(OH)O^-]/[ArCH=O][OH^-]) for addition of hydroxide ions to ortho-substituted benzaldehydes

Substituent	K_{OH}			Ø	log K_{OH}	log K_{OH}^1 + log K_{OH}^{2f}
	Ref.[39]	Ref.[41]				
		Eq[a]	Kin[b]			
2-CH_3	0.095	---	---	0.095	-1.02	
2-Cl	2.6	2.44	2.5	2.5	0.40	
2,4-$(Cl)_2$	6.0	6.4	6.8	6.4	0.81	-0.02
2,6-$(Cl)_2$	10.8	15.2	18	14.7	1.16	0.80
2-NO_2	15	---	---	15	1.18	
2-Cl-6-NO_2	36	---	---	36	1.56	1.58!
2-Cl-5-NO_2	62	35	57	51.3	1.71	1.30
2,4-$(NO_2)_2$	215	---	---	215	2.33	2.35!

[a] Ref.[41], from spectroscopy; [b] Ref.[41], from kinetics; [c] log K_{OH} for 4-Cl -0.42; [d] log K_{OH} for 5-NO_2 0.90; [e] log K_{OH} for 4-NO_2 1.17; [f] sum of log K_{OH} for both substituents, indicating nonadditivity of substituent effects with exception of these marked

2.3.2. Addition of hydroxide ions to benzaldehydes

Substituted benzaldehydes ***23***, present in aqueous solutions predominantly in the nonhydrated form, are a target of a nucleophilic attack by hydroxide ions. Equilibrium constants defined as K_{OH} = [C(OH)O^-]/[C=O][OH^-] of the addition reaction (4) have been obtained



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$$ArCHO + OH^- \equiv ArCH(OH)O^- \quad (4)$$

by spectroscopic[37-42] and kinetic[41] methods (Tables 3 and 4). The effect of substituents in meta- and para-position in these benzaldehydes follows[40] the Hammett equation) log $K_{OH} = \Delta\Phi$ for $\Delta = 2.3$. Better fit of $\Phi_{p\text{-}X}$ constants than $\Phi^-_{p\text{-}X}$ constants for X = 4-COO^-, 4-CN and 4-NO_2, indicates that - as in the addition of water molecules - limited resonance interaction occurs between the formyl group and the above substituents in para-position.

Whereas the value of the reaction constant Δ for correlation of equilibrium constants remains practically unchanged in mixtures containing between 1% and 90% v/v of ethanol, the dependences are shifted along the pK_{OH} axis, as the value of pK_{OH} for unsubstituted benzaldehyde varies from +1.05 in 1% ethanol to +0.48 in 90% v/v ethanol. Completely different is the effect of cosolvent on the addition reaction in water-DMSO mixtures [42], where the value of Δ increases from 2.6 in 10% DMSO to 2.8 in 50% DMSO, 2.9 in 80% DMSO and 3.3 in 90% DMSO. Increased value of Δ with increasing fraction of DMSO may reflect the increasing activity of hydroxide ions, proved to occur in water-DMSO mixtures.

For ortho-substituted benzaldehydes the values of K_{OH} (Table 4) have been claimed[40] to be a linear function of pK_a-values of corresponding ortho-substituted benzoic acids. The effects of ortho-substituents on the free energy of the addition reaction are in most instances not additive. Nevertheless, additivity was observed for 2-chloro-6-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde. This is rather unexpected, as for nitro group, oppositely, a steric hindrance of coplanarity might have been expected.

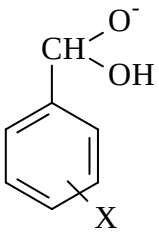
$$ArCHO + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ARCH(OH)O^-$$

Table 5. Rate constants for the addition of hydroxide ions to the formyl group of benzaldehydes and reverse reaction

Substituents	log k_1	log k_{-1}	Φ_m and Φ_p
2-Cl	4.2[a]	3.8[a]	
3-Cl	3.8[a]; 4.8[b]	3.7[a]; 4.8[b]	+0.37
4-Cl	4.8[b]	5.3[b]	+0.23
2,4-$(Cl)_2$	4.6[a]	3.8[a]	
2,6-$(Cl)_2$	4.8[a]	3.6[a]	
3,4-$(Cl)_2$	4.2[a]; 5.9[b]	3.9[a]; 5.7[b]	+0.60
3,5-$(Cl)_2$	5.2[b]	4.3[b]	+0.74
2-NO_2	4.6[a]	3.7[a]	
3-NO_2	4.7[a]; 4.7[b]	3.7[a]; 3.7[b]	+0.71
4-NO_2	4.9[a]; 5.0[b]	3.7[a]; 3.8[b]	+0.74
4-Cl; 3-NO_2	4.9[a]	3.6[a]	+0.94
2-Cl; 5-NO_2	5.3[a]	3.6[a]	

[a] Ref.[41]. [b] ref.[43].

The rates of formation of the geminal diol anion was followed both by a measurement of polarographic limiting currents of oxidation of geminal diol anions ***24*** formed[43] and by a temperature jump spectroscopic method[41] (Table 5). For both nitro compounds, studied by both principally different techniques, the agreement of values obtained by two techniques was found to be excellent. For 3-chlorobenzaldehydes polarographic measurements yielded higher values of both rate constants, k_1 and k_{-1}. The faster reaction observed electrochemically may be due to adsorption of the more hydrophobic chlorinated species at the electrode surface. It seems that for 3-chloro derivatives the condition for using the electrochemical data, namely that the chemical reaction accompanying the electron transfer is a homogeneous process, is not fulfilled.



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Neither the rate of addition of hydroxide ions to the aldehydic group with constant k_1 nor that of the elimination of hydroxide ions from the geminal diol anion with constant k_{-1} follows the Hammett equation. One possible interpretation of this behavior may be the participation of more than one reaction path.

Table 6. Addition of methanol and methoxide ions to substituted benzaldehydes in methanolic solutions K_{CH3OH} = [ArCH(OCH$_3$)OH]/[ArCHO][CH$_3$OH], K_{CH3O-} = [ArCH(OCH$_3$)O$^-$]/[ArCHO][CH$_3$O$^-$]

Substituent	Φ	K_{CH3OH}	log K_{CH3OH}	K_{CH3O-}	log K_{CH3O-}
4-OCH$_3$	-0.27	0.012	-1.92	0.095	-1.02
4-CH$_3$	-0.17	0.034	-1.47	0.040	-1.40
3-CH$_3$	-0.07	0.070	-1.15	0.095	-1.02
H	0.0	0.090	-1.05	0.14	-0.85
3-OCH$_3$	+0.06	0.090	-1.05	0.20	-0.70
4-Cl	+0.23	0.24	-0.62	0.80	-0.10
4-Br	+0.23	0.27	-0.57	0.93	-0.03
3-Cl	+0.37	0.45	-0.35	2.2	0.34
3-Br	0.39	0.43	-0.37	2.8	0.45
3-NO$_2$	+0.71	2.1	0.32	23	1.36
4-NO$_2$	+0.78	3.0	0.48	50	1.70
4-OC$_6$H$_5$	-0.03	0.022[a]	-1.66		
4-F	+0.06	0.113[a]	-0.95		
3-F	+0.34	0.40[a]	-0.40		
4-CF$_3$	+0.55	1.13[a]	0.05		
3-CN	+0.68	1.71[a]	0.23		
4-CN	+0.66	1.83[a]	0.26		

[a] These data from ref.[45], all others from ref.[44].

2.3.3. Addition of methanol and methoxide ions to substituted benzaldehydes in methanolic solutions

The additions of methanol and methoxide ions to 0.2 M solutions of substituted benzaldehydes ***23*** in methanolic solutions was studied using H-NMR[44]. Values of constants for both additions of methanol and methoxide ions (Table 6) follow Hammett's ΔΦ plots, with reaction constants Δ, expressing the susceptibility to substituent effects, equal to 2.0 for the alcohol and 3.2 for the alkoxide ion. These values for reactions in methanolic solutions cannot be directly compared to additions of hydroxide ions in aqueous solutions. Other studies of hemiacetal formation[45] were also carried out in methanol. Direct comparison is prevented by the difference in solvation of the formyl group in water or methanol as a solvent.

The variation of the value of the equilibrium constant for the addition of hydroxide ions in mixed water-ethanol solvents[42] with fraction of the alcohol, may be attributed by competition between formation of the hydrate and the hemiacetal.

2.3.4. Covalent addition of water and alcohols to aryl alkyl ketones

Information regarding covalent hydration of alkyl aryl ketones is currently limited to data obtained for 2,2-dichloro-1-aryl-ethanones ***25***[46] and 2,2,2-trifluoro-1-arylethanones ***26***[47-51]. The values of K_h

differ considerably for data obtained by spectroscopy[48,49] and those obtained by two independent electrochemical methods[48]. For T,T,T-trifluoroacetophenone ***27*** DC polarography clearly indicates that $K_h > 100$ and thus it seems that the value of 250 obtained by cyclic voltammetry[48] is the most reliable one. UV-spectrophotometric data may be affected both by the uncertainty of the estimate of the molar absorptivity of the unhydrated form and by the limited accuracy of the measurement of the n 6 B^* absorbance at 285 to 290 nm in aqueous solutions[48]. Good agreement has been claimed[50] for data obtained by ^{19}F NMR in 0.1 M solutions of the ketone in the presence of 0.1 M methanesulfonic acid and data obtained using UV spectra at concentration of the ketone several order of magnitudes smaller in an absence of an added acid. The values of log K_h of substituted T,T-dichloroacetophenones ***28***[46] are correlated using Φ with $\Delta = 1.62$, those for substituented T,T,T-trifluoroacetophenones ***27*** were a linear function of substituent constants Φ^+ with $\Delta^+ = 1.6$, which indicates a resonance interaction between the substituent and the carbonyl group[49].

$CHCl_2COAr$	CF_3COAr
25	***26***
$Ar = C_6H_5$	$Ar = C_6H_5$
28	***27***

The values of $K_h = [C(OH)_2]/[CO]$ and $K_{hyd} = [C(OH)_2]/[CO][H_2O]$ are both affected by the solvent composition, but only the latter are comparable. Comparison of K_{hyd} in water and acetonitrile as a solvent (Table 7) shows small differences, but much larger difference for DMF as solvent. For mixtures of D_2O and DMSO authors[50,51] compared values of K_h and for 4-OCH_3 and 4-$N(CH_3)_2$ substituted trifluoroacetophenone ***27*** reported dependence of K_h on concentration of DMSO with a maximum. The value of K_{hyd} (Table 8) can be shown to decrease monotonously with increasing concentration of water. This behavior can result from an increase in activity of water with increasing concentration of DMSO, but also from differences in solvation of the carbonyl group and substituents by water and by DMSO.

For addition of methanol using methanol as a solvent the equilibrium constant for hemiacetal formation $K_{hemi} = [C(OR)OH]/[CO][ROH]$ the value of 270 has been reported for T,T,T-trifluoroacetophenone ***27***[30]. This value is two orders of magnitude larger than the values of K_{hyd} obtained for this compound in water, acetonitrile or DMF (Table 7). The differences in solvation of the carbonyl group by water and methanol as well as of the solvent-solvent interactions between water and methanol may all play a role in the observed change.

Table 7. Equilibrium constants for hydration ($K_h = [C(OH)_2]/[CO]$ and for reaction with water ($K_{hyd} = K_h/[H_2O]$) for reactions of alkyl aryl ketones

Substance	K_h	K_{hyd}
$C_6H_5COCH_3$	6.6×10^{-6}[a]	1.2×10^{-7}[a]
$C_6H_5COCHCl_2$	0.33[b]	6.6×10^{-3}[b]
4-$CH_3C_6COCHCl_2$	0.17[b]	3.4×10^{-3}[b]
4-$BrC_6H_4COCHCl_2$	0.64[b]	1.3×10^{-2}[b]
3-$NO_2C_6H_4COCHCl_2$	4.60[b]	9.2×10^{-2}[b]
$C_6H_5COCF_3$	66[c]; 78[d]; >100[e]; 250[f]	1.2[c]; 1.4[d]; >1.8[e]; 4.5[f]; 1.0[g]; 7.1[h]
4-OCH_3-$C_6H_4COCF_3$	6.9[d]	
4-$N(CH_3)_2$-$C_6H_4COCF_3$	0.14[d]	
4-CH_3-$C_6H_4COCF_3$	28.8[d]	
3-CH_3-$C_6H_4COCF_3$	58.9[d]	
4-F-$C_6H_4COCF_3$	81.3[d]	
3-CHO-$C_6H_4COCF_3$	97.7[d]	
3-F-$C_6H_4COCF_3$	316[d]	
3-NO_2-$C_6H_4COCF_3$	1412[d]	

[a] Ref.[49]. [b] ref.[46], 10% acetonitrile. [c] ref.[48]. UV-spectra, 0.2-5% C_2H_5OH. [d] ref.[49]. at 31.4°C. [e] ref.[48], DC polarography. [f] ref.[48], cyclic voltammetry. [g] ref.[48], acetonitrile with 0.2% water. [h] ref.[48], DMF with 0.3% water.

