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## Theoretical Studies on the Gas-Phase Pyrolysis of Esters The effect of $\alpha$ - and $\beta$ -methylation of Ethyl Formates<sup>1</sup>

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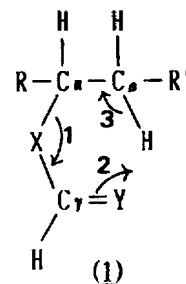
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The gas-phase thermolysis reactions of  $\alpha$ - and  $\beta$ -methylated ethyl formates,  $Y = CH-X-CHR_1CH_2R_2$  where  $X = Y = O$  or  $S$  and  $R_1 = R_2 = H$  or  $CH_3$ , are investigated theoretically using the AM1 method. The experimental 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  $C_\alpha$  or  $C_\beta$  is shown to elevate the  $\pi$ -HOMO of the donor fragment ( $Y = C$ ) and depress the  $\sigma^*$ -LUMO of the acceptor fragment ( $C_\beta-H$ ), increasing the nucleophilicity of  $Y$  toward  $\beta$ -hydrogen which in turn increases the reactivity. The two bond breaking processes of the  $C_\alpha-X$  and  $C_\beta-H$  bonds are concerted but not synchronous so that the reaction takes place in two stages as Taylor suggested. The initial cleavage of  $C_\alpha-X$  is of little importance but the subsequent scission of  $C_\beta-H$  occurs in a rate determining stage.

### Introduction

The gas-phase thermal decomposition reaction of esters has been studied extensively.<sup>2</sup> Taylor<sup>2a</sup> 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  $C_\beta$  is less electron rich than  $C_\alpha$  is electron deficient.

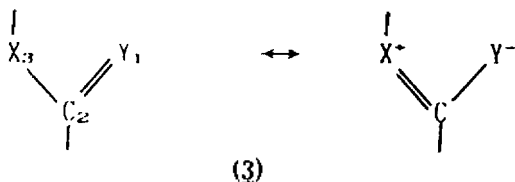
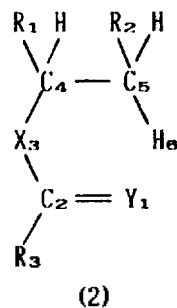
There is, however, still a controversial problem of the rate determining step; some investigators interpreted their data in favor of the  $C_\alpha-O$  bond polarization<sup>2a</sup> whereas some in



favor of the cleavage of the  $C_\beta-H$  bond<sup>2i-2j</sup> as the rate determining process. Experimentally monomethylation at the  $\alpha$ -

(R = CH<sub>3</sub>) as well as  $\beta$ -carbon (R' = CH<sub>3</sub>) led to a greater reactivity<sup>2b</sup>;  $\alpha$ -methylation stabilizes the TS by electron donation to the incipient  $\alpha$ -carbonium ion, but the effect of  $\beta$ -methylation is not well understood.<sup>2d</sup> The rate enhancement by a  $\beta$ -CH<sub>3</sub> group was variously interpreted as due to long range stabilization of the remote  $\alpha$ -carbonium ion<sup>2a</sup> 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,<sup>3</sup> we reported on the gas-phase thermal decomposition reactions of alkanolic esters, Y = C(R<sub>3</sub>)-X-CHR<sub>1</sub>CH<sub>2</sub>R<sub>2</sub> where X = Y = O or S with R<sub>1</sub> = R<sub>2</sub> = H and R<sub>3</sub> = H, CH<sub>3</sub> or NH<sub>2</sub> in (2), studied theoretically using the semiempirical MO methods of MNDO<sup>4</sup> and AM1<sup>5</sup>. 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<sup>6</sup>; the most important factors controlling the reactivity are the  $\pi$ -donating ability factors controlling the reactivity are the  $\pi$ -donating ability of the  $\pi$ -HOMO of the donor fragment, (Y<sub>1</sub> = C<sub>2</sub>), and the accepting ability of the  $\sigma^*$ -LUMO of the acceptor fragment, (C<sub>5</sub>-H<sub>6</sub>), i.e., the ease of nucleophilic attack of Y<sub>1</sub> upon  $\beta$ -hydrogen, H<sub>6</sub>, in (2). However the difference in reactivity was found to arise originally from the ease of  $p$ - $\pi$  conjugation in the ground state (GS),<sup>7</sup> (3), depending on the groups X and Y for the fixed R groups; the stronger the  $p$ - $\pi$  conjugation the higher is the  $\pi$ -HOMO of the donor (Y<sub>1</sub>-C<sub>2</sub>) and the lower is



