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Theoretical Studies on the Gas-Phase Pyrolysis of Esters The effect of α- and β-methylation of Ethyl Formates[1]

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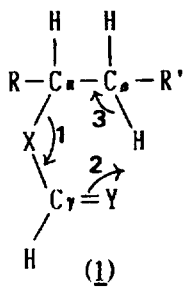
The gas-phase thermolysis reactions of α- and β-methylated ethyl formates, Y = CH-X-$CHR_1CH_2R_2$ where X = Y = O or S and R_1 = R_2 = H or CH_3, are investigated theoretically using the AM1 method. The experimental reactivity order is reproduced correctly by AM1 in all cases. The thermolysis proceeds through a six-membered cyclic transition state conforming to a retro-ene reaction, which can be conveniently interpreted using the frontier orbital theory of three-species interactions. The methyl group substituted at C_α or C_β is shown to elevate the π-HOMO of the donor fragment (Y = C) and depress the σ^*-LUMO of the acceptor fragment (C_β-H), increasing the nucleophilicity of Y toward β-hydrogen which in turn increases the reactivity. The two bond breaking processes of the C_α-X and C_β-H bonds are concerted but not synchronous so that the reaction takes place in two stages as Taylor suggested. The initial cleavage of C_α-X is of little importance but the subsequent scission of C_β-H occurs in a rate determining stage.

Introduction

The gas-phase thermal decomposition reaction of esters has been studied extensively.[2] Taylor[2a] proposed a fairly detailed picture of the transition state (TS) for pyrolysis of ethyl esters, (1): the TS has a six-membered cyclic structure in which electrons move in a cyclic manner, not at precisely the same time but sequentially as numbered in (1) so that C_β is less electron rich than C_α is electron deficient.

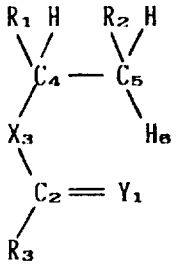
There is, however, still a controversial problem of the rate determining step; some investigators interpreted their data in favor of the C_α-O bond polarization[2a] whereas some in favor of the cleavage of the C_β-H bond[2i-2j] as the rate determining process. Experimentally monomethylation at the α-



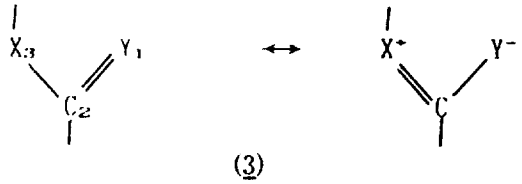
(1)

($R = CH_3$) as well as β-carbon ($R' = CH_3$) led to a greater reactivity[2b]; α-methylation stabilizes the TS by electron donation to the incipient α-carbonium ion, but the effect of β-methylation is not well understood.[2d] The rate enhancement by a β-CH_3 group was variously interpreted as due to long range stabilization of the remote α-carbonium ion[2h] or due to steric acceleration by the relief of hindrance between substituents on the carbon atom which changes from sp^3 to more crowded sp^2 in the TS.

In a previous work,[3] we reported on the gas-phase thermal decomposition reactions of alkanoic esters, $Y = C(R_3)$-X-$CHR_1CH_2R_2$ where $X = Y = O$ or S with $R_1 = R_2 = H$ and $R_3 = H$, CH_3 or NH_2 in (2), studied theoretically using the semiempirical MO methods of MNDO[4] and AM1[5]. The decomposition was found to proceed through a six-membered cyclic transition state (TS) conforming to a concerted process of the retro-ene reaction, with the correct experimental reactivity order reproduced by AM1. The reactivity was conveniently interpreted using the frontier orbital (FMO) theory of three-species interactions[6]; the most important factors controlling the reactivity are the π-donating ability factors controlling the reactivity are the -donating ability of the π-HOMO of the donor fragment, ($Y_1 = C_2$), and the accepting ability of the σ^*-LUMO of the acceptor fragment, (C_5-H_6), *i.e.*, the ease of nucleophilic attack of Y_1 upon β-hydrogen, H_6, in (2). However the difference in reactivity was found to arise originally from the ease of p-π conjugation in the ground state (GS),[7] (3), depending on the groups X and Y for the fixed R groups; the stronger the p-π conjugation the higher is the π-HOMO of the donor (Y_1-C_2) and the lower is



(2)



(3)

the σ^*-LUMO of the acceptor (C_5-H_6) leading to an easier nucleophilic attack by Y_1 upon β-hydrogen, H_6.