Table 8. Values of hydration constants $K_h = [C(OH)_2]/[CO]$ and $K_{hyd} = [C(OH)_2]/[CO][H_2O]$ for T,T,T-trifluroacetophenones ***27*** in mixtures of D_2O and DMSO[50,51]

mol % D_2O	M_{D2O}	4-OCH_3[a]		4-$N(CH_3)_2$		4-$NHCH_3$		4-NH_2	
		K_h	K_{hyd}	K_h	K_{hyd}	K_h	K_{hyd}	K_h	K_{hyd}
100	50							0.51	0.010
90	34.9					0.24	0.0069	0.39	0.011
80	25.8	14.1	0.55	0.23	0.015	0.21	0.0081	0.34	0.013
70	18.9					0.20	0.0106		
60	13.9	18.2	1.31	0.26	0.019	0.19	0.0137	0.28	0.020
50	10.2					0.20	0.0196		
40	6.8	15.8	2.32	0.24	0.035	0.17	0.025	0.18	0.026
30	4.95	12.9	2.60	0.19	0.038	0.15	0.030		
20	3.0	8.9	2.97	0.14	0.046	0.09	0.030	0.08	0.027
10	1.4	4.9	3.5	0.08	0.057				

Table 9. Most reliable values of K_h[52] for hydration equilibrium constants (K_h) of pyridinecarboxaldehydes ***29-31*** and related compounds at 25°C

Compound	K_h	Compound	K_h
2-Formylpyridine	0.48	2-Formyl-N-methylpyridinium	420
3-Formylpyridine	0.14	3-Formyl-N-methylpyridinium	26.3
4-Formylpyridine	1.11	4-Formyl-N-methylpyridinium	270
2-Formylpyridinium ion	62.5	2-Formylpyridinium-N-oxide	>2
3-Formylpyridinium ion	6.7	3-Formylpyridinium-N-oxide	>1.4
4-Formylpyridinium ion	45.5	4-Formylpyridinium-N-oxide	>4.5

Some additional values[53]: 4-Formyl-3-hydroxypyridine: K_h = 0.75, for its zwitterionic form K_h = 0.84, for its anion K_h = 0.20; 4-formyl-3-hydroxypyridinium ion K_h = 13.1.

Table 10. Lower-limits of K_h estimated from polarographic data[54] for some six-membered heterocycles

Compound	K_h	Compound	K_h
2-Formyl-6-methylpyridine	>0.6	2-Formyl-6-methylpyridinium	>0.17
2,6-Diformylpyridine	>0.12	2,6-Diformylpyridinium	>8
2-Acetylpyridine	>0.12	2-Acetylpyridinium	>0.28
3-Acetylpyridine	>0.01	3-Acetylpyridinium	>0.02
4-Acetylpyridine	>0.12	4-Acetylpyridinium	>0.28
		4-Acetyl-N-methylpyridinium	
2-Formylquinolinium	>27.6		
4-Formylquinolinium	>6.4		

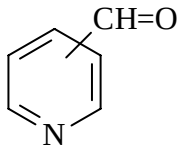
Table 11. Equilibrium constants $K_{hyd} = [C(OH)_2]/[CO][H_2O]$ ($K_{hyd} = K_h/[H_2O]$) for some aza-aromatic aldehydes at 34.5°C in D_2O-DMSO-d_6 mixtures[55]

Compound	K_{hyd}	$K_h/[H_2O]$[a]
2-Formylpyridine	0.0086	0.0087
3-Formylpyridine	0.0036	0.0025
4-Formylpyridine	0.032	0.020
2-Formylquinoline	0.023	
3-Formylquinoline	small	
4-Formylquinoline	0.051	
4-Formyl-1,5-naphthyridine	0.084	
2-Formyl-1,8-naphthyridine	0.13	
4-Formyl-1,8-naphthyridine	0.098	

[a] Equilibrium constants $K_{hyd} = K_h/[H_2O]$ for hydration in aqueous solutions (Table 9) for comparison.

2.3.5. Covalent addition of water and alcohols to formyl pyridines and some other formyl heterocycles

The most reliable values of hydration equilibrium constants (K_h = [$PyCH(OH)_2$/[PyCHO]) for some formyl pyridines ***29***, N-alkylpyridinium-carboxaldehydes ***30*** and formyl pyridine-N-oxides ***31*** are summarized[52] in Table 9. These values have been obtained using UV and NMR spectra, calorimetry, polarography (to determine the lower limit of K_h), as well as cyclic and linear sweep voltammetry. Comparison of values of K_h obtained for 4-formyl pyridine using different techniques is given in ref.[48]. Lower limits of values of K_h for some additional pyridine and quinoline compounds[54] are given in Table 10. Pyridine derivatives with a positively charged nitrogen are more strongly hydrated than corresponding conjugate bases without a charge. The formation of the geminal diol is favored in the sequence $^{+}$N-O < $^{+}$N-H < $^{+}$N-CH_3. For compounds with an uncharged pyridine ring the hydration increases in the sequence 3-CHO < 2-CHO < 4-CHO, indicating a strong resonance contribution in positions 2- and 4-. For positively charged species the sequence of reliable values of K_h is for the N-protonated and N-alkylated forms 3-CHO < 4-CHO < 2-CHO, indicating a strong ortho-effect, possibly a direct field effect.



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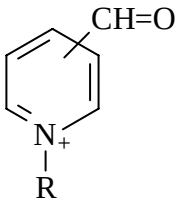

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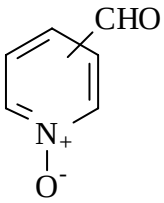

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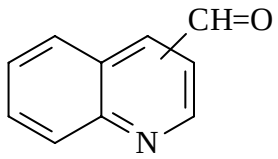
Substitution by a methyl group in 6-position decreases markedly the reactivity of the protonated form towards the addition of water. As can be expected, the reactivity of acyl derivatives is markedly lower than that of the corresponding formyl derivatives (Tables 9 and 10). Introduction of another formyl group in 6-position decreases markedly (in particular when the probability factor would be introduced) the reactivity of the formyl group both in the unprotonated and in the protonated form. Annelation of a benzene ring decreases reactivity of both the 2- and 4-formyl derivatives.

NMR studies in mixtures of D_2O and DMSO-d_6[55] yielded for formyl pyridines ***29*** values of K_{hyd} comparable with those obtained in purely aqueous solutions (Table 11). For protonated forms of

pyridine derivatives an annelation of a benzene ring resulted - as mentioned above - in a decrease in reactivity of the formyl group. For the unprotonated forms of 2- and 4-formyl derivatives, the reactivity - at least for 2- and 4-formyl derivatives - of the quinoline compounds ***32*** is larger than that of the pyridine analoga (Tables 10 and 11).



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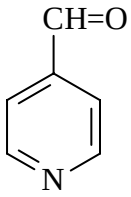
Most extensive values of K_{hemi} = [PyCH(OR)OH]/[PyCHO][ROH] for addition of alcohols to formyl pyridines ***29*** have been obtained when using the reacting alcohol also as a solvent (Table 12). The effect of the extension of the alkyl chain of the alcohol seems to be small, with the formation of the hemiacetal derived from ethanol being usually the least favored. When comparing the data for K_{hemi} obtained in individual alcohols as solvents for formation of hemiacetals of 4-formyl pyridine ***33*** in water (Table 12), a good agreement is shown for methanol (where the solvation of the carbonyl group seems to be similar to that in water). The significant differences in K_{hemi} in ethanol and propanol as a solvent when compared to those in water may be interpreted as due to differences in solvation of the carbonyl groups. When the reaction of 4-formyl pyridine ***33*** with alcohols is followed using DMSO as a solvent, the reactivity decreases considerably with branching on the ∀-carbon of the alcohol (Table 12). As above, it seems that the solvation of the carbonyl group plays a particularly important role.



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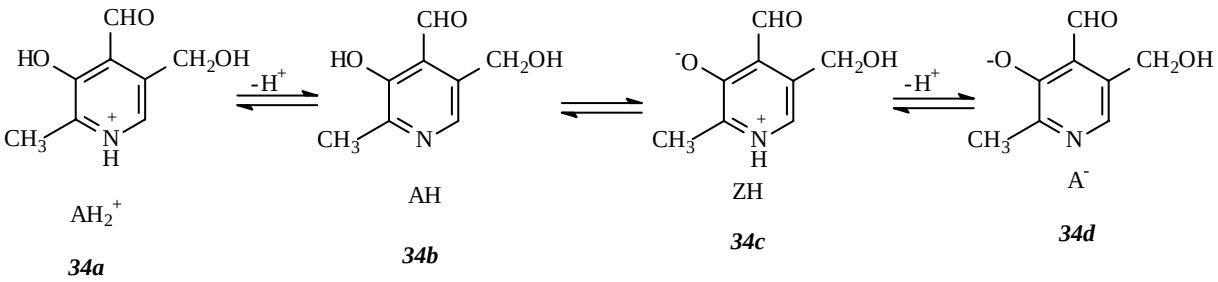
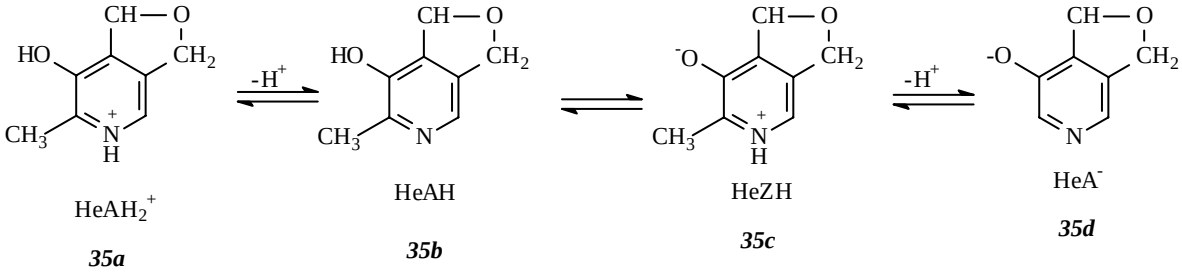
Among physiologically important derivatives of formyl pyridines, most attention has been paid to pyridoxal ***34*** and pyridoxal-5'-phosphate ***35***. In aqueous solutions of varying pH pyridoxal can exist predominantly in cationic (AH_2^+), uncharged (AH) or zwitterionic (ZH) or
anionic (A^-) forms:

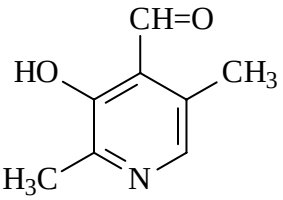




and each of these acid-base controlled species can also exist in a hemiacetal form:
Neglecting concentrations of hydrated forms of AH, ZH and A^- as negligibly small, the following values at 20°C were reported: for $K_{he}^1 = [HeAH]/[AH] = 5.41$; for $K_{he}^2 = [HeZH]/[ZH] = 117.5$ and for $K_{he}^3 = [HeA^-]/[A^-] = 2.98$. For the protonated form AH_2^+ it is not possible to exclude a contribution of the hydrated form.

For 5'-deoxypyridoxal ***36***, where the group 5-CH_2OH is replaced by 5-CH_3, the possibility of the intramolecular hemiacetal formation is excluded and the hydration is considerable. Using the same symbols as for pyridoxal with $CH(OH)_2$ indicating the hydrated form, the following values were reported at 20°C [54]: for $K_h^a = [AH_2^+ \bullet CH(OH)_2]/[AH_2^+] = 3.0$, for $K_h^b = [ZH \bullet CH(OH)_2]/[ZH] = 0.38$. This can be compared with values in a study [49] attempting to separate the values for AH and ZH for 5'-deoxypyridoxal ***37***, where for $K_h^a = [AH_2^+ \bullet CH(OH)_2]/[AH_2^+] = 2.2$, for $K_h^b = [ZH \bullet CH(OH)_2]/[ZH] = 0.57$, for $K_h^c = [AH \bullet CH(OH)_2]/[AH] = 0.087$ and for $K_h^d = [A^-CH(OH)_2]/[A^-] = 0.085$. For N-methyldeoxypyridoxal ion ***37*** were reported[53] the values $K_h = 1.8$ and for corresponding zwitterion $K_h = 0.56$.

For the effect of 1,4-dioxane on hydration of 5'-deoxypyridoxal ***37*** comparison of constants $K_{hyd} = K_h/[H_2O]$ rather than that of K_h is preferred. Table 13 indicates that at 20°C the value of K_{hyd} for the protonated form AH_2^+ increases gradually with concentration of dioxane, perhaps due to variation in solvation of the formyl group. For the neutral-zwitterionic form ZH on the other hand the value of K_{hyd} remains practically constant (Table 13).



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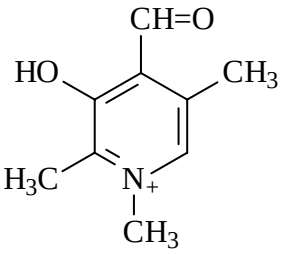

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Table 12. Reactions of pyridinecarboxaldehydes with alcohols (K_{hemi} = [PyC(OR)OH]/[PyCHO][ROH]

Compound	Alcohol	K_{hemi}[a]		
2-PyCHO	MeOH	0.25		
	EtOH	0.11		
	n-PrOH	0.13		
3-PyCHO	MeOH	0.12		
	EtOH	0.08		
	n-PrOH	0.09		
4-PyCHO	MeOH	0.56	0.50[b]	0.58[c]
	EtOH	0.49	0.27[b]	0.28[c]
	n-PrOH	0.59	0.25[b]	
	2-PrOH			0.088[c]
	t-BuOH			0.0043[c]

[a] Values from ref.[56] in individual alcohol as solvent. [b] values in water-alcohol mixtures[57], corrected for hydration. [c] values in DMSO at 34.5°C, fraction of alcohol not mentioned[55].

