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The Simultaneous α–Addition of a Cation and an Anion onto an Isocyanide

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The Simultaneous α–Addition of a Cation and an Anion onto an Isocyanide[#]

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Abstract

The MultiComponent Reactions (MCRs) of amines, carbonyl compounds, acids, and isocyanides begins with equilibria of the first three educts (the starting materials of chemical reactions) and intermediate products. Subsequently, the practically irreversible formation of α–adducts of the intermediate products and isocyanides are formed and rearrange into their final products. The α–adducts of the MCRs are collections of two component reactions, but under suitable conditions the α–adducts can also directly be formed from three components. The energy levels of the main intermediate products of the reaction are determined by quantum chemical methods. The HF/6–31G(d) and DFT with B3LYP/6–31G(d) calculations predict that the cations, anions and isocyanides directly form the α–adduct.

Keywords. MultiComponent Reactions (MCRs); isocyanides; α–additions from three components; quantum chemistry; energy levels of intermediates.

1 INTRODUCTION

In principle, all chemical reactions are equilibrium between one or two chemical species. Preferred preparative processes proceed irreversibly and convert up to two educts into their products. Exceptions occur in the solid phase in which three chemical components can simultaneously participate to produce products.

Within organic chemistry, the reactions of two components are most often used, and relatively few MultiComponent Reactions (MCRs) containing three or more educts are encountered. In modern isocyanide chemistry more MCRs of three to nine chemical compounds can form their products by collections of subreactions with two components [1–3]. The MCRs of isocyanides form intermediate products by equilibrating reactions, then subsequently irreversibly form α–adducts by

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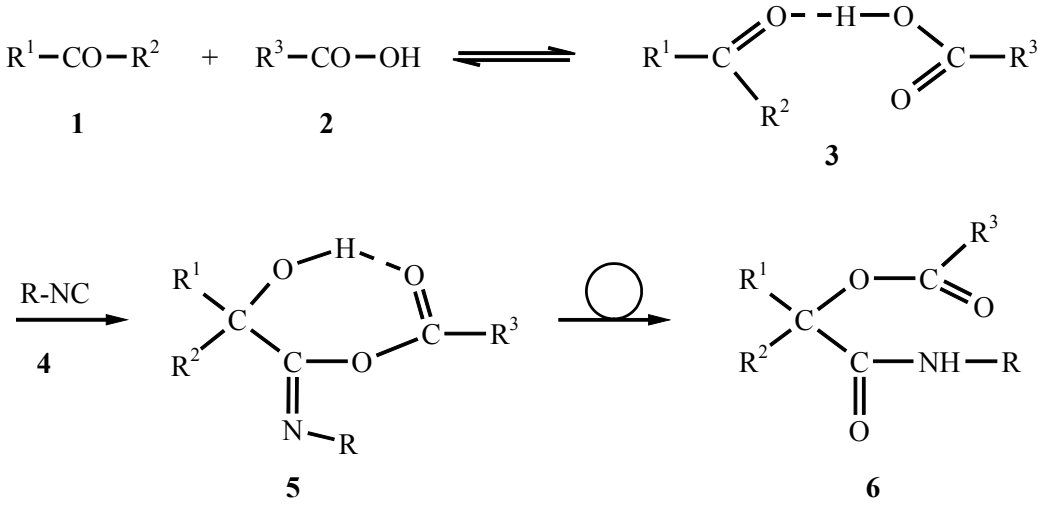
the α–addition of cations and anions onto the isocyanides.

The chemistry of isocyanides is unusual since isocyanides contain divalent carbon atoms [4,5], and all reactions of isocyanides are conversions of divalent carbon atoms into products with tetravalent carbon atoms. It is conceivable that the pre–final steps of MCRs of the isocyanides can also directly undergo three component reactions.

Three fundamental types of MCRs exist [3]: the MCRs of type I are a collection of equilibria between the educts, intermediate products, and final products. In type II MCRs, the educts and intermediate products equilibrate, but their final products are formed irreversibly. The type III MCRs correspond to a sequence of practically irreversible subreactions that proceed towards the products.