In order to unravel further the mechanism of the gas-phase pyrolysis of esters, we carried out AM1 calculations on ethyl formates with a methyl group at the α- or β-carbon atom, *i.e.*, $R_1 = CH_3$ with $R_2 = R_3 = H$ (iso-propyl formate) and $R_1 = R_3 = H$ with $R_2 = CH_3$ (*n*-propyl formate) in (2).

Calculation

The calculations were carried out with the AM1 method.[5] All geometries were fully optimized. TSs were located by the reaction coordinate method,[8] refined by the gradient norm minimization[9] and characterized by conforming only one negative eigenvalue in the Hessian matrix.[10]

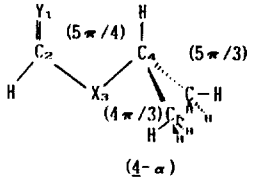
Table 1. Heats of Formation (ΔH_f) of Ground (GS) and Transition States (TS) and Activation Enthalpies (ΔH^*) (kcal/mol) by AM1

X	Y	R_1	R_2	ΔH_f		ΔH^*
				GS	TS	
O	S	H	H	-19.17	26.99	46.16[a]
		CH_3	H	-23.29	18.47	41.76
		H	CH_3	-25.97	20.38	46.35
S	S	H	H	23.81	74.12	50.31[a]
		CH_3	H	20.10	68.50	48.40
		H	CH_3	17.02	66.56	49.54
O	O	H	H	-97.02	-33.49	63.53[a]
		CH_3	H	-101.00	-40.55	60.45
		H	CH_3	-103.86	-41.51	62.35
S	O	H	H	-39.92	24.29	64.21[a]
		CH_3	H	-43.62	19.13	62.75
		H	CH_3	-46.71	16.25	62.96

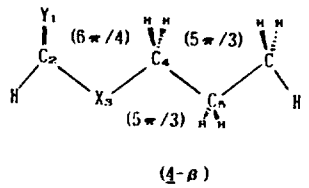
[a]Ref. 3.

Results and Discussion

The heats of formation (ΔH_f) for the reactants and TSs are shown in Table 1 together with the activation enthalpies (ΔH^*) for the thermal decomposition of the esters. In general, β-methylation leads to more stable ground (4-α and 4-β) and transition states. The stabilities of the ground



(4-α)



(4-β)

states are mainly determined by one-electron energies. $2\Sigma\epsilon_i$, which in turn is largely dependent on the π-nonbonded interactions[11]; in (4-α) there are two stabilizing, ($5\pi/4$) and ($5\pi/3$), and one destabilizing, ($4\pi/3$), π-nonbonded structures,[12] whereas in 4-β, there are three stabilizing structures, one ($6\pi/4$) and two ($5\pi/3$).

Reference to Table 1 reveals that the activation barrier is lower and hence the reactivity is higher with α-methylation ($R_1 = CH_3$, $R_2 = R_3 = H$) than with β-methylation ($R_2 = CH_3$, $R_1 = R_3 = H$) in all cases of X, Y = O or S. Furthermore the β-methylated compounds have lower activation barriers than the unsubstituted ($R_1 = R_2 = R_3 = H$) series, except for (O-C = S), for which the activation enthalpies differ negligibly small amount between the unsubstituted and β-methylated compounds. We also note that the difference in the barrier, $\delta\Delta H^* (= \Delta H^*_{(\beta\text{-Me})} - \Delta H^*_{(\alpha\text{-Me})})$, decreases from -4.6 to 0.2 kcal/mol as the barrier heights increase from O-C = S to S-C = O; this corresponds to a decrease in selectivity along with a decrease in reactivity and constitutes violation of the reactivity selectivity principle (RSP).[13]