the  $\sigma^*$ -LUMO of the acceptor (C<sub>5</sub>-H<sub>6</sub>) leading to an easier nucleophilic attack by Y<sub>1</sub> upon  $\beta$ -hydrogen, H<sub>6</sub>.

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  $\alpha$ - or  $\beta$ -carbon atom, i.e., R<sub>1</sub> = CH<sub>3</sub> with R<sub>2</sub> = R<sub>3</sub> = H (iso-propyl formate) and R<sub>1</sub> = R<sub>3</sub> = H with R<sub>2</sub> = CH<sub>3</sub> (*n*-propyl formate) in (2).

### Calculation

The calculations were carried out with the AM1 method.<sup>5</sup> All geometries were fully optimized. TSs were located by the

**Table 1.** Heats of Formation ( $\Delta H_f$ ) of Ground (GS) and Transition States (TS) and Activation Enthalpies ( $\Delta H^*$ ) (kcal/mol) by AM1

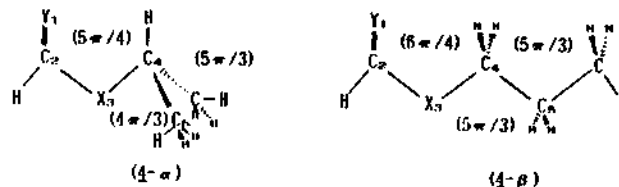
X	Y	R <sub>1</sub>	R <sub>2</sub>	$\Delta H_f$		$\Delta H^*$
				GS	TS	
O	S	H	H	-19.17	26.99	46.16 <sup>a</sup>
		CH <sub>3</sub>	H	-23.29	18.47	41.76
		H	CH <sub>3</sub>	-25.97	20.38	46.35
S	S	H	H	23.81	74.12	50.31 <sup>a</sup>
		CH <sub>3</sub>	H	20.10	68.50	48.40
		H	CH <sub>3</sub>	17.02	66.56	49.54
O	O	H	H	-97.02	-33.49	63.53 <sup>a</sup>
		CH <sub>3</sub>	H	-101.00	-40.55	60.45
		H	CH <sub>3</sub>	-103.86	-41.51	62.35
S	O	H	H	-39.92	24.29	64.21 <sup>a</sup>
		CH <sub>3</sub>	H	-43.62	19.13	62.75
		H	CH <sub>3</sub>	-46.71	16.25	62.96

<sup>a</sup>Ref. 3.

reaction coordinate method,<sup>8</sup> refined by the gradient norm minimization<sup>9</sup> and characterized by conforming only one negative eigenvalue in the Hessian matrix.<sup>10</sup>

### Results and Discussion

The heats of formation ( $\Delta H_f$ ) for the reactants and TSs are shown in Table 1 together with the activation enthalpies ( $\Delta H^*$ ) for the thermal decomposition of the esters. In general,  $\beta$ -methylation leads to more stable ground ( $4-\alpha$  and  $4-\beta$ ) and transition states. The stabilities of the ground



states are mainly determined by one-electron energies,  $2\sum\epsilon_i$ , which in turn is largely dependent on the  $\pi$ -nonbonded interactions<sup>11</sup>; in (4- $\alpha$ ) there are two stabilizing, (5 $\pi$ /4) and (5 $\pi$ /3), and one destabilizing, (4 $\pi$ /3),  $\pi$ -nonbonded structures,<sup>12</sup> whereas in 4- $\beta$ , 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  $\alpha$ -methylation (R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = R<sub>3</sub> = H) than with  $\beta$ -methylation (R<sub>2</sub> = CH<sub>3</sub>, R<sub>1</sub> = R<sub>3</sub> = H) in all cases of X, Y = O or S. Furthermore the  $\beta$ -methylated compounds have lower activation barriers than the unsubstituted (R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H) series, except for (O-C = S), for which the activation enthalpies differ negligibly small amount between the unsubstituted and  $\beta$ -methylated compounds. We also note that the difference in the barrier,  $\delta\Delta H^* (= \Delta H^*_{(\beta-Me)} - \Delta H^*_{(\alpha-Me)})$ , 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).<sup>13</sup>