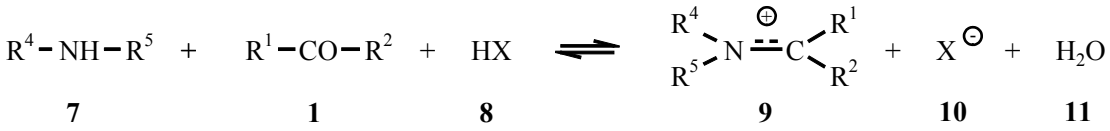
The chemistry of the MCRs began in 1850, when Strecker [6] introduced the formation of α–aminoalkylcyanides from ammonia, aldehydes, and hydrogen cyanide. This was the first three component reaction of type I; its equilibrating products always occur together with a variety of by–products. In 1929 Bucherer and Bergs [7] began to add carbon dioxide as a fourth component of the Strecker reaction, and pure cyclic hydantoin products were formed. The closure of rings is in most cases (in practice) irreversible, which seems to be energetically preferred. Since 1850 the α–amines alkylcyanides NH_2–CHR–CN were hydrolyzed into the α–amino acid NH_2–CHR–CO_2H. From 1929 the hydantoins could be prepared irreversibly and in higher yields, which can also be hydrolyzed with acid and water into the α–amino acids. In 1882 Hantzsch [8] and Radziszewski [9] began to accomplish MCRs of type II whose last step was always the irreversible ring closure of heterocyclic products. In preparative chemistry the type III MCRs are rarely accomplished [10], whereas in living cells the majority of compounds are formed by MCRs of type III whose subreactions are selectively accelerated towards their products.

2 THE MCRS OF THE ISOCYANIDES

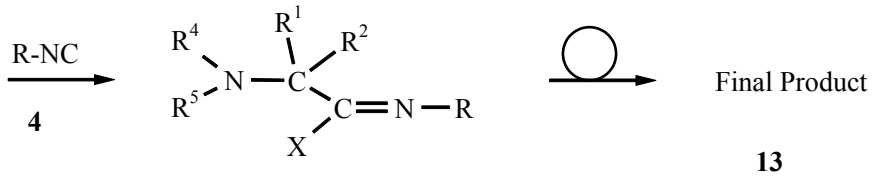


1 **2** **3** **4** **5** **6**

In 1921 the Passerini reaction (P–3CR) [2,11] **1** + **2** + **4** → **6** was introduced as the first three component reaction of carbonyl compounds, **1**, carboxylic acids, **2,** and isocyanides, **4**. Their products, **6**, are formed via the hydrogen bridged adduct, **5**, with its carbonyl compounds and carboxylic acid in suitable solvents [2,12,13]. However, hydrogen bridged adducts such as **3** can also be considered as the two components **1** and **2**. Then α–addition of the isocyanide can be considered as a three component reaction.



7 **1** **8** **9** **10** **11**



4 **12** **13**

In 1959, the four component reaction (U–4CR [3–5,17]) of amines, **7**, carbonyl compounds, **1**, acids, **8**, and isocyanides, **4,** were introduced [2,4,14 –17]. In this reaction, the amines and carbonyl compounds can equilibrate with the α–aminoalkyl–cations, **9**, and the anions of the acid components, **10**. In suitable polar solvents, these ions are solvated and they are mutually attracted, so that they can be close to each other.

In usual chemical reactions the educts have their characteristic functional groups. All the products of a certain reaction always contain the same typical skeleton, and only the substituents of the educts and products differ. Practically, all chemical reactions have their 'scope and limitation' so that not all of the educts with the characteristic functional group can form their products.

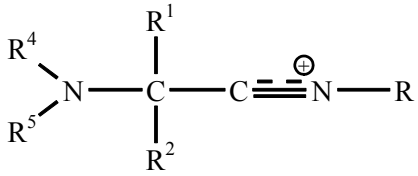
In contrast, the U–4CR has practically no such limitations. This means that any educts of the U–4CR react as expected, whereas in many other reactions only certain educts react. Thus, all of the conceivable combinations of the educts form their products. In contrast to the usual chemical reactions, the amines and acids of the U–4CR form a variety of skeletally different products. As the amine components NH_3, R^4–NH_2, R^4–NH–R^5, NH_2OH and R–NH–NH_2 can thus react, and the acids or their anions H_2O, $Na_2S_2O_3$, H_2Se, R^4R^5NH, R^4HN–CN, HN_3, HNCO, HNCS, R^3–CO_2H, R^3–COSH, R^3O–CO_2H etc. can form structurally even more different products [2,4].