Table 13. Dependence of K_h = $[C(OH)_2]/[CO]$ and K_{hyd} = $[C(OH)_2]/[CO][H_2O]$ for 5-deoxypyridoxal ***36*** on concentration of 1,4-dioxane in mixtures with water at 20°C[58]

X_D[a]	K_h^{+b}	K_{hyd}^{+b}	$K_h^{\pm c}$	$K_{hyd}^{\pm c}$
0.000	3.0	0.055	0.38	0.0069
0.103	3.24	0.065	0.29	0.0058
0.206	3.47	0.079	0.28	0.0063
0.307	3.85	0.10	0.27	0.0070
0.409	4.08	0.12	0.29	0.0088
0.509	4.41	0.16	0.29	0.0106
0.608	4.10	0.19	0.16	0.0073
0.707	3.98	0.24	0.06	0.0037

[a] Weight fraction of dioxane. [b] values for the monoprotonated form of 5-deoxypyridoxal ***36***. [c] values for the zwitterion-neutral form of 5-deoxypyridoxal ***36***.

Table 14. Covalent hydration constants ($K_h = [C(OH)_2]/[CO]$) for individual forms of pyridoxal-5'-phosphate

		K_h			
pH	Predominating form	DCP[a]	CV[b]	UV[c]	NMR[d]
<2.6	***38a***	>0.1[e]	0.17[g]; 0.31[h]		3.0[k]
<4.8	***38b***	>0.2[e]	0.26[g]; 5.48[h]	3.2[i]	
<7.3	***38c***	>0.3[e]; 0.25[f]	0.14[g]	0.28[i]	0.20[k]; 0.86[l]; 0.66[m]
<0.95	***38d***	>1.5[e]			
<12.7	***38e***	>0.5[e]			

[a] DC polarography. [b] cyclic voltammetry. [c] UV-spectra. [d] NMR spectra. [e] limit estimated form i = f(pH) plots in ref.[59] for i_d = 3.0 :A. [f] from ref.[60]. [g] from ref.[59]. [h] from ref.[61]. [I] from ref.[53], corrected for zwitterionic form only. [k] from ref.[62]. [l] from ref.[63]. [m] from ref.[64].

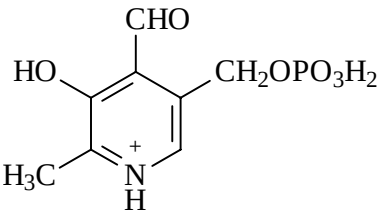
Table 15. Covalent addition of water to some heterocycles bearing carbonyl groups ($K_h = [C(OH)_2]/[CO]$)

Compound	K_h
2-Formylthiazole	>0.6[a]; .0.25[b]
2-Formylthazolinium ion	>15[a]
2-Formylbenzothiazole	.0.9[b]
4(5)-Formylimidazole	>1.0[a]
4(5)-Formylimidazolium ion	large[a]
2-Formylimidazolium ion	large[c]
2-Formyl-1-methylimidazolium ion	large[c]
2-Formyl-1-benzylimidazolium ion	large[c]
2-Formyl-5-nitrofuran	>0.78[d]
2-Formyl-5-nitrothiophene	>0.31[d]
3-Formylcinnoline	large[b]
9-Formylacridine	0.07[e]
9-Formylacridinium ion	2.5[e]
1,10-Phenanthrolinium-5,6-dione	2.0[f]

[a] Ref.[67]. [b] ref.[66]. [c] ref.[67]. [d] ref.[4]. [e] ref.[68]. [f] ref.[69].

In pyridoxal-5'-phosphate ***35*** the substitution of the hydroxyl group in the side-chain in position 5 also prevents formation of an intramolecular cyclic hemiacetal. The covalent hydration (Table 14) strongly depends on ionic form ***38a-38e*** and it cannot be excluded that due to insufficient description of the composition of the studied solution some of the data in Table 14 might not have been correctly assigned. This - apart from the considerable difference in concentration of the pyridoxal derivative used - may explain the rather large discrepancies among data in Table 14. Furthermore,

the species described here as having a dissociated OH group and protonated pyridine nitrogen can be present in the same pH-range as uncharged pyridine nitrogen and undissociated OH group. Replacement of OPO_3H^- in the side chain of pyridoxal by a sulfate, carboxylate or sulfonate grouping has only a small effect on individual K_h-values[53].



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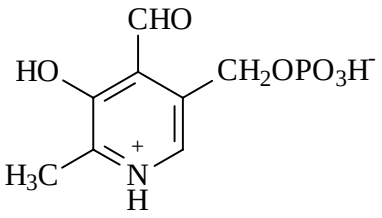

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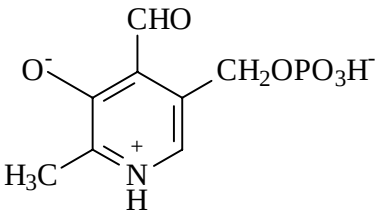

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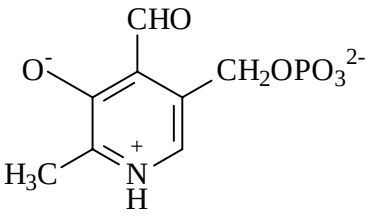
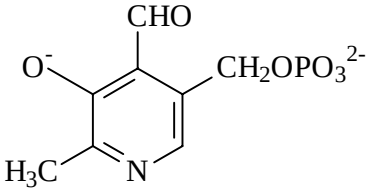


38d



38e

In the presence of ethanol[65] a competition between hydration and formation of a hemiacetal takes places at pH 2. The two equilibria involved, namely

$$^{+}HPyCHO + H_2O \equiv {}^{+}HPyCH(OH)_2 \quad (8)$$

and

$$^{+}HPyCHO + EtOH \equiv {}^{+}HPyCH(OEt)OH \quad (9)$$

are characterized by equilibrium constants $K_{hyd} = [^{+}HPyCH(OH)_2]/[^{+}HPyCHO][H_2O]$ which contrary to constant K_h includes the concentration of water and $K_{he} = [^{+}HPyCH(OEt)OH]/[^{+}HPyCHO][EtOH]$. For the value of $K_{hyd} = K_h/[H_2O]$ using for $K_h = 3.2$ we obtain for aqueous solutions at pH 2 $K_{hyd} = 0.058$. The equilibrium constant K_{he} can be transformed into and from reported[65] values of $[HPyCH(OEt)OH]/[^{+}HPyCHO] + [^{+}HPyCH(OH_2)]$ at each [EtOH] it is possible to obtain the following values: 20% v/v EtOH $K_{he} = 0.22$; 40% v/v EtOH $K_{he} = 0.28$; 60% v/v EtOH $K_{he} = 0.44$; 80% v/v EtOH $K_{he} = 0.46$.

$$K_{he} = \frac{[^{+}HPyCH(OE)OH]}{[^{+}HPyCHO] + [^{+}HPyCH(OH)_2]} \cdot \frac{1 + K_{hyd}[H_2O]}{EtOH} \quad (10)$$

The increasing trend in K_{he} with increasing concentration of ethanol is not caused by predominant acetal formation, as expression considering interaction of pyridoxal-5'-phosphate ***35*** with two moles of EtOH have shown even much worse correlation. Some acetal formation may be involved, but too limited number of data is available to allow estimate of both K_{he} and K_{acetal}.

Some additional information dealing with the covalent addition of water to carbonyl groups attached to a heterocyclic ring is summarized in Table 15. Protonation of ring nitrogen or introduction of a nitro group results in an increase in hydration even in formyl derivatives of furan or thiophene, which in the absence of a nitro substituent are negligibly hydrated.

Table 16. Addition of hydroxide ions to formyl groups in some five-membered heterocyclic rings[66] $K_{OH} = [ArCH(OH)O^-]/[ArCHO][OH^-]$

Compound	K_{OH}
2-Formylfuran	0.17
2-Formyl-5-methylfuran	0.022
2-Formyl-5-nitrofuran	150[a]
2-formylthiophene	0.062
2-Formyl-5-bromothiophene	0.23
2-Formyl-3-methylthiophene	0.017
2-Formylpyrrole	<0.001
2-Formyl-1-methypyrrole	.0.0003
3-Formyl-1-phenyl-2,5-dimethylpyrrole	.0.01
2-Formylindole	<0.001
3-Formylindole	<0.01
3-Formyl-N-ethylcarbazole	1.12
2-Formyl-imidazoleiminate anion	.3.1[a]

[a] Parent compound substantially hydrated, $K = [ArCH(OH)O^-]/\{[ArCHO] + [ArCH(OH)_2]\}[OH^-]$.

Table 17. Equilibrium constants $K_{add} = [R^1C_6H_4CH(OR)\text{-}NHC_6R^2]/[R^1C_6H_4CH{=}NC_6H_4R^2][ROH]$ at 25°C in methanol-acetonitrile (9:1)[78] and methanol[79,80] as a solvent

Compound		Solvent, $K(M^{-1})$		Nucleophile
R^1	R^2	MeOH-MeCN	MeOH	
H	H	0.0015[a]	0.0492[b]; 0.047[c]	MeOH
H	4-Cl	0.0035[a]	---	MeOH
H	3-Cl	0.0086[a]	0.211[c]	MeOH
H	3-NO_2	0.0230[a]	0.855[c]	MeOH

Table 17. Continued

H	4-CN	---	3.19[c]	MeOH
H	4-NO_2	---	7.33[c]	MeOH
4-OCH_3	H	---	0.0146[b]	MeOH
4-OC_6H_5	H	---	0.0266[b]	MeOH
4-CH_3	H	---	0.0282[b]	MeOH
3-OCH_3	H	---	0.0472[b]	MeOH
4-F	H	---	0.0495[b]	MeOH
3-F	H	---	0.0970[b]	MeOH
3-Cl	H	---	0.101[b]	MeOH
4-Br	H	---	0.0682[b]	MeOH
3-Br	H	---	0.112[b]	MeOH
4-CF_3	H	---	0.161[b]	MeOH
4-CN	H	---	0.175[b]	MeOH
3-CN	H	---	0.189[b]	MeOH
3-NO_2	H	---	0.197[b]	MeOH
4-NO_2	H	0.0071[a]	---	MeOH
4-NO_2	4-OCH_3	0.0006[a]	---	MeOH
4-NO_2	4-CH_3	0.0036[a]	---	MeOH
4-NO_2	4-Cl	0.0164[a]	---	MeOH
4-NO_2	3-Cl	0.0315[a]	---	MeOH
4-NO_2	3-NO_2	0.0650[a]	0.200[b]	MeOH

Compound		Solvent	K(M^{-1})	Nucleophile
R^1	R^2			
4-NO_2	3-Cl	EtOH	0.024[a]	EtOH
4-NO_2	3-Cl	n-BuOH	0.037[a]	n-BuOH
4-NO_2	3-Cl	i-PrOH	0.110[a]	i-BrOH
4-NO_2	3-Cl	sec-BuOH	0.076[a]	sec-BuOH
4-NO_2	3-Cl	t-BuOH	0.220[a]	t-BuOH

[a] From ref.[78] in 90% MeOH, 10% MeCN; [b] from ref.[79], in MeOH; [c] from ref.[80], in MeOH.

Table 18. Hydration equilibrium constants (K_h = [>C(OH)NH-]/[>C=N-] for some substituted pteridines (1,3,5,8-tetraazanaphthalenes)[128]

Substituent	K_h				
	Pteridine	2-Hydroxypteridine		6-Hydroxypteridine	
	Neutral	Neutral	Anion (O^-)	Neutral	Anion (O^-)
H	0.29	320	0.14	125	0.045
2-CH_3	0.36	---	---	80	0.028
4-CH_3	0.028	6	0.014	75	0.016
6-CH_3	---	110	0.10	---	---
7-CH_3	0.040	35	0.58	1.29	0.001

2.3.6. Additions of hydroxide ions to the formyl group attached to five-membered heterocycles

The majority of five-membered heterocyclic compounds with a single heteroatom bearing a formyl group in position 2 or 3 demonstrates in aqueous solutions at pH smaller than about 10 or 11 limited hydration. In more alkaline solutions these compounds, nevertheless, manifest considerable reactivity towards a nucleophilic attack of hydroxide ions on the carbonyl group. The reactivity of the 2-formyl group increases in the sequence of derivatives of pyrrole < thiophene < furan (Table 16). Annelling of a benzene ring in formyl indoles affects little the reactivity of the aldehydic group towards the nucleophilic attack. Introduction of electronegative substituents increases the positive charge on the carbonyl carbon with a resulting increase in reactivity of the carbonyl group. On the other hand, substitution by a methyl group in positions 3- or 5- results in the decrease in reactivity of the formyl group.

3. Covalent additions to azomethine bonds

The equilibria and rates of reactions leading to establishment of equilibria between imines and water or alcohols or their conjugate bases depend on the structure of the imine. Not only the values of equilibrium and rate constants involved, but even the mechanism of such reactions depend not only on the structure of the parent carbonyl compound and on the nature of the amine involved, but even on the pH-range studied.

One general rule seems to be followed in all systems studied, according to which the protonated or alkylated iminium forms of the azomethine compound are better targets of the nucleophiles than their conjugate bases.