The ester decomposition proceeds by a retro-ene process,<sup>14</sup> which can be conveniently interpreted by three-spe-

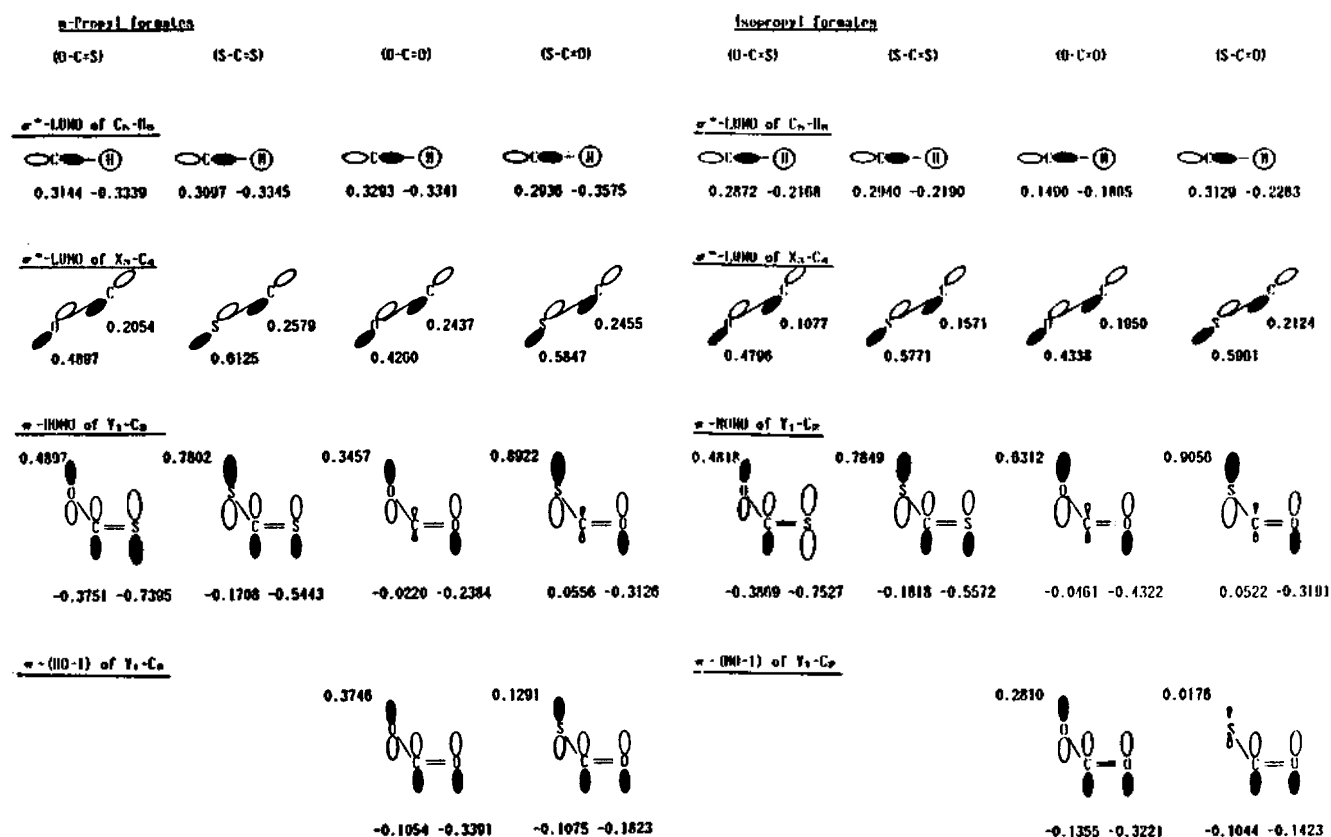
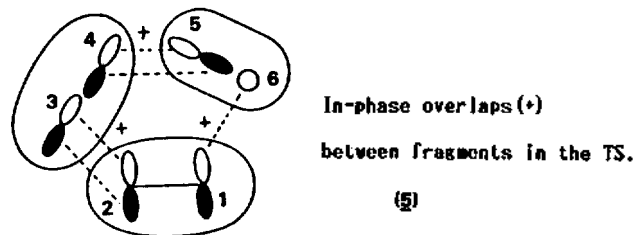