3 THE MECHANISTIC ASPECTS OF THE ISOCYANIDE MCRS

The optimal yields of the isocyanide MCRs can only be reached if particular optimal reaction conditions are used for each case. The reaction mechanisms of the P–3CR and the U–4CR are quite

different. In methanol at 0 °C, the four components of an U–4CR equilibrate with the pair of ions **9** and **10**, forming the product in an almost quantitative yield. No P–3CR competes against the U–4CR. In methylenechloride, the same four educts form the hydrogen–bridged adducts, **3**, and they undergo a P–3CR into the product in a quantitative yield, while the amine component does not participate then [3,16].

It is conceivable that the cations, anions, and isocyanides can directly form the α–adducts **9** + **10** + **4** → **12** and subsequently rearrange into the final products **13**. However, the ions **9** and **10** of the α–adducts can also be formed by two steps: the intermediate **14** could come from the cation **9** with the isocyanide **4**, and in the next step, the anion **10** could be added into the α–adduct **12**. It is also conceivable that first the anion **10** is added to the isocyanide **4,** and subsequently the intermediate **15** reacts with the cation **9** into the α–adduct **12**.



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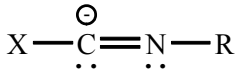

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Thus, it must be determined which reaction mechanisms have energetic advantages over other possibilities. Then one must compare the energetic levels of **12**, **14** + **10** and **15** + **9**. A simple model of this reaction forming **12** is investigated. In this model, R^1 and R^4 = H; R, R^2, and R^5 = CH_3; and HX = CH_3CO_2H. The quantum chemistry can thus generally indicate the preferred reaction mechanism of the U–4CR.

4 THE ENERGETIC LEVELS OF THE U-4CR INTERMEDIATES

For the purpose of performing quantum mechanical calculation of electronic structures of the main intermediate products of the reaction, the *ab initio* GAMESS program [18] interfaced [19] with the molecular mechanics program CHARMM [20] was used. This approach enables us to apply the ABNR minimization routine of CHARMM [20], an alternative procedure to the standard geometry optimization introduced in the GAUSSIAN suite of programs. The GAUSSIAN 98 program [21] was employed for comparison.

The optimized geometries were calculated at two different levels of theory: Hartree–Fock (HF) [22] and density functional theory (DFT) using the Becke three parameter nonlocal exchange functional and the nonlocal correlation functional of Lee, Yang and Parr (B3LYP) [23]. The standard 6–31G(d) [24] basis set was used for each calculation.

The energy of all the compounds in the reaction scheme **9** + **10** + **4** → **12** was then extensively minimized (200 steps using ABNR) for two different methods, HF/6–31G(d) and DFT with

B3LYP/6–31G(d). In order to validate the GAMESS/CHARMM approach, the calculations were compared with the results of the GAUSSIAN 98 program for the total energies at the HF level. The same values of geometry parameters and energies were obtained.

We set up the calculation by performing the energy minimization of eight possible conformations of structure **12**. These conformations were obtained by rotating three torsional angles; each equals 0 or 180 degrees, respectively, so all of the conformational space of the system was explored. The conformation with the lowest energy value was chosen for further analysis of the system.

To asses the stability of the intermediate structures, the total energy and the difference between the total and zero energy were calculated. The results for the HF/6–31G(d) and B3LYP/6–31G(d) of these calculations using GAMESS program, interfaced with CHARMM utilizing the ABNR minimization routine, are presented in Table 1. The starting models for calculations were obtained by breaking the covalent bonds between the subsystems **10**, **4** and **9** in structure **12** by setting the distance to 3 Å. When the starting models are fully minimized, they either transform into structure **12** or some other structure on the potential energy surface, but never to structures **14** or **15**. To establish if structures **14** and **15** are even possible, we also calculated the isolated intermediates **14** and **15**, but found they disintegrate. Since structures **14** and **15** do not posses a minimum on the potential energy surface, we can conclude that the α–adduct **12** preferentially reacts by a three component reaction. Details on the starting and minimized structures are presented in the supplementary material.