3.1. Covalent additions to azomethine bonds in compounds derived from aliphatic or alicyclic carbonyl compounds

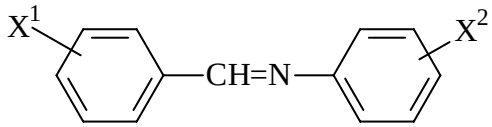
Limited information is available on the additions to Schiff bases derived from aliphatic or alicyclic carbonyl compounds and amines. Extensive information exists dealing with the acid and base catalysed hydrolysis of such Schiff bases, in which the initial step is considered to be either an addition of water or hydroxide ions to yield a carbinol amine. But this unstable intermediate

undergoes a rapid elimination of the amine and formation of a carbonyl compound. Available treatments of kinetic data do not allow a separation of the equilibrium constant for the formation of the carbinolamine and the rate constants involved.

3.2. Covalent additions to benzylidene derivatives

In the hydrolysis of Schiff bases derived from benzaldehyde several mechanisms may operate, depending on substituents on benzaldehyde, on the structure of the amine, on pH and buffers used. Depending on the predominant factor either the addition of water or the cleavage of the carbinolamine, formed as intermediate, can be rate determining. In aqueous solutions, furthermore, the addition can involve either a water molecule or the hydroxide ion as the nucleophile. Probably due to this complexity, the equilibrium constants for additions of H_2O or OH^- to such Schiff bases have not been in most cases isolated[70-74].

To our best knowledge there is only one report[75] indicating the possibility of following simultaneously the concentration changes of both the starting benzylidene anilines ***39*** and the final product, benzaldehyde, using polarography. From the difference in these two concentrations it is possible to obtain the concentration changes of the carbinolamine intermediate. For K_{add} = [carbinolamine]/[benzaldehyde] authors reported the value $K_{add} = 0.19$, which was found practically independent of temperature between 20° and 40°C.



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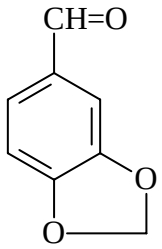
Addition of an alcohol to a iminium cation of the type $ArCH=NR^+_2$ was proposed[76] to interpret the effect of methanol on the reaction of piperidine with piperonal ***40***. In the base catalysed addition of methanol in a solvent consisting of 90% v/v methanol and 10% v/v acetonitrile the equilibrium constant K_{add} = $[R^1C_6H_4CH(OMe)\text{-}NHC_6H_4R^2]/[R^1C_6H_4CH=NC_6H_4R^2][MeOH]$ (Table 17) is increased by electron-withdrawing substituents in both the aniline and benzylidene ring[77]. These values can be correlated with Φ^+ substituent constants ($\Delta^+ = 1.41$, r = 0.994) at 25°C for N-(p-nitrobenzylidene) substituted anilines ***39***, $X^1 = NO_2$, X^2 = varied, $\Delta^+ = 1.43$ (r = 0.995) for N-benzylidene substituted anilines ***39***, X^1 = H, X^2 = varied and $\Delta^+ = 0.86$ for N-substituted benzylidene anilines ***39***, X^1 = varied, X^2 = H. For the effect of the structure of alcohols in their addition to piperonal ***40*** Taft equation has been used in the form $\log [(K_{add})_x/(K_{add})_{Me}] = \Delta^*\Phi^* + *E_s$ (where Φ^* and E_s are polar and steric substituent constants and Δ^* and $*$ are polar and steric reaction constants. The polar effect of substituents ($\Delta^* = -8.2$) is stronger than the steric one ($* = 0.48$). Furthermore, the values of constants K_{add} depend on the alcohol involved and increase in the sequence: EtOH < MeOH < n-BuOH < sec BuOH < i-PrOH < t-ButOH.



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The substituent effects on equilibrium constants K_{add} were also correlated[78,79] using the Young-Jencks equation $\log K_{add} = \Delta^n\Phi^n + \Delta^r(\Phi^+ - \Phi^n) + C$. Here were used substituent constants Φ^+ and Φ^n which, respectively, correspond to situations when the overall polar and B-electron donating direct resonance contributions coexist and when moreover the direct resonance effect is suppressed by the presence of an sp^2 carbon between the ring and the reaction centers. This allowed to separate for substitution on the benzylidene ring [78] the overall polar effect of the substituted ring ($\Delta^n = 0.87$) which includes the resonance induced polar effects from the direct resonance effect ($\Delta^r = 0.54$) due to conjugation of the ring with the azomethine group. For substitution on the aniline ring the values of $\Delta^n = 1.79$ and $\Delta^r = 1.86$ are almost equal and consequently $\log K_{add}$ can be also correlated with Φ^-. The relatively low value of Δ^r was attributed to a compensation of the effects on the energy of the ∀-aminoether (the adduct) by electron withdrawing substituent effects on the stability of the imino form[79].

Recently, covalent hydration of protonated forms of imines has been observed when such imines were generated electrochemically as intermediates in the reduction of oximes, semicarbazones and hydrazones[80]. Such protonated imines react also with two molecules of alcohols, yielding an acetal or ketal. The reactivity increases in the sequence: H_2O, MeOH < EtOH < i-PrOH < t-BuOH.

3.3. Covalent additions to heterocyclic rings

To add water, the reactivity of the azomethine bond in the ring of N-containing heterocycles must be activated, either by the presence of an electronegative substituent or by an increase in the number of heterocyclic nitrogens, providing in effect additional azomethine groupings. Alternatively, the reactivity may be increased by an annelled aromatic ring.

Another type of increased activation to a nucleophilic attack by ROH or RO^- (where R = H or an alkyl group) is achieved, when the reacting heterocyclic compound can be present in the reaction mixture in a cationic iminium form. For the less reactive heterocyclic compounds, protonation is often insufficient to provide a reactive cationic form. This is a consequence of the fact that in the acidity range, where the addition of ROH is sufficiently base catalyzed or where the addition of RO^- predominates, the heterocyclic compound is predominantly present in its conjugate base form, due to its lower pK_a-value. It is, nevertheless, possible to increase the reactivity of the heterocyclic species by converting it into an iminium form, stable even in more alkaline solutions, for example by N-alkylation or conversion into an N-oxide.

If the species attacking the heterocyclic cation is an OH^- ion, such interaction is termed "pseudobase formation" and for the heterocyclic cation Q^+ the equilibrium can be expressed either as:

$$Q^+ + OH^- \overset{K}{\rightleftharpoons} Q\text{-}OH \qquad (11)$$

or as

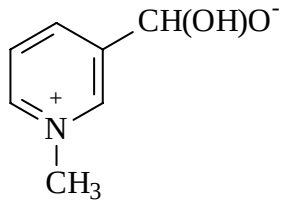
$$Q^+ + H_2O \overset{K_R^+}{\rightleftharpoons} Q\text{-}OH + H^+ \qquad (12)$$

For the latter equation the equilibrium constant K_{R+} is defined as $K_{R+} = [H^+][Q\text{-}OH]/[Q^+]$ and is related to the association constant K in the first reaction through an ionic product of water (K_w) by $K = K_{R+}/K_w$. Numerical values of pK_{R+} for numerous heterocycles have been reported[8].

Pseudobase formation by a nucleophilic addition to heteroaromatic cations is closely related to additions of OH^- or RO^- ions to benzenoid compounds bearing strongly electron withdrawing groups, such as NO_2, resulting in formation of Φ-complexes termed Meisenheimer complexes[81-83]. Presence of more than one nitro group is usually needed to decrease sufficiently the electron density on the ring carbon which is attacked.

3.3.1. Heterocycles with one heteratom

Whereas for the majority of studied N-alkyl pyridinium derivatives no indication of addition of water or formation of a pseudobase by addition of OH^- has been reported[8], for a geminal diol anion, derived from N-methyl-3-formyl pyridinium ion ***41***, bearing a $CH(OH)O^-$ group in position 3- (but not for those with such a group in positions 2- or 4-) formation of a pseudobase has been observed[84] with $pK_{R+} = 14.4$. Similar possible reactions for 3-CN, 3-COOR or 3-NO_2 are masked by other reactions, such as hydrolysis.



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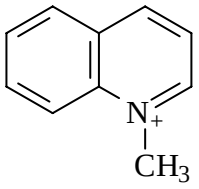
The reactivity towards addition of hydroxide ions increases with the number of annelled benzene rings, with the pK_{R+} value dependent also on the position of the annelled ring. Thus the following values of pK_{R+} were estimated[85]: N-methylquinolinium ***42*** pK_{R+} . 16.5, N-methylisoquinolinium ***43*** pK_{R+} . 15.3, for 5,6- ***44*** and 7,8-N-methylbenzoquinolinium ***45*** $pK_{R+} > 1$, N-methylphenanthridinium ***46*** $pK_{R+} = 11.94$ and N-methylacridinium ***47*** $pK_{R+} = 9.86$. The loss of resonance energy upon formation of the pseudobase is considered to be the major factor in these structural effects.



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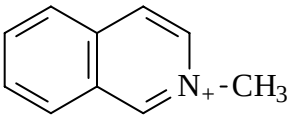

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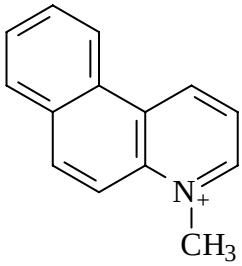

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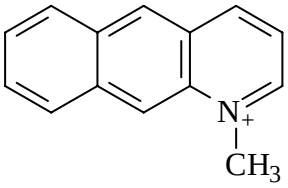

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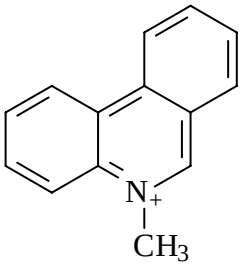

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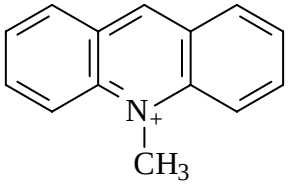
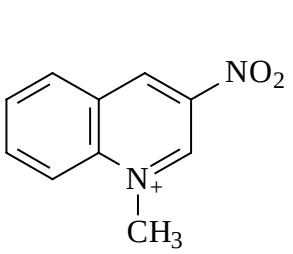


47

As indicated above, an introduction of an electron - withdrawing substituent - either on the ring carbon or on the quarternary nitrogen atom destabilizes the cation relative to the pseudobase and this results in lowering of the pK_{R+} value (relative to that of the unsubstituted compound). Such effects are sometimes dramatic, as, for example, the replacement of the methyl group in the N-methylquinolinium cation ***42*** by an N-cyano group results in a decrease in the value of pK_{R+} by more than 17 pK_{R+}-units. Effects of substituents on ring nitrogen atom were successfully treated using Taft Φ^* substituent constants[8] with Δ^* values indicating that polar effects of these substituents predominate over steric effects.

In polycyclic heterocycles with a single ring nitrogen the substitution on the heterocyclic ring is more effective than on an annelled benzene ring. Thus pK_{R+} values for 3-nitroquinolinium ***48*** (6.8) and 4-nitroquinolinium ***49*** (5.3) cations[8] are considerably lower than those for the corresponding 5-, 6-, 7- and 8-nitroderivatives ***50***, which vary from 9.7 to 12.3. Substituent effects on carbon atoms both in the heterocycle and in the annelled benzene rings can be correlated with Hammett Φ substituent constants. The magnitude of Δ obtained in these correlations indicates that the transmission of substituent effects from the homocyclic ring via C-4 of the heterocyclic ring is in these systems not negligible[8]. Even substituents in pendant phenyl rings can be correlated using Φ constants. The Δ values obtained in such correlations are smaller, but indicate that even substituents on a pendant phenyl group can have considerable influence on the position of the equilibrium between the cationic species and the adduct.

Addition of hydroxide ions to 2-aryl-1-methyl-1-pyrrolinium ions ***51*** results predominantly in formation of a ring opened product, 4-methylaminobutyrophenone ***52***.



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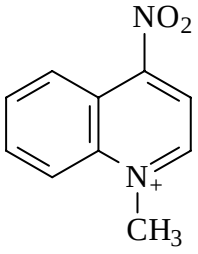

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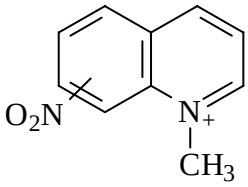
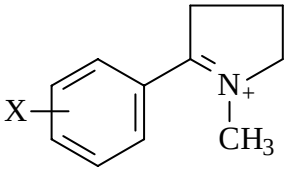


50

In equilibrium the adduct, pseudobase, is present[86] in less than 10%. Similar reactions have been reported[8,87] for pyridinium and related cations, but quantitative information about position of equilibria in such systems is missing.



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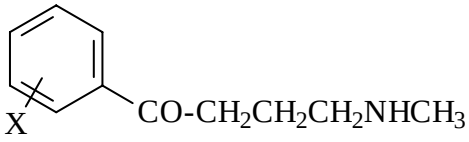


52

Heteroaromatic cations containing O, S or Se as the sole heteroatom are far more susceptible to formation of pseudobases than corresponding N-methyl cations. The values of pK_{R+} are small, in some instances even negative. In most cases the stability of pseudobases increases in the sequence but investigations of equilibria in these systems are often complicated by consecutive ring-opening reactions[8].