Figure 1. Frontier orbital of *n*-propyl formates and isopropyl formates by AM1.

cies interaction<sup>3,6</sup> within the framework of frontier orbital (FMO) theory;<sup>15</sup> thus the in-phase interactions<sup>16</sup> between the  $\pi$ -HOMO of the donor, ( $Y_1-C_2$ ), and the two  $\sigma^*$ -LUMO<sub>S</sub> of the acceptors, ( $X_3-C_4$ ) and ( $C_5-H_6$ ), in the TS (5) will be the key factors controlling the reactivity.

FMO patterns (Figure 1) for the three fragments, irrespective of whether  $\alpha$ - or  $\beta$ -methylated, are entirely similar to those of the unsubstituted ethyl formates<sup>3</sup>; the *p*-AO lobes of the  $\pi$ -HOMO of the donor, ( $Y_1=C_2$ ), decreases in the order that corresponds to the decreasing reactivity:<sup>2a,2f</sup> (O-C=S) > (S-C=S) > (O-C=O) > (S-C=O), and  $\sigma^*$ -LUMO<sub>S</sub> of the ( $C_5-H_6$ ) fragment are substantially higher than  $\sigma^*$ -



LUMO<sub>S</sub> of the ( $X_3-C_4$ ) fragment (Table 2).

Table 2 shows that the  $\pi$ -HOMO levels of the donor, ( $Y_1-C_2$ ), are raised whereas the  $\sigma^*$ -LUMO levels of the acceptor,

Table 2. Energy Levels (eV) of  $\pi$ -HOMO of Donor ( $Y_1-C_2$ ) and  $\sigma^*$ -LUMOs of Acceptors ( $X_3-C_4$ ) and ( $C_5-H_6$ ) for  $\alpha$ - and  $\beta$ -CH<sub>3</sub>-ethyl formates ( $Y = CHXCHR_1CHR_2$ ) by AM1

Alkyl		O-C=S	S-C=S	O-C=O	S-C=O
<i>n</i> -Propyl R <sub>1</sub> = H R <sub>2</sub> = CH <sub>3</sub>	$\pi$ -HOMO ( $Y_1-C_2$ )	-10.1823	-9.4714	-11.4511 (-12.6944) <sup>a</sup>	-10.0294 (-13.9752) <sup>a</sup>
	$\sigma^*$ -LUMO ( $X_3-C_4$ )	1.9879	1.3229	2.0881	1.2729
	$\sigma^*$ -LUMO ( $C_5-H_6$ )	3.3937	3.4059	3.5176	3.4862
<i>i</i> -Propyl R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H	$\pi$ -HOMO ( $Y_1-C_2$ )	-10.1089	-9.4527	-11.5126 (-12.5123) <sup>a</sup>	-10.0410 (-13.1550) <sup>a</sup>
	$\sigma^*$ -LUMO ( $X_3-C_4$ )	1.9150	1.2251	2.0510	1.2633
	$\sigma^*$ -LUMO ( $C_5-H_6$ )	3.3819	3.4045	3.4763	3.5076
Ethyl <sup>b</sup> R <sub>1</sub> = H R <sub>2</sub> = H	$\pi$ -HOMO ( $Y_1-C_2$ )	-10.2031	-9.4815	-11.6501 (-13.7892) <sup>a</sup>	-10.0473 (-14.1629) <sup>a</sup>
	$\sigma^*$ -LUMO ( $X_3-C_4$ )	1.9786	1.3096	2.0836	1.2661
	$\sigma^*$ -LUMO ( $C_5-H_6$ )	3.4304	3.4546	3.5454	3.5507

<sup>a</sup>The levels in parenthesis are for the (HO-1)th  $\pi$ -orbital. <sup>b</sup>Ref. 3.