The ester decomposition proceeds by a retro-ene process,[14] which can be conveniently interpreted by three-spe-

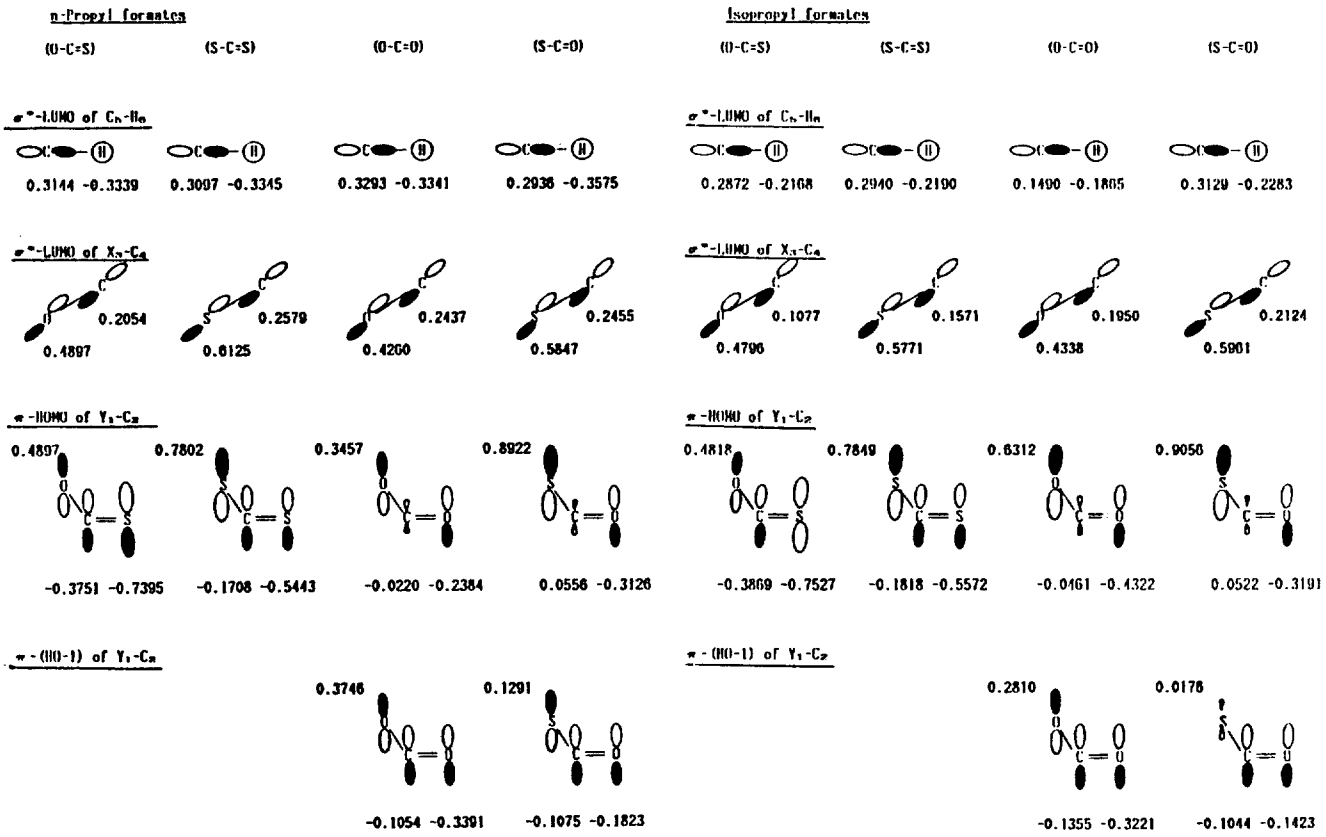
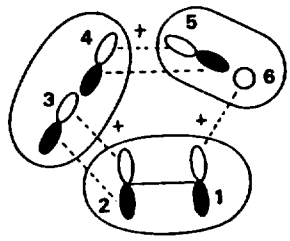


Figure 1. Frontier orbital of *n*-propyl formates and isopropyl formates by AM1.

cies interaction[3,6] within the framework of frontier orbital (FMO) theory;[15] thus the in-phase interactions[16] between the π-HOMO of the donor, (Y_1-C_2), and the two σ^*-LUMO$_S$ of the acceptors, (X_3-C_4) and (C_5-H_6), in the TS (5) will be the key factors controling the reactivity.