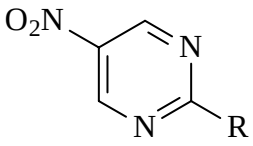
3.3.2. Heterocycles with two heteratoms

$$-\overset{+}{N}Me << -\overset{+}{S}= < -\overset{+}{Se}= < -\overset{+}{O}-$$

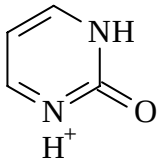
An introduction of an additional nitrogen atom into the heterocyclic ring results in destabilization of the aromatic heterocycle relative to the corresponding adduct. The increase in reactivity towards nucleophilic addition indicates a decrease in delocalization in the ground state which is reflected as a decrease in aromaticity, but depends also on the stabilization of the hydrated form. The effect of ring nitrogen is sometimes considered to be approximately equal to that of a nitro group at the same position in a homocyclic ring. This increase in reactivity is large enough to enable an attack of H_2O or ROH not only on the cationic, but sometimes even on the unprotonated form. When the heterocycle bears an uncharged group which undergoes dissociation, the resulting anion is usually less hydrated than the uncharged conjugate acid.

The effect of the presence of a second nitrogen in heterocyclic diazines differs considerably depending on the mutual position of the two nitrogen atoms. Available information indicates larger

susceptibility to such nucleophilic attacks by pyrimidine derivatives than by pyridazines or pyrazines. Addition of water was reported for 5-nitropyrimidine ***53a***, as well as for its 2-methyl ***53b*** and 2-benzyl ***53c*** derivatives[88]. Based on acid-catalyzed hydrogen exchange the value of K_h for protonated form of 2-oxopyrimidine ***54***, where the addition occurs across N(3)=C(4) double bond, was estimated[89] to be between 0.01 and 0.001.



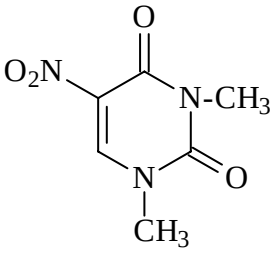
53a R=H
53b R=CH_3
53c R=$CH_2C_6H_5$



54

In solution of 1,3-dimethyl-5-nitrouracil ***55*** the addition is assumed to occur across the C(5)=C(6) double bond[90], whereas for 1-methyl-4-dimethylamino-5-nitro-2-oxopyrimidine ***56*** it was postulated to take place across the N(3)=C(4) double bond[91]. For the addition of water to ***55*** was reported[90] the value of K_h . 1 x 10^{-4}, whereas for that of hydroxide ions the value of K_{OH} = 1.8 x 10^5. Equilibrium constants were found also for other nucleophiles, such as for anion of 2-mercaptoethanol (4.5 x 10^3) and HSO_3^- (1.85 x 10^4). In a DMSO-d_6 solution of 1-methyl-5-nitropyrimidine ***57a*** as well as of 1-methyl-4-methoxy-5-nitropyrimidine ***57b*** an addition of MeOH takes place across the N(1)=C(2) double bond, in a para position relative to the nitro group. Similar addition to 1-methyl-2-methoxy-5-nitropyrimidine ***58*** occurs across the N(3)=C(4) double bond, i.e. in ortho position to the nitro group[92]. In none of these studies attempts have been made to follow the establishment of the equilibria.

Assuming that the protonated form of the unsubstituted 2-aminopyrimidine ***59a*** is not substantially hydrated[93], the decrease of polarographic currents indicated for the protonated form of 4-methyl-2-aminopyrimidine ***59b*** $K_h > 0.13$ and for the 4,6-dimethyl derivative ***59c*** $K_h > 0.27$. Hence the effects of the methyl groups in 4- and 6-position seem to be additive. For sulfometuron methyl (N-[(4,6-dimethylpyrimidin-2-yl)aminocarbonyl]-2-methoxycarbonylbenzenesulfonamide ***60***) with substitution on the amino group, for the protonated form was found $K_h > 0.58$.



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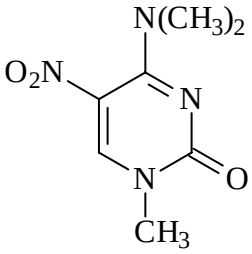

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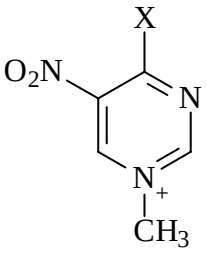
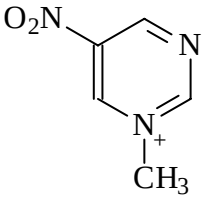
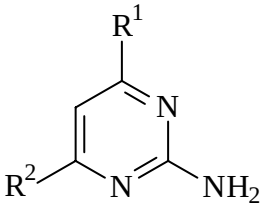


57a X=H
57b X=OCH_3

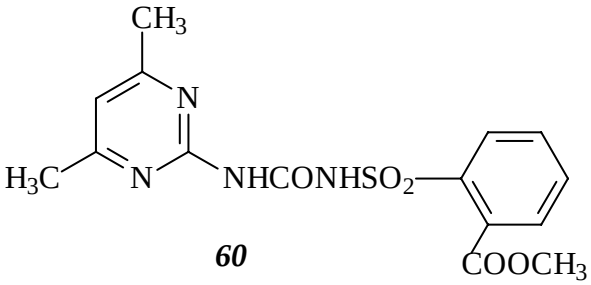


58

The protonated forms of these compounds add also alcohols, with two molecules of ROH reacting with one molecule of the 2-aminopyrimidine derivative to yield a ketal. For sulfometuron methyl ***60*** in aqueous solutions at pH 4.7 the values of $K_{ket} = [>C(OR)_2]/[C=N][ROH]^2$ varied from 0.00075 for EtOH, to 0.0070 for i-PrOH, to 0.0185 for t-BuOH, increasing with nucleophilicity of the alcohol. It is proposed that the attack occurs on the exocyclic imino group in a tautomeric form of the 2-aminopyrimidine derivative, or on the C(2)=N(3) double bond[93].

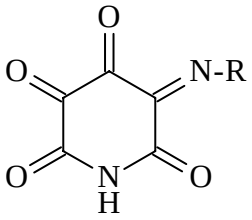


59a $R^1=R^2=H$
59b $R^1=CH_3$, $R^2=H$
59c $R^1=R^2=CH_3$



60

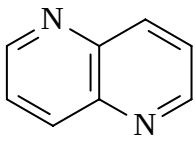
In another pyrimidine derivative, alloxan ***61a*** and its 3-methyl derivative ***61b*** the hydration involves addition to the 5-carbonyl.



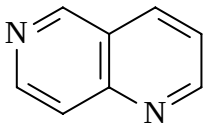
61a R=H
61b R=CH_3

In unsubstituted bicyclic compounds bearing two ring nitrogens, no appreciable hydration has been observed, when the two nitrogens are placed in different rings, as in 1,5- ***62a***, 1,6- ***62b***, 1,7- ***62c*** and 1,8-naphthyridine ***62d***[9,95]. For bicyclic compounds bearing both nitrogens in the same ring, the mutual position of the two heteroatoms is essential for their behavior. Thus whereas quinoxaline ***63*** and phthalazine ***64*** are not noticeably hydrated, the 1,3-isomer, quinazoline ***65***, has a K_h of the protonated form equal[9] about 1.1; for the neutral molecule the value of K_h was[95] 5.5 x 10^{-5}. For addition of hydroxide ions to neutral molecule the value K_{OH} = 1.5 x 10^8 was reported[94] together with values for other nucleophiles, like HSO_3^- (3.25 x 10^8) SO_3^{2-} (1.1 x 10^8), NH_2OH (3.6 x 10^5), ∃-mercaptoethanol (3.7 x 10^4) and its anion (6.3 x 10^6) and H_2S (3.1 x 10^3). The addition of water takes place across the N(3)=C(4) double bond[96]. Substitution of the protonated form of quinazoline by OH, OCH_3, CH_3 and NH_2 groups results in a varying degree of hydration[9]. Among the studied compounds the hydration was most pronounced for the nitro derivatives which are to a small but measurable degree hydrated even in the uncharged, conjugate base form[97]. Strong hydration has been reported also for quinazoline-3-oxide ***66*** and its derivatives[98]. Presence of anionic substituents decreased the reactivity towards nucleophilic attacks by water.

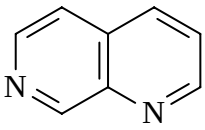
Similarly, as in the case of addition of water, there is a considerable difference in the reactivity towards the addition of hydroxide ions, resulting in formation of pseudobases, depending on the mutual position of ring nitrogens. Thus this reactivity increases from that of 2-methylphthalazinium ion ***67*** (pK_{R+} = 11.04) to that of 1-methyl-quinoxalinium ion ***68*** (pK_{R+} = 8.62) to that of 3-methylquinazolinium ion ***69*** (pK_{R+} # 7)[86]. The reactivity also sharply increases for dications when compared with those of monocations. Whereas pK_{R+} values of 1-methyl-1,5- ***70***, 6-methyl-1,6- ***71***, 7-methyl-1,7- ***72*** and 1-methyl-1,8-naphthyridium ***73*** ions have pK_{R+} between 12.3 and 13.1[86], with 2-methyl-2,7-naphthyridinium cation ***74*** having pK_{R+} = 10.58[99], the dications of naphthyridines with two methyl groups on nitrogens 1,5 ***75*** (pK_{R+} = 4.93), 1,6 ***76*** (pK_{R+} = 2.1) and 2,7 ***77*** (pK_{R+} = 3.84) are much more reactive. In these cases the addition of the hydroxide ion occurs[99] on carbon 4. The readily formed pseudobases in aqueous solutions reflect the extreme electron deficiency of the heteroaromatic dications produced by quaternization of both ring nitrogens of the naphthyridines[86].



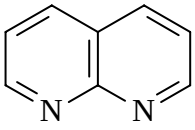
62a



62b



62c



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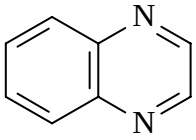

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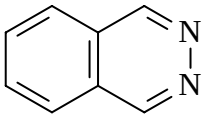

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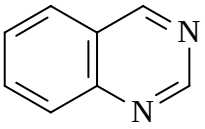

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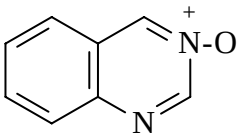

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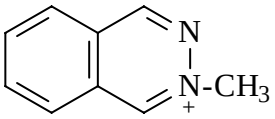

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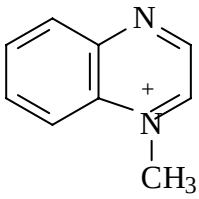

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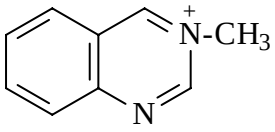

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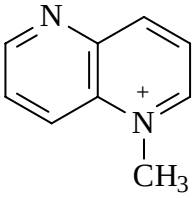

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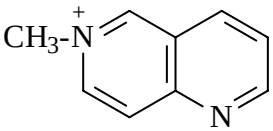

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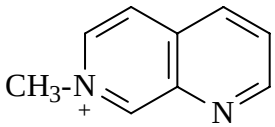

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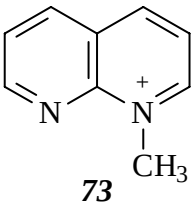

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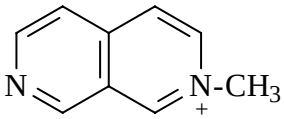
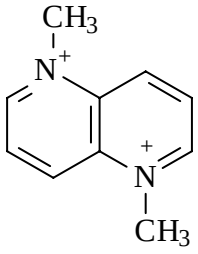
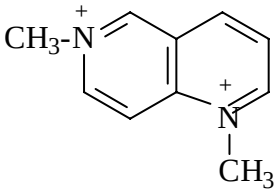
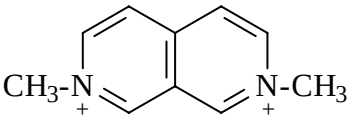
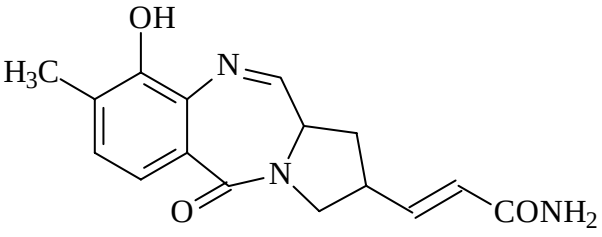








Water and methanol add to the N(10)=C(11) double bond in anthramycin[100] ***78***.

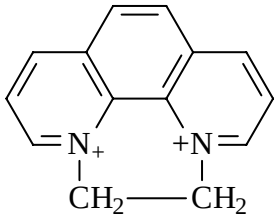


78

For heteroaromatic dications the addition occurs on carbon adjacent to heterocyclic nitrogen. Thus the following values of pK_{R+} were found for 5,6-dihydropyrazinol[1,2,3,4-*lmn*]-***79*** (9.64), 5*H*-6,7-dihydro-1,4-diazepinol[1,2,3,4-*lmn*]- ***80*** (9.17) and pyrazino[1,2,3,4-*lmn*]-1,10-phenanthrolium ***81*** (6.22) dications. In aqueous solution addition of one water molecule predominates, in methanolic solutions bis methoxide adducts are also formed[101].

3.3.3. Heterocycles with three heteroatoms

Additions of water and alcohols will be discussed separately for 1,2,4-triazines, 1,3,5-triazines and other heterocyclic compounds with three heteroatoms.