**Table 3.** Formal Charges (Electronic Unit) and Bond Lengths(Å), and Their Charges  $\Delta q$  and  $\Delta d$ , for Pyrolysis of Esters

X	Y	R <sub>1</sub>	R <sub>2</sub>	Charges(e.u.)			Bond Length(Å)					
				Atom	GS	TS	$\Delta q^a$	Bond	GS	TS	$\Delta d^a$	
O	S	CH <sub>3</sub>	H	S <sub>1</sub>	-0.072	-0.237	-0.165	S <sub>1</sub> -C <sub>2</sub>	1.545	1.613	0.067	
				C <sub>2</sub>	-0.080	0.034	0.114	C <sub>2</sub> -O <sub>3</sub>	1.354	1.276	-0.078	
				O <sub>3</sub>	-0.217	-0.399	-0.182	O <sub>3</sub> -C <sub>4</sub>	1.441	1.993	0.552	
		C <sub>4</sub>	-0.028	0.177	0.205	C <sub>4</sub> -C <sub>5</sub>	1.513	1.418	-0.095			
		C <sub>5</sub>	-0.249	-0.419	-0.170	C <sub>5</sub> -H <sub>6</sub>	1.117	1.277	0.160			
		H <sub>6</sub>	0.090	0.250	0.160							
	H	CH <sub>3</sub>	S <sub>1</sub>	-0.061	-0.200	-0.139	S <sub>1</sub> -C <sub>2</sub>	1.545	1.617	0.072		
	C <sub>2</sub>		-0.093	0.043	0.136	C <sub>2</sub> -O <sub>3</sub>	1.358	1.276	-0.082			
	O <sub>3</sub>		-0.214	-0.377	-0.163	O <sub>3</sub> -C <sub>4</sub>	1.440	1.915	0.475			
	S	S	CH <sub>3</sub>	H	C <sub>4</sub>	-0.034	0.122	0.156	C <sub>4</sub> -C <sub>5</sub>	1.517	1.411	-0.106
					C <sub>5</sub>	-0.164	-0.408	-0.244	C <sub>5</sub> -H <sub>6</sub>	1.121	1.344	0.223
					H <sub>6</sub>	0.094	0.261	0.165				
S <sub>1</sub>			0.033	-0.007	-0.040	S <sub>1</sub> -C <sub>2</sub>	1.537	1.614	0.077			
C <sub>2</sub>			-0.389	-0.361	0.028	C <sub>2</sub> -S <sub>3</sub>	1.659	1.575	-0.084			
S <sub>3</sub>			0.206	-0.020	-0.226	S <sub>3</sub> -C <sub>4</sub>	1.753	2.253	0.500			
H		CH <sub>3</sub>	H	C <sub>4</sub>	-0.209	-0.003	0.206	C <sub>4</sub> -C <sub>5</sub>	1.508	1.392	-0.116	
				C <sub>5</sub>	-0.224	-0.403	-0.179	C <sub>5</sub> -H <sub>6</sub>	1.118	1.451	0.333	
				H <sub>6</sub>	0.095	0.193	0.098					
		S <sub>1</sub>	0.038	0.040	0.002	S <sub>1</sub> -C <sub>2</sub>	1.537	1.618	0.081			
		C <sub>2</sub>	-0.396	-0.400	-0.004	C <sub>2</sub> -S <sub>3</sub>	1.662	1.576	-0.086			
		S <sub>3</sub>	0.219	0.052	-0.167	S <sub>3</sub> -C <sub>4</sub>	1.737	2.134	0.397			
O	O	CH <sub>3</sub>	H	C <sub>4</sub>	-0.290	-0.104	0.186	C <sub>4</sub> -C <sub>5</sub>	1.510	1.392	-0.118	
				C <sub>5</sub>	-0.156	-0.336	-0.180	C <sub>5</sub> -H <sub>6</sub>	1.122	1.544	0.422	
				H <sub>6</sub>	0.089	0.165	0.076					