FMO patterns (Figure 1) for the three fragments, irrespective of whether α- or β-methylated, are entirely similar to those of the unsubstituted ethyl formates[3]; the *p*-AO lobes of the π-HOMO of the donor, ($Y_1 = C_2$), decreases in the order that corresponds to the decreasing reactivity:[2e,2f] (O-C = S)>(S-C = S)>(O-C = O)>(S-C = O), and σ^*-LUMO$_S$ of the (C_5-H_6) fragment are substantially higher than σ^*-



In-phase overlaps (+) between fragments in the TS. (5)

LUMO$_S$ of the (X_3-C_4) fragment (Table 2).

Table 2 shows that the π-HOMO levels of the donor, (Y_1-C_2), are raised whereas the σ^*-LUMO levels of the acceptor,

Table 2. Energy Levels (eV) of π-HOMO of Donor (Y_1-C_2) and σ^*-LUMOs of Acceptors (X_3-C_4) and (C_5-H_6) for α- and β-CH_3-ethyl formates (Y = $CHXCHR_1CHR_2$) by AM1

Alkyl		O-C = S	S-C = S	O-C = O	S-C = O
n-Propyl	π-HOMO (Y_1-C_2)	-10.1823	-9.4714	-11.4511	-10.0294
R_1 = H				(-12.6944)[a]	(-13.9752)[a]
R_2 = CH_3	σ^*-LUMO (X_3-C_4)	1.9879	1.3229	2.0881	1.2729
	σ^*-LUMO (C_5-H_6)	3.3937	3.4059	3.5176	3.4862
i-Propyl	π-HOMO (Y_1-C_2)	-10.1089	-9.4527	-11.5126	-10.0410
R_1 = CH_3				(-12.5123)[a]	(-13.1550)[a]
R_2 = H	σ^*-LUMO (X_3-C_4)	1.9150	1.2251	2.0510	1.2633
	σ^*-LUMO (C_5-H_6)	3.3819	3.4045	3.4763	3.5076
Ethyl[b]	π-HOMO (Y_1-C_2)	-10.2031	-9.4815	-11.6501	-10.0473
R_1 = H				(-13.7892)[a]	(-14.1629)[a]
R_2 = H	σ^*-LUMO (X_3-C_4)	1.9786	1.3096	2.0836	1.2661
	σ^*-LUMO (C_5-H_6)	3.4304	3.4546	3.5454	3.5507

[a]The levels in parenthesis are for the (HO-1)th π-orbital. [b]Ref. 3.

Table 3. Formal Charges (Electronic Unit) and Bond Lengths(Å), and Their Charges Δq and Δd, for Pyrolysis of Esters