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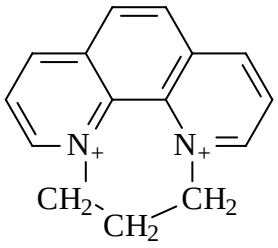

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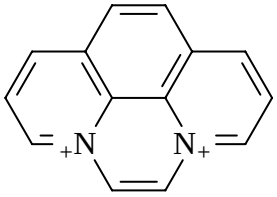
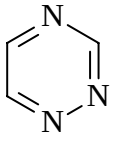


81

3.3.3.1. Reactions of 1,2,4-triazines

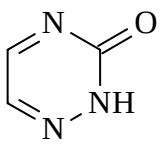
The chemistry of 1,2,4-triazines ***82*** has been reviewed at numerous occasions[10,102-105]. There exists a considerable similarity between the chemical properties of 1,2,4-triazines ***82*** and quinazolines ***65*** - particularly in their reactivity in addition and elimination reactions[106,107].



82

First report on addition of 1,2,4-triazines is probably that dealing with addition of water or EtOH to the protonated form of 3-aminotriazines[108]. Addition of water or alcohols to 1,2,4-triazines is facilitated by a positive charge on heterocyclic nitrogen and by the presence of some electron-withdrawing substituents. The directing effect of substituents on addition of water, methanol and ethanol has not been studied in sufficient detail to draw definite conclusions, but in majority of cases of 3-oxo derivatives[109-113] ***83***, but also for the 5,6-diphenyl-3-thiol derivatives[114] ***84***, and even the unsubstituted 1,2,4-triazine ***82*** in strongly acidic medium, these additions occur across the

N(4)=C(5) double bond. Whereas in 3-oxo-6-phenyl-1,2,4-triazine ***85*** addition of water and ethanol takes place, no such addition has been observed for 3-oxo-5-phenyl-1,2,4-triazine[113] ***86***. The unsubstituted 1,2,4-triazin-3-one ***87*** is so reactive towards water that only the hydrate with a (5)C-OH group can be isolated. Some of the adducts of alcohols at C(5) are so stable that they can be isolated[115]. For 2,4,6-trimethyl-1,2,4-triazin-5-one ***88*** addition of water and methanol was reported[116] across the C(3)=N(4) double bond. Addition of water across this bond was also assumed in interpretation of the mechanism of H 6 D exchange in 1,2,4-triazines[117]. When the nucleophilic attack on C(5) is hindered or blocked by a bulky substituent, then the addition takes place at C(6)[105]. 1,2,4-Triazinium ions bearing no substituent at both C(5) and C(6) can undergo addition of two methoxide ions, with additions to both N(1)=C(6) and N(4)=C(5) double bonds[105]. In all above instances the goal was just identification of the structure of the adduct with no information offered about the equilibria in solutions.



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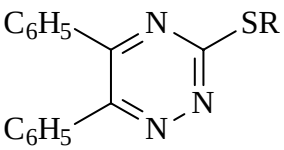

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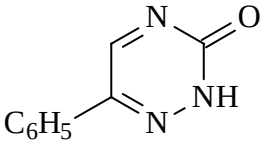

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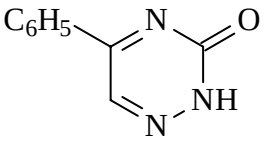

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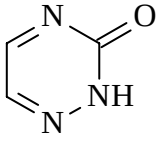

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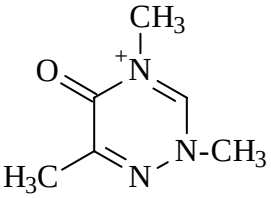
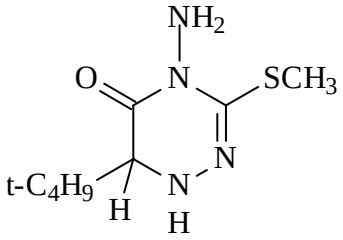


88

Electrochemical studies[118-120] of 4-amino-3,6-disubstituted-1,2,4-triazin-5(4H)-ones ***89***, in which tautomeric changes cannot be involved, indicated that out of two azomethine bonds present the reduction of the C(6)=N(1) double bond occurs at potentials considerably more positive than that of the C(2)=N(3) bond. The difference in the reactivity of these two bonds enables comparison of hydration of these two bonds. As the polarographic limiting currents studied are affected not only by the position of equilibria, but also by the rate of their establishment, it is possible to estimate only the lower limit of K_h values, but in most instances the measured equilibrium value of K_h is only slightly higher than the limiting value. Comparison of reduction currents indicates that in these compounds the 1,6-azomethine bond is more strongly hydrated than the 2,3-bond. Thus for 1-amino-3-methyl-6-phenyl-1,2,4-triazine-5(4H)-one ***89a*** was found for the hydration of the 1,6-bond the values of $K_h > 0.24$ (in water) and $K_h > 0.23$ (in 30% acetonitrile)[119], whereas for the 2,3-bond in 4-amino-3-methyl-6-phenyl-1,6-dihydro-1,2,4-triazin-5(4H)-one ***90*** these values were $K_h > 0.13$ (in water) and $K_h > 0.06$ (in 30% acetonitrile). In solutions in a mixture containing 70% v/v water and 30% v/v organic solvent the ratio [hydrated]/[nonhydrated] increased in the sequence: MeCN (0.43) < MeOH (0.45) < EtOH (0.54) < i-PrOH (0.69) < PrOH (0.75) < BuOH (0.72) < t-BuOH (1.22).

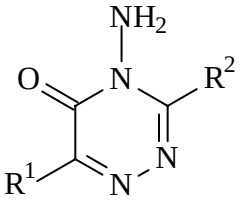
For the hydration of the 1,6-bond in 4-amino-6-tert-butyl-3-methylthio-1,2,4-triazin-5(4H)-one ***89b*** was estimated[120] that $K_h > 1.0$ (in 30% acetonitrile) and for the hydration of the 2,3-bond in 4-amino-6-tert-butyl-3-methylthio-1,6-dihydro-1,2,4-triazin-5(4H)-one ***91*** was obtained the value $K_h > 0.21$ (in 30% acetonitrile).



91

3.3.3.2. Reactions of 1,3,5-triazines

The information concerning additions of water and alcohols to 1,3,5-triazines ***92*** is much more restricted than that available for 1,2,4-triazines ***82***. Unsubstituted 1,3,5-triazine ***92*** readily reacts with water, but the adduct is further cleaved. Thus for 4-chloro-2,6-dimethoxy-1,3,5-triazine ***92a*** in DMSO addition of hydroxide ions at C(4) has been reported[121]. For 2,4-dioxo-1,3,5-triazine ***93*** and



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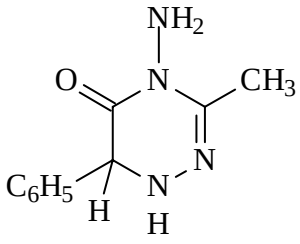
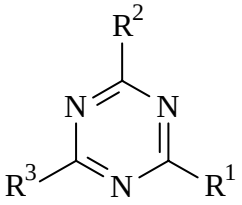


90

89a $R^1=C_6H_5$, $R^2=CH_3$

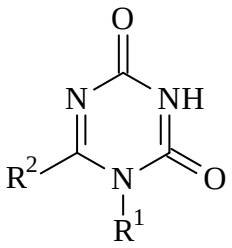
89b $R^1=t\text{-}C_4H_9$, $R^2=SCH_3$

its 1-methyl derivative ***93a*** addition of water, MeOH, EtOH, PrOH, BuOH and $C_5H_{11}OH$ across the C(6)=N(1) is so favored that the crystalline adduct has been isolated [119]. No crystalline products of these two compounds were isolated in the presence of i-PrOH, sec-BuOH and tert-BuOH and similarly no such adducts were isolated for 1,3-dimethyl-, 6-ethyl- ***93b*** and 6-phenyl-2,4-dioxo-1,3,5-triazines ***93c***[122].



92 $R^1=R^2=R^3=H$

92a $R^1=R^3=OCH_3$, $R^2=Cl$



93 $R^1=R^2=H$

93a $R^1=CH_3$, $R^2=H$

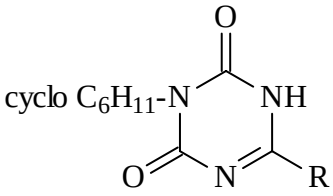
93b $R^1=H$, $R^2=C_2H_5$

93c $R^1=H$, $R^2=C_6H_5$

For 2-dimethylamino-4,6-dioxo-5-cyclohexyl-1,3,5-triazine ***94*** comparison of polarographic limiting currents at pH 3 enabled[123] determination of the lower limit of $K_h > 0.33$ and for it desdimethylamino derivative ***94a*** $K_h > 0.27$. These values were obtained in water as a solvent. Spectrophotometric measurements in acetonitrile as a solvent with concentration of water varying 0.1 and 1.0 M yielded[123] $K_h = 1.3$.

3.3.3.3. Reactions of triazanaphthalenes

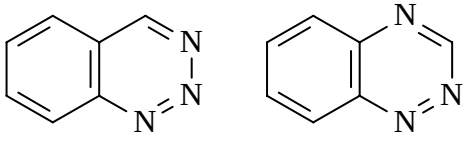
The easy hydrolysis of 1,2,3-triazanaphthalenes ***95*** is attributed to initial addition of water across the N(3)=C(4) double bond[11].



94 $R=N(CH_3)_2$

94a R=H

On the other hand, spectra of 1,2,4-triazanaphthalenes ***96***[124] indicate very limited hydrations.

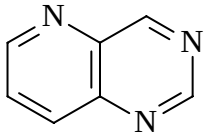


95 ***96***

On the other hand, all the 1,3,X-triazanaphthalenes are, in the protonated form, strongly hydrated[124] and 1,3,5- ***97*** ($K_h = 0.0045$), 1,3,7- ***98*** ($K_h = 0.023$) as well as 1,3,8-triazanaphthalene ***99***

(K_h = 0.002) are measurably hydrated even in neutral form[97]. The 1,4,6-triazanaphthalene ***100*** is also hydrated in both forms, naturally much more strongly in the protonated (K_h = 95) than in the unprotonated one[125] (K_h = 0.0001). In all these 1,3,X- and 1,4,6-triazanaphthalenes the addition of water occurs across the N(1)=C(2) double bond. The protonated form of 1,4,5-triazanaphthalene adds two molecules across the N(1)=C(2) and C(3)=N(4) double bonds[126].

Substitution of the 1,4,6-triazanaphthalene by a 3-methyl group ***100a*** decreases substantially the hydration in both forms, the protonated (K_h = 9) and unprotonated (K_h = 9 x 10^{-6}) and substitution by two methyl groups at C(2) and C(3) ***100b*** practically eliminates it[125]. Substitution by a 2-hydroxy group in 1,3,8-triazanaphthalene ***101***[127] or by 3-hydroxy group in 1,4,6-triazanaphthalene ***100c***[128] decreases considerably the value of K_h in the unprotonated form.



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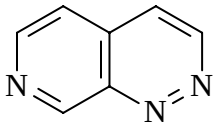

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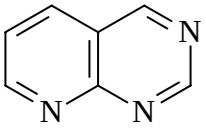

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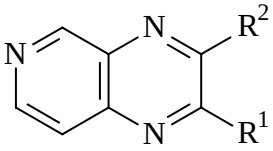


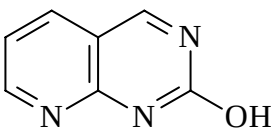
100 $R^1=R^2=H$

100a $R^1=H$, $R^2=CH_3$

100b $R^1=R^2=CH_3$

100c $R^1=H$, $R^2=OH$

Even larger decrease is caused by the anion of the OH group. A marked decrease in K_h is observed by substitution of a 2-hydroxy group in 1,4,5-triazanaphthalene ***102*** where the hydration occurs across the C(3)=N(4) double bond[129].



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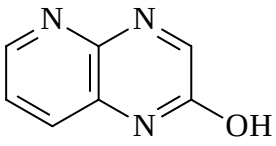


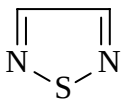
102

3.3.3.4. Other heterocycles with three heteroatoms

Whereas 1,2,5-thiadiazole ***103*** manifests typical properties of aromatic rings and does not covalently add water or alcohols in a measurable degree, the derivatives of 1,2,5-thiadiazole-1,1-dioxide ***104*** are nonaromatic, since the lone pairs of sulfur are not available for sharing with B-electrons of the

azomethine bonds. Thus 3- and 4-alkyl or aryl substituted 1,2,5-thiadiazole-1,1-dioxides have the ability to bind covalently water and alcohols. Spectroscopic[130,131] and electrochemical[131-134] studies proved additions of numerous alcohols to the thiaziazole ring either in a acetonitrile solution or using the same alcohol both as a reagent and as a solvent. The equilibria in acetonitrile solutions are rather slowly established. For example, the equilibrium for the addition of s-BuOH to 3,4-diphenyl-1,2,5-thiadiazole-1,1-dioxide ***104a*** takes several hours to be established[131]. The role of the establishment of an equilibrium depends on concentration of water in the organic solvent but little on the acidity[131]. The addition is observed not only for separated B-electron systems, such as represented by the 3,4-diphenyl derivative, but also for connected, liked the phenanthro-9,10 derivative ***105*** and also for fused B-electron systems, like the acenaphtho-1,2 derivative of 1,2,5-thiadiazole-1,1-dioxide ***106***[134]. Authors presume[131] a 1:1 reaction and claim good agreement of values obtained by UV-spectra and by voltammetry for K_{het} = [T•ROH]/[T][ROH], where T stands for a 1,2,5-thiadiazole-1,1-dioxide ***104*** substituted in 3- and 4-positions and T•ROH for an adduct of this compound.