Table 1. HF/6–31G(d) and B3LYP/6–31G(d) Total Energies (Total E) and Differences in Energies (ΔE = Total E – Zero) for the Cation **9**, Anion **10**, Isocyanide **4**, Intermediates **9+4**, **10+4**, and α–Adduct **12** Calculated with the GAMESS Program Interfaced with CHARMM using the ABNR Minimization Routine (X + Y Denotes the Systems X, Y being Close to Each Other but not Covalently Bonded; X, Y = **4**, **9, 10**)

System	Energy (E)			
	HF/6-31G(d)		B3LYP/6-31G(d)	
	Total E (a.u.)	ΔE (kcal/mol)	Total E (a.u.)	ΔE (kcal/mol)
Single system				
E(**9**)	–172.4840236068		–173.638934435	
E(**10**)	–227.2250684896		–228.497911649	
E(**4**)	–131.8943641846		–132.716572702	
Pairs				
Zero/E(**10**)+E(**4**)	–359.1194326742	0	–361.214484351	0
E(**10**+**4**)	–359.1463949453	–16.919		
E(**15**)	disintegrates into **10**+**4**			
Zero/E(**9**)+E(**4**)	–304.3783877914	0	–306.355507137	0
E(**9**+**4**)	–304.3994301005	–13.204		
E(**14**)	disintegrates in to **9**+**4**			
Whole system				
Zero/E(**9**)+E(**10**)+E(**4**)	–531.6034562810	0	–534.853418786	0
α-adduct				
E(**12**)	–531.8443608683	-151.170	–535.117392015	-165.646

5 CONCLUSIONS

Our study has revealed that α–adduct with R^1 and R^4 = H, R, R^2, and R^5 = CH_3 has the preferred structure **12** according to the results of quantum chemical calculations. It was found that the α–adduct **12** can directly be formed by the α–addition of **9** and **10** onto the isocyanide **4** as a three component reaction. Not included in this work was the study of the barriers for these reactions in order to estimate the probabilities for each of the reaction pathway. For this type of calculations, the REPLICA/PATH [25] method, which interpolates the structures for the minimal energy pathway between two or more minimized structures, will be used. These results, to obtain the transition structures and their corresponding energies, which represent the barrier energies for the reactions, will be published separately.

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Biographies

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Milan Hodošček is research scientist at the National Institute of Chemistry, Ljubljana, Slovenia. From 1990 to 1993 and 1998 he was a Visiting Fellow at the National Institutes of Health, Bethesda, MD, USA. He is currently working as a co–developer of a CHARMM software system for macromolecular simulations. His main interest is in developing QM/MM methods and parallelizing the program CHARMM.

Ivar Ugi is Professor of organic chemistry at the Technical University Munich, Garching, Germany. He obtained his Ph.D. in 1954 at the University of Munich. His habilitation on aryl pentazoles and isocyanides followed in 1959. From 1962 to 1968, he worked in the Central Research Laboratories of the Bayer AG in Leverkusen, where he was the chairman of the commission for basic research and head of research for the last three years. In 1964 he was awarded the research prize of the scientific academy in Göttingen. From 1968 to 1971 he was a professor at the chemical institute of the University of South California, Los Angeles, CA (USA), and then became a professor for organic chemistry at the Technical University Munich, Garching (Germany), holding the Hans Fischer chair, where he remained until 1999. He is a member of the Royal Swedish Academy of Science in Upsala (since 1987), the Estonian Academy of Science (since 1991), and the US Academy of Sciences in New York (since 1994). In 1988 he received the Challenge Future Prize from the Philip Morris Foundation, in 1992 the Emil Fischer Medal from the Gesellschaft Deutscher Chemiker for his discovery of the four–component condensation and the development of mathematical models for the logical structures of chemistry, in 1995 the Ugi–Dugundji–Medal, awarded for the first time, to honor his achievement in applying mathematics and information technology to chemistry, and in 1999 he was awarded the Max Bergman Medal.