X	Y	R_1	R_2	Charges(e.u.)				Bond Length(Å)			
				Atom	GS	TS	Δq^a	Bond	GS	TS	Δd^a
O	S	CH_3	H	S_1	−0.072	−0.237	−0.165	S_1–C_2	1.545	1.613	0.067
				C_2	−0.080	0.034	0.114	C_2–O_3	1.354	1.276	−0.078
				O_3	−0.217	−0.399	−0.182	O_3–C_4	1.441	1.993	0.552
				C_4	−0.028	0.177	0.205	C_4–C_5	1.513	1.418	−0.095
				C_5	−0.249	−0.419	−0.170	C_5–H_6	1.117	1.277	0.160
				H_6	0.090	0.250	0.160				
		H	CH_3	S_1	−0.061	−0.200	−0.139	S_1–C_2	1.545	1.617	0.072
				C_2	−0.093	0.043	0.136	C_2–O_3	1.358	1.276	−0.082
				O_3	−0.214	−0.377	−0.163	O_3–C_4	1.440	1.915	0.475
				C_4	−0.034	0.122	0.156	C_4–C_5	1.517	1.411	−0.106
				C_5	−0.164	−0.408	−0.244	C_5–H_6	1.121	1.344	0.223
				H_6	0.094	0.261	0.165				
S	S	CH_3	H	S_1	0.033	−0.007	−0.040	S_1–C_2	1.537	1.614	0.077
				C_2	−0.389	−0.361	0.028	C_2–S_3	1.659	1.575	−0.084
				S_3	0.206	−0.020	−0.226	S_3–C_4	1.753	2.253	0.500
				C_4	−0.209	−0.003	0.206	C_4–C_5	1.508	1.392	−0.116
				C_5	−0.224	−0.403	−0.179	C_5–H_6	1.118	1.451	0.333
				H_6	0.095	0.193	0.098				
		H	CH_3	S_1	0.038	0.040	0.002	S_1–C_2	1.537	1.618	0.081
				C_2	−0.396	−0.400	−0.004	C_2–S_3	1.662	1.576	−0.086
				S_3	0.219	0.052	−0.167	S_3–C_4	1.737	2.134	0.397
				C_4	−0.290	−0.104	0.186	C_4–C_5	1.510	1.392	−0.118
				C_5	−0.156	−0.336	−0.180	C_5–H_6	1.122	1.544	0.422
				H_6	0.089	0.165	0.076				
O	O	CH_3	H	O_1	−0.355	−0.434	−0.079	O_1–C_2	1.229	1.287	0.058
				C_2	0.260	0.292	0.032	C_2–O_3	1.358	1.281	−0.077
				O_3	−0.288	−0.461	−0.173	O_3–C_4	1.466	1.917	0.471
				C_4	0.034	0.221	0.187	C_4–C_5	1.516	1.414	−0.102
				C_5	−0.216	−0.534	−0.318	C_5–H_6	1.116	1.345	0.229
				H_6	0.086	0.346	0.260				
		H	CH_3	O_1	−0.351	−0.353	−0.002	O_1–C_2	1.229	1.298	0.069
				C_2	0.257	0.298	0.041	C_2–O_3	1.360	1.285	−0.075
				O_3	−0.287	−0.363	−0.076	O_3–C_4	1.434	1.704	0.270
				C_4	−0.016	0.129	0.113	C_4–C_5	1.517	1.414	−0.103
				C_5	−0.190	−0.585	−0.395	C_5–H_6	1.122	1.502	0.380
				H_6	0.100	0.354	0.254				
S	O	CH_3	H	O_1	−0.292	−0.295	−0.003	O_1–C_2	1.231	1.302	0.071
				C_2	0.058	0.010	−0.048	C_2–S_3	1.690	1.600	−0.090
				S_3	0.093	−0.078	−0.171	S_3–C_4	1.751	2.110	0.359
				C_4	−0.193	0.070	0.263	C_4–C_5	1.508	1.403	−0.105
				C_5	−0.225	−0.585	−0.360	C_5–H_6	1.119	1.493	0.374
				H_6	0.099	0.331	0.232				
		H	CH_3	O_1	−0.290	−0.269	0.021	O_1–C_2	1.231	1.305	0.074
				C_2	0.052	−0.010	−0.062	C_2–S_3	1.691	1.602	−0.089
				S_3	0.104	−0.008	−0.112	S_3–C_4	1.735	2.012	0.277
				C_4	−0.272	−0.028	0.244	C_4–C_5	1.509	1.406	−0.103
				C_5	−0.157	−0.537	−0.380	C_5–H_6	1.122	1.559	0.437
				H_6	0.091	0.328	0.237				

[a] Δq and Δd are variations in charge and bond length from ground (GS) to transition state (TS).