These authors reported[131] practically identical values of K_{het} for MeOH, EtOH, n-PrOH and s-BuOH, somewhat smaller values of K_{het} for i-BuOH and 2-phenylethanol but significantly smaller values of K_{het} for i-PrOH, s-BuOH and allylalcohol and practically no reaction for tert-BuOH. For the reaction with EtOH in different solvents, the value of K_{het} decreased in a sequence: MeCN, propylene carbonate < DMSO < DMF < N,N-dimethylacetamide, tert-BuOH. The values of K_{het} correlate with Kamlet-Taft empirical hydrogen bond ∃-parameter. Determination of K_{het} in aqueous solutions (or of K_h) is prevented by the subsequent hydrolysis[135] (see below). In DMSO, in which the slowest rate of hydrolysis was observed[131], with a water content varying between 0.1 and 0.2 M, the value of K_{het} for water in DMSO was about three times larger than that for EtOH in this solvent.



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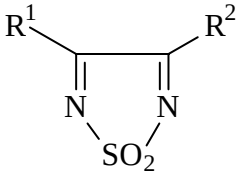
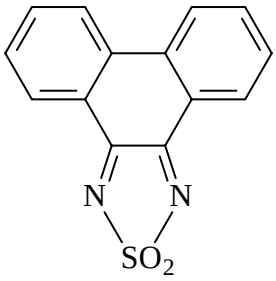


104 $R^1=R^2=H$

104a $R^1=R^2=C_6H_5$



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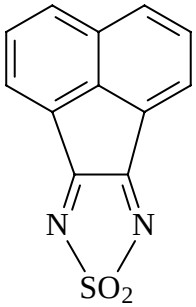
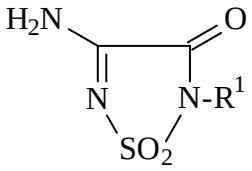


106

In strongly alkaline media using ethanol as a solvent the authors[136] assumed an addition of EtOH followed by an abstraction of proton from the NH-group adjacent to the $C(CH_3)OEt$ group rather than an addition of the EtO^- ion.



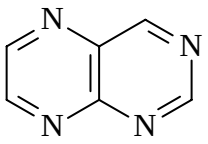
107a R^1=cyclo C_6H_{11}

107b $R^1=C_6H_5CH_2CH_2$

In the course of hydrolysis of 3,4-diphenyl-1,2,5-thiazole-1,1-dioxide ***104a*** in mixtures of ethanol and water, a competition between the addition of EtOH and H_2O is assumed to occur in the first step of hydrolysis[135]. A competition between additions of H_2O and OH^- was postulated[137] in the hydrolysis of two sulfonamides, namely of 4-amino-2-cyclohexyl- ***107a*** and 4-amino-2-phenylethyl-2,3-dihydro-3-oxo-1,2,5-thiazole-1,1-dioxides ***107b***.

3.3.4. Heterocycles with four ring heteroatoms

3.3.4.1. Additions to pteridines (1,3,5,8-tetraazanaphthalenes) *108*



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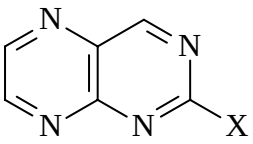
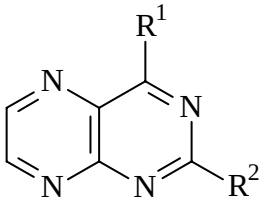


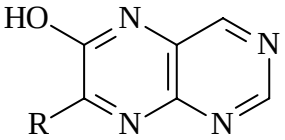
109a X=CH_3

109b X=OH



110a $R^1=CH_3$, R^2=H

110b $R^1=CH_3$, R^2=OH



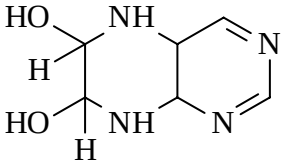
111a R=H

111b R=CH_3

Pteridines comprise a group of compounds, for which the role of the covalent addition of water was recognized early[11] and for which the greatest number of experimental data is available[10,11,128]. For the unprotonated form of the unsubstituted pteridine ***108***, for example, spectrophotometric data[123] yielded K_h = 0.37, whereas from the ratio of limiting polarographic currents of the hydrated

and unhydrated forms[138] was obtained the value of $K_h = 0.27$. It follows that in this case the limiting currents are practically diffusion controlled (as the establishment of the equilibrium takes several minutes and the equilibrium is hence not perturbed by electrolysis). Hydration of the protonated form of the parent pteridine and all its studied methyl derivatives is usually so strong that values of K_h have not been determined. For the unsubstituted pteridine and its 2-methyl derivative ***109a***, but also for the 2-hydroxypteridine derivatives ***109b*** (Table 18) the addition of water occurs across the N(3)=C(4) double bond. A substitution of a methyl group at C(4) decreases the ratio of the hydrated to the anhydrous species both for pteridine ***110a***[139] and for 2-hydroxypteridine ***110b***[140,141] (Table 18). For 6-hydroxypteridines ***111a***, which add water across the C(7)=N(8) bond, an introduction of a methyl group at C(7) in ***111b*** results in a large decrease in K_h (Table 18).

The protonated form of the unsubstituted pteridine ***108*** adds first one molecule of water to form the 3,4-monohydrate. Nevertheless, this adduct is slowly converted into a thermodynamically preferred 5,6,7,8-dihydrate ***112***. In equilibrium is present 21% of the monohydrate and 79% of the dihydrate[142].



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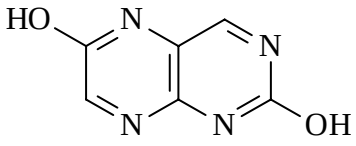

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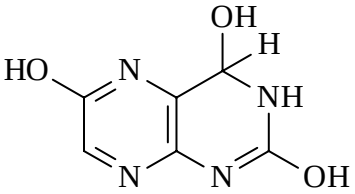

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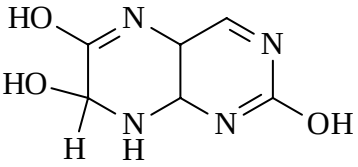
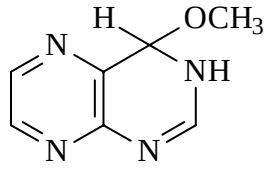


115

Thus if the reaction of 2,6-dihydroxypteridine ***113*** in a buffer pH 7.06 is stopped after 6 min after mixing the aqueous solution of the buffer with a solution of the anhydrous dianion, the thermodynamically less stable 3,4-adduct **114** predominates (64%) in the solution, containing only 10% of the 7,8-adduct and 26% of the parent 2,6-dihydroxypteridine. If the reaction mixture is analyzed after 2-3 hours, the 7,8-adduct ***115*** becomes predominant (92%) with only 7.6% of the 3,4-adduct and 0.4% of the parent compound[143]. Similar type of reaction is observed in methanol, used both as a solvent and as a reactant acidified by trifluoroacetic acid. In such solutions the primary monoadduct across the N(3)=C(4) double bond is gradually converted into an adduct involving two molecules of methanol, across the N(5)=C(6) and C(7)=N(8) double bonds. In this case the equilibrium is even more shifted in favor of the di-adduct, present in equilibrium in 95%, whereas the 3,4-monoadduct was present only in 5%[144]. In solvent-reactant 2-propanol acidified with a large

excess of trifluoroacetic acid, a 2:1 adduct is similarly formed. In acidified solution in tert-butyl alcohol was observed decomposition[144].

Unprotonated form of pteridine also adds the alcohol in a neutral methanolic solution to yield first a 3,4-monoadduct ***116***, gradually converted into a 5,6,7,8-di-adduct ***117***. At equilibrium in this solvent was found 8% of pteridine, 8% of the 1:1 adduct and 84% of the 2:1 adduct[144]. Similar reaction in ethanol yielded also 1:1 and 2:1 adducts, whereas 2-propanol formed preferably the 1:1 adduct and tert-butyl alcohol did not react. In the presence of sodium methoxide in a methanolic solution pteridine yielded immediately a 2:1 adduct. Furthermore, 2-hydroxy- ***118*** and 6-hydroxypteridines ***119*** (but not the 7-hydroxypteridine ***120***) add methanol or ethanol across the N(3)=C(4) double bond[140,145]. Addition of alcohols to various substituted pteridines was also mentioned in other contributions[146-150].



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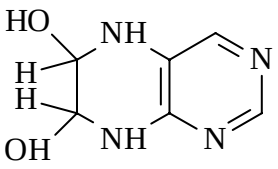

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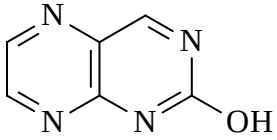

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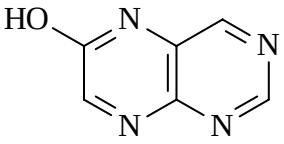

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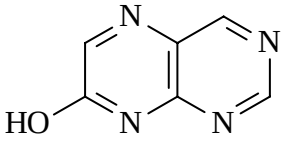
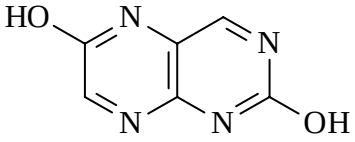


120

For 2,6-dihydroxypteridine ***121*** the initially formed 3,4-adduct is gradually converted to the thermodynamically more stable 7,8-adduct[151], but only one molecule of water is added. Substitution by a 4-methyl group suppressed the 3,4-addition, so that 2,6-dihydroxy-4-methylpteridine ***122*** yielded only a 7,8-adduct.



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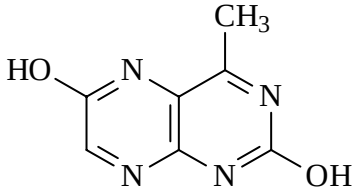
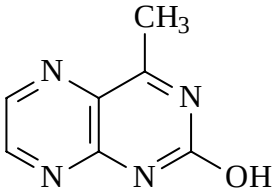


122

Comparison of individual hydroxypteridines shows that 2-hydroxypteridine ***118***, its 4- ***123***, 6- ***124*** and 7-methyl ***125*** and 6,7-dimethyl ***126*** derivatives, as well as 6-hydroxypteridine ***119*** and its 2- ***127***, 4- ***128***, and 7-methyl ***129*** derivatives, but also the 2,6-dihydroxy- ***121*** and 2-amino-4,6-dihydroxypteridines ***130*** are all (in the unprotonated form) hydrated. On the other hand no hydration

was observed for 4-hydroxy- ***131*** and 7-hydroxypteridine ***120***, nor for 2,4- ***132***, 2,7- ***133***, 4,7- ***134*** and 6,7-dihydroxypteridine ***135***, nor for 2-amino-4-hydroxypteridine ***136***[152,153].

Hydration is assumed to facilitate the electrooxidation of the protonated form of 6-hydroxypteridine ***119*** (present predominantly in the 6-oxo form) on a pyrolytic glassy carbon electrode[154].



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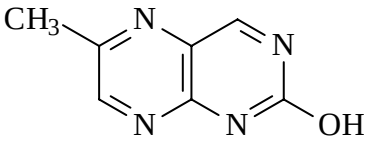

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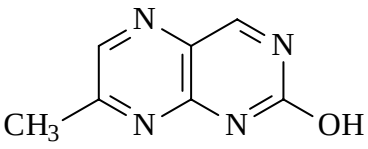

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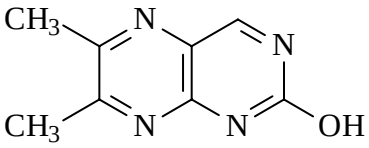

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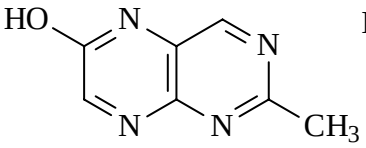

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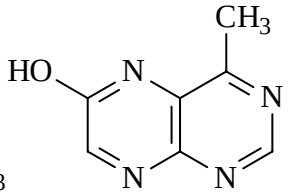

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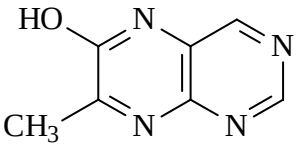

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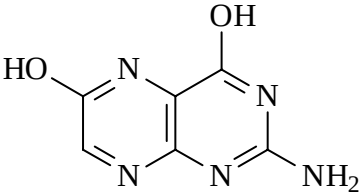

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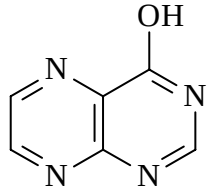

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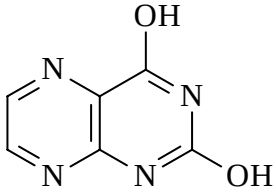

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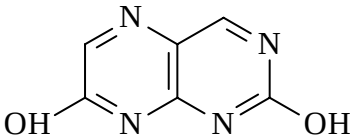

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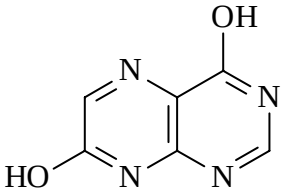

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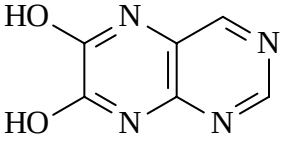

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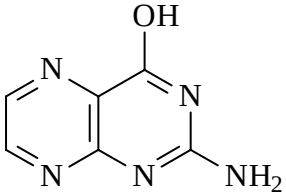
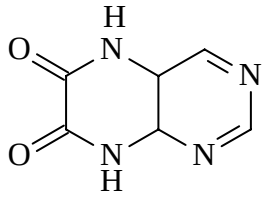


136

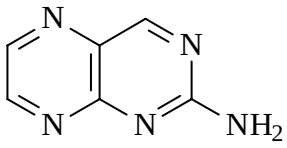
The unprotonated, unhydrated form of this compound is assumed not to be oxidized, contrary to common situation when conjugate base is more easily oxidized than corresponding acid form. Product of electrooxidation of 6,7-dihydroxypteridine ***135***, assumed to be 6,7-dioxopteridine ***137***, is considered to be strongly hydrated.