(C_5–H_6), are lowered for both the α- and β-methylated series relative to the corresponding levels of the unsubstituted ester series.[3] This is in accord with the enhanced reactivity of the α- and β-methylated series, since the elevation of the donor HOMO level coupled with the depression of the acceptor LUMO level will facilitate charge transfer between

the two levels[17] and lead to an easier nucleophilic attack by Y_1 upon β-hydrogen, H_6. We also note that the extents to which (Y_1–C_2) π-HOMO is raised and (C_5–H_6) σ^*-LUMO is lowered are invariably greater with the α- compared to the β-methylated series, which is again in line with the greater reactivity of the α-compared to the β-methylated series.

Thus the activation enthalpies, ΔH^*, are lowered and hence the reactivities are increased as the π-$HOMO_S$ of the (Y_1–C_2) fragment are elevated and the σ^*-$LUMO_S$ of the (C_5–H_6) fragment are depressed. This is accompanied by the decrease in the C_5–H_6 bond polarization (Δq) and the degree of bond breaking (Δd) in the TS (Table 3). Thus as the σ^*-LUMO of (C_5–H_6) gets higher, bond polarization (Δq) and the degree of bond cleavage (Δd) of the C_5–H_6 bond in the TS increases and the reactivity of the pyrolysis decreases (ΔH^* increase). This is in line with the principle of narrowing of inter-frontier level separation,[18] according to which the higher the LUMO, and the lower the HOMO, the further the reaction should progress along the reaction coordinate in order to narrow down the inter-frontier level gap sufficiently to achieve the necessary amount of charge transfer in the TS, $\Delta E_{ct} = H_{ij}^2/\Delta\epsilon$, where $\Delta\epsilon$ is the inter-frontier energy gap and H_{ij} is the interaction matrix between the two FMO_S. The total energy of the reaction system rises however until the TS is reached so that ΔH^* becomes higher as the reaction progresses further along the reaction coordinate. These trends apply equally to the σ^*-LUMO of (C_5–H_6) of both the α- and β-methylated series. In between the two series, however, Δq and Δd for (C_5–H_6) together with ΔH^* are always greater with the less reactive (higher ΔH^*) β-methylated series, which is also in accord with the principle of inter-frontier level gap narrowing.

Inspection of Table 3 shows that polarization (Δq) and the degree of bond cleavage (Δd) of the X_3–C_4 bond decrease in the order of decreasing reactivity, O–C = S>S–C = S>O–C = O>S–C = O, irrespective of whether α- or β-methylation, with the more reactive α-methylated series having, in all cases, the greater Δd and Δq values compared to β-methylated series. This order is in fact in line with the degree of carbonium ion stabilization at C_4; due to the p-π conjugation of type (3), the bond polarization and bond cleavage will be in the order of reactivity: O–C = S>S–C = S>O–C = O>S–C = O. This, however, suggests that breaking of the X_3–C_4 bond is not rate determining, since a greater bond cleavage or bond polarization should require higher ΔH^* values, *i.e.*, less reactivity,[19] in contrast to the reverse order of reactivity found in Table 1. Thus, the incipient bond cleavage of the X_3–C_4 bond is not rate-limiting, but the cleavage of the C_5–H_6 bond taking place subsequently is actually the rate determining (vide supra). In this sense, Taylor's proposition[2a] of the electron shift involved in the reaction in an anticlockwise direction following the sequence as numbered in (1) is quite reasonable; bond cleavage of the X_3–C_4 bond is initiated due to the instability rendered to the bond by the p-π conjugation, (3), in the ground state. Once the X_3–C_4 bond starts to cleave, the electrons will be transferred to β-hydrogen, which will in turn starts the electron shift to form a double bond. These processes proceed in successive stages*, since if the electron shifts were synchronous, the degree of bond polarization (Δq) (and bond cleavage (Δd)) of the C_5–H_6 bond will parallel that of the X_3–C_4 bond, which is in quite contrast to what we obtained: a greater Δq or Δd of one bond, *e.g.* X_3–C_4, is shown to give a smaller Δq or Δd of the other, *e.g.* C_5–H_6, and vice versa (Table 3). Thus the processes may be concerted but are certainly not synchronous, and take place in succesive stages according to the sequence as numbered in (1). This interpretation can, of course, accommodate a large C_β-deuterium (C_5–D_6) kinetic isotope effect of $k_H/k_D = 2.1$ found experimentally, since cleavage of the C_5–H_6 bond takes place in the last, rate determining stage.