137

Substituted 2-aminopteridines ***138*** add water across the N(3)=C(4) double bond and the extent of hydration is diminished by a substitution by a methyl group at C(4). Substitution by another methyl group at C(7) practically eliminates the hydration. The extent of water addition to protonated forms of 2-aminopteridines ***138*** decreases from about 99% to about 1% in the sequence[155]: unsubstituted > 6-CH_3 > 7-CH_3 > 6,7-$(CH_3)_2$ > 4-CH_3 > 4,6-$(CH_3)_2$ > 4,7-$(CH_3)_2$.

Whereas 2,4-dihydroxypteridine ***132*** practically does not add covalently water, as mentioned above, the N-methyl substituted species, 3,8-dimethyl-2,4-dioxo-1,3,5,8-tetraazanaphthalene ***139*** is reported[11] to be hydrated. The protonated form of 2,6-dioxo-1,3,5,8-tetraazanaphthalene ***140*** adds initially under kinetic control water across the N(3)=C(4) bond. This monoadduct is gradually converted into the thermodynamically more stable dihydrate, with water molecules added across the N(5)=C(6) and C(7)=N(8) double bonds[142].



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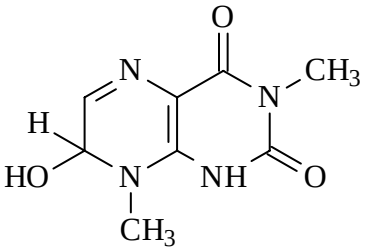

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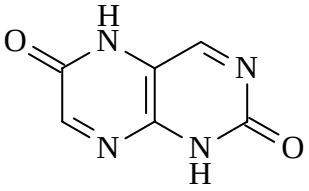
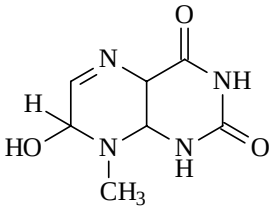


140

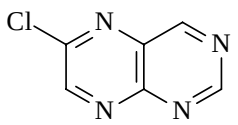
In the unprotonated form 8-methyl-2,4-dioxo-1,3,5,8-tetraazanaphthalene ***141*** is present only in about 0.2% in the hydrated form.



141

The presence of two isopropyl groups at C(6) and C(7) resulted in an increase of the content of the hydrated form to about 1.2%. Introduction of two phenyl groups in the same position resulted in a similar, though smaller effect. The effect of substituents on C(6) and C(7) was attributed[10] to a mutual steric interference of these groups resulting in a distortion of the pyrazine ring and a relief of steric strain by hydration.

Unprotonated forms of 6-chloro- ***142***, 7-chloro- ***143*** and 6,7-dichloropteridine ***144*** add water across the C(3)=N(4) double bond to the extent of 31, 30 and 36%. The corresponding cations in acidic media are almost completely hydrated, but undergo ring-opening[156]. Uncharged 2-mercaptopteridine ***145*** is present in 99.7% in the form hydrated across the C(7)=C(8) double bond (K_h = 380), whereas for the anion bearing a $-S^{(-)}$ group K_h decreased[152] to 0.24.



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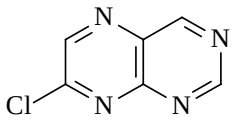

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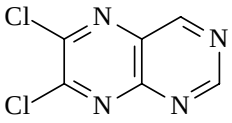

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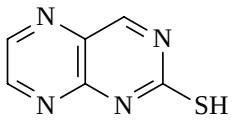
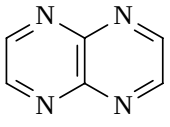


145

Addition of OH^- at C(4) has been proposed based on electrochemical data[138], but a dissociation of the hydrated form cannot be excluded.

3.3.4.2. Reaction of other tetraazanaphthalenes



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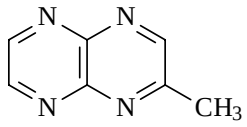

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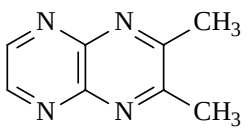
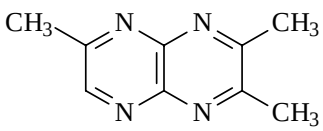


148



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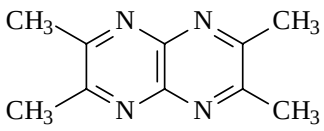
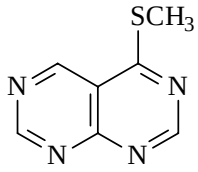


150

Protonated forms of 1,4,5,8-tetraazanaphthalenes ***146***, similarly as its 2-methyl ***147*** and 2,3-dimethyl ***148*** derivatives are strongly (>95%) hydrated. On the other hand, the unprotonated forms of these three compounds, as well as protonated forms of the 2,3,6-trimethyl- ***149*** and 2,3,6,7-tetramethyl-1,4,5,8-tetraazanaphthalenes ***150*** do not show measurable hydration. The addition of water occurs across the 1,2- or 7,8-bond[157].

Hydration of the 4-methylthio-1,3,6,8-tetraazanaphthalene ***151***, both in the unsubstituted and in its 2-methyl ***152*** and 2,7-dimethyl ***153*** derivatives, occurs across the C(5)=N(6) double bond[158]. These compounds add also methanol.



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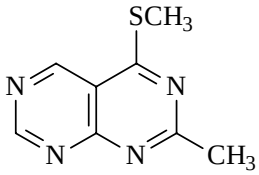

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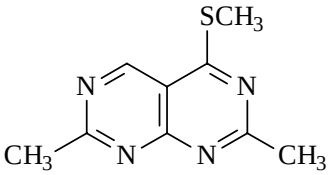
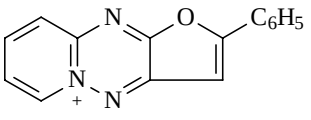


153

3.3.4.3. Other heterocycles with four heteroatoms

The tricyclic furo[2,3-e]pyrido[1,2,b]-as-triazinium ***154*** salt reacts with aqueous base and undergoes ring-opening, but methoxide ions add to the C(10a)=N(5) double bond[159]. Covalently hydrated dication is assumed to be the reactive intermediate in conversion of triazolo[4,3-c]pyrazines ***155*** to their [2,3-c]-isomers. Monocation is considered to be less reactive and the addition of water to the pyrimidine ring occurs across the N(1)=C(2) bond[160]. Similarly, formation of an adduct of OH^- ions to a triazole[1,5-*a*]pyrimidin-5(4*H*)-one ***156*** has been considered to be the initial step in a hydrolysis[161].



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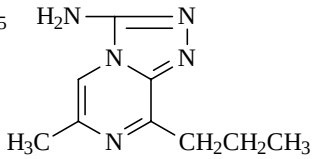

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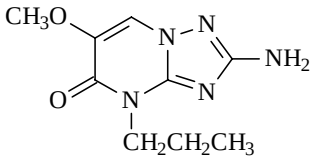
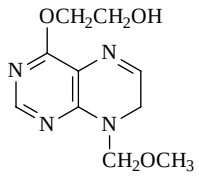


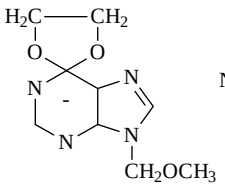
156

3.3.5. Heterocycles with five heteroatoms

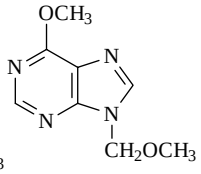
The most important group of compounds bearing four heteroatoms located in two rings are purines. In spite of a considerable effort no hydration has been observed either for protonated or unprotonated purines. Exceptions are two 9-methoxymethyl purines[162]: 6-(∃-hydroxyethoxy)-9-methoxymethyl purine ***156a*** which in presence of tert. butoxide in tert. butyl alcohol yields in an intramolecular nucleophilic attack the anionic complex ***156b***. Similarly, 6-methoxy-9-methoxymethyl purine ***156c*** adds in tert. butyl alcohol in the presence of potassium methoxide a methoxide ion to form an adduct ***156d***. On the other hand, some oxidation products of purines may be hydrated. In particular the species bearing two imino groups assumed to be formed as an intermediate in the electrooxidation of uric acid ***157***[163-165], xanthine ***158***[165,166], adenine ***159***[167] and guanine ***160***[168] were anticipated to add one or two molecules of water. This assumption was based on identification of products of cleavage of such intermediates and was supported by the decrease of the reduction current attributed to the diimine with increasing concentration of methanol, added to the aqueous solution.



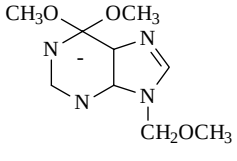
156a



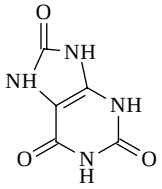
156b



156c



156d



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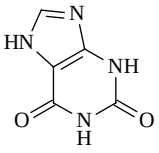

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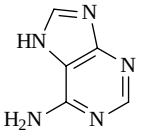

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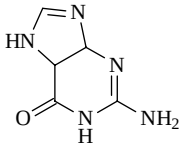
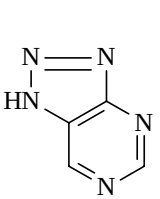
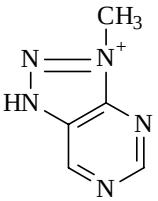


160

Introduction of the fifth nitrogen in 8-azapurines (*v*-triazolo[4,5-*d*]pyrimidines ***161***) increases the electrophilic reactivity of the heterocycle. Protonated forms of most 8-azapurines, as long as they are not substituted at C(6), have been shown[169-172] to add water across the N(1)=C(6) double bond and form 1,6-dihydro-6-hydroxy derivatives. No hydration was detected for the unprotonated form of 8-azapurine. Whereas cations of 7- ***162*** and 8-methyl-8-azapurines ***163*** as well as of 2-amino derivatives ***164*** were practically completely hydrated[171], insertion of a methyl group at C(6) virtually prevented the hydration of the 8-azapurine derivative. In unprotonated forms, substantial hydration was observed for 2-amino- ***164*** and 2-oxo-8-azapurine[170] ***165***. The latter compound was shown to react also with methanol, to form a 1:1 adduct, with addition taking place across the N(1)=C(6) double bond. In this case it proved possible to isolate the adduct of the unprotonated form. On the other hand, methanol adducts of the unprotonated forms of 8-azapurine ***161*** and its 2-amino derivative ***164*** were not sufficiently stable, but cations of their hydrated forms crystallized as hydrochlorides[173].



161



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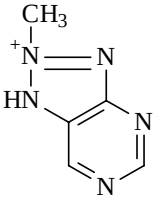

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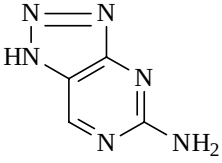

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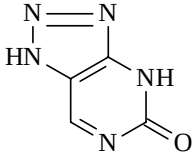
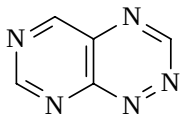


165

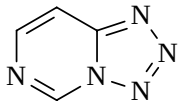
Among 1,2,4,6,8-pentaazanaphthalenes (or pyrimidino[5,4-e]-*as*-triazines) ***166*** addition of water occurs in the pyrimidine ring, across the C(5)=N(6) double bond.



166

The hydrate is not stable enough to be isolated, but well-defined compounds were obtained using addition of methanol and ethanol[174]. Hydration was observed[175] to occur in the same position even for pyrimidinotriazines bearing at C(5) a trifluoromethyl group, together with an amino group at C(7) and hydrogen or a dimethyl amino group at C(3).

In tetrazolo[1,5-c]pyrimidine ***167*** addition of water took place also in the pyrimidine ring, across the C(5)=N(6) double bond[158].



167

4. Conclusions

Additions of negatively charged nucleophiles of the type of OH^- or OR^- ions to activated aromatic rings, resulting in formation of sigma complexes or pseudobases received in the past considerable attention. Among additions of uncharged nucleophiles, like H_2O or ROH, to carbonyl or azomethine bonds, only hydration of aliphatic carbonyl compounds and that of pteridines have been investigated in some detail. The present review tried to indicate the principal similarity and principal generality of equilibria, involving nucleophilic additions to C=O and C=N double bonds, whether present in a side chain of an aromatic system or as an activated (often protonated) azomethine bond in N-heterocycles. Even when qualitatively the role of covalent additions of water and alcohols has been recognized in numerous types of compounds, many questions remain open, for example how the mutual positions of heteroatoms, the kind and position of substituents, or the kind and position of annelled rings affect such equilibria. On the other hand, the number of available reliable quantitative data for equilibrium constants involved is very limited. Thus both qualitative recognition of such interactions and determination of equilibrium constants involved offers wide areas for future investigations. And we do not mention kinetics of such reactions, which is beyond the scope of the present communication. One question in particular remains open - what, if any, such reactions play a role in physiological processes, in particular enzyme reactions.

Acknowledgements

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