It has been suggested that β-methylation partially contributes to long range stabilization of the incipient carbonium ion at the α-carbon (C_4). However this seems unlikely since the long range α-carbonium ion stabilization should lead to a greater bond polarization (Δq) and bond cleavage (Δd) of the X_3–C_4 bond for the β-methylated rather than for the unsubstituted ethyl formates obtained in Table 3.

We conclude that a methyl group, being a σ- as well as π-donor, substituted at either α- or β-carbon elevates the π-HOMO of the donor (Y_1–C_2) and depresses the σ^*-LUMO of the acceptor (C_5–H_6), which increases the nucleophilicity of Y_1 toward H_6 resulting in the increase in reactivity.

This effect is greater with the α-methyl group, since C_α is nearer to the donor, (Y_1–C_2). The initial cleavage of the X_3–C_4 bond takes place in a relatively fast stage, but the subsequent scission of the C_5–H_6 bond occurs in a rate determining stage. The whole process is concerted but not synchronous.

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*A two-stage reaction is one which is concerted but not synchronous; the two changes in bonding can take place successively and one of them may be rate-limiting.[20]

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Acid–Base and Spectroscopic Properties of 1,4–Benzodiazepines in Sodium Dodecyl Sulfate Micellar Solutions

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Acid–base equilibria and spectroscopic properties of diazepam and chlorodiazepoxide were investigated in sodium dodecyl sulfate (SDS) micellar solutions as functions of pH. The results were compared with the behaviors in homogeneous aqueous media. The presence of SDS increased the pK_a of chlorodiazepoxide to 6.3 from 4.7, while it has little effect on the pK_a of diazepam. The acidic protonated form of diazepam was moderately fluorescent when the solution was excited at 350 nm, and emission intensity of the species was enhanced about 5 fold by the presence of SDS. On the other hand, the acidic solution of chlorodiazepoxide was non-fluorescent, but the neutral solution of the compound was fluorescent upon excitation at 350 nm. The emission peak of the neutral chlorodiazepoxide shifted to shorter wavelength region without significant change in the emission intensity upon the addition of SDS. Procedures for assay of the individual drugs from their mixture by the use of SDS micelle were discussed.

Introduction

Surfactants are amphiphilic molecules composed of a hydrophobic portion and a hydrophilic portion. At certain concentration (cmc), surfactat molecules aggregate to form a self-assembled aggregates, micelles. Micelle solubilizes and/or binds many organic substances and ionic species. The physico-chemical properties of chemical species are usually significantly modified upon binding on micelles. Hence, the micellar systems have been used as novel media for chemical and photochemical reactions.[1] Recently, the micellar chemical and photochemical reactions.[1] Recently, the micellar systems have also been employed to modify and improve many analytical schemes.[2]

1,4-Benzodiazepines are a class of physiologically active drugs and widely prescribed as anti-anxiety agents. Thus assay of the drugs in formulation and biological fluids has been the subject of intensive studies. Much emphasis has been placed on the electro-chemical methods for the analysis of 1,4-benzodiazepines.[3-5] Absorption[6] and fluorescence[7-10] spectrophotometry were also utilized to determine some of 1,4-benzodiazepines. Recently, the interaction of 1,4-benzodiazepines with surfactants and resultant enhancement of fluorescence emission were reported.[7-10] Also studies on the kinetics of hydrolysis[11] and solubilization[12] of the drugs in micellar solutions were described.

1,4-Benzodiazepines are protonated in acidic media. The protonated and deprotonated species of organic molecules usually show different chemical stability and physico-chemical properties. Since the acid-base equilibria of organic molecules are greatly influenced by the presence of ionic micelles,[2b] the studies on the acid-base behavior and pH-dependent spectroscopic properties of 1,4-benzodiazepines in micellar solutions would provide valuable information on the chemistry of the compounds. The results can be utilized to develop a micelle-improved spectroscopic method for the analysis of the drugs.

In this report, we present the studies of acid-base and