		O <sub>1</sub>	-0.355	-0.434	-0.079	O <sub>1</sub> -C <sub>2</sub>	1.229	1.287	0.058			
		C <sub>2</sub>	0.260	0.292	0.032	C <sub>2</sub> -O <sub>3</sub>	1.358	1.281	-0.077			
		O <sub>3</sub>	-0.288	-0.461	-0.173	O <sub>3</sub> -C <sub>4</sub>	1.466	1.917	0.471			
	H	CH <sub>3</sub>	H	C <sub>4</sub>	0.034	0.221	0.187	C <sub>4</sub> -C <sub>5</sub>	1.516	1.414	-0.102	
				C <sub>5</sub>	-0.216	-0.534	-0.318	C <sub>5</sub> -H <sub>6</sub>	1.116	1.345	0.229	
				H <sub>6</sub>	0.086	0.346	0.260					
		O <sub>1</sub>	-0.351	-0.353	-0.002	O <sub>1</sub> -C <sub>2</sub>	1.229	1.298	0.069			
		C <sub>2</sub>	0.257	0.298	0.041	C <sub>2</sub> -O <sub>3</sub>	1.360	1.285	-0.075			
		O <sub>3</sub>	-0.287	-0.363	-0.076	O <sub>3</sub> -C <sub>4</sub>	1.434	1.704	0.270			
S	O	CH <sub>3</sub>	H	C <sub>4</sub>	-0.016	0.129	0.113	C <sub>4</sub> -C <sub>5</sub>	1.517	1.414	-0.103	
				C <sub>5</sub>	-0.190	-0.585	-0.395	C <sub>5</sub> -H <sub>6</sub>	1.122	1.502	0.380	
				H <sub>6</sub>	0.100	0.354	0.254					
		O <sub>1</sub>	-0.292	-0.295	-0.003	O <sub>1</sub> -C <sub>2</sub>	1.231	1.302	0.071			
		C <sub>2</sub>	0.058	0.010	-0.048	C <sub>2</sub> -S <sub>3</sub>	1.690	1.600	-0.090			
		S <sub>3</sub>	0.093	-0.078	-0.171	S <sub>3</sub> -C <sub>4</sub>	1.751	2.110	0.359			
	H	CH <sub>3</sub>	H	C <sub>4</sub>	-0.193	0.070	0.263	C <sub>4</sub> -C <sub>5</sub>	1.508	1.403	-0.105	
				C <sub>5</sub>	-0.225	-0.585	-0.360	C <sub>5</sub> -H <sub>6</sub>	1.119	1.493	0.374	
				H <sub>6</sub>	0.099	0.331	0.232					
		O <sub>1</sub>	-0.290	-0.269	0.021	O <sub>1</sub> -C <sub>2</sub>	1.231	1.305	0.074			
		C <sub>2</sub>	0.052	-0.010	-0.062	C <sub>2</sub> -S <sub>3</sub>	1.691	1.602	-0.089			
		S <sub>3</sub>	0.104	-0.008	-0.112	S <sub>3</sub> -C <sub>4</sub>	1.735	2.012	0.277			
H	CH <sub>3</sub>	H	C <sub>4</sub>	-0.272	-0.028	0.244	C <sub>4</sub> -C <sub>5</sub>	1.509	1.406	-0.103		
			C <sub>5</sub>	-0.157	-0.537	-0.380	C <sub>5</sub> -H <sub>6</sub>	1.122	1.559	0.437		
			H <sub>6</sub>	0.091	0.328	0.237						

<sup>a</sup>  $\Delta q$  and  $\Delta d$  are variations in charge and bond length from ground (GS) to transition state (TS).

(C<sub>5</sub>-H<sub>6</sub>), are lowered for both the  $\alpha$ - and  $\beta$ -methylated series relative to the corresponding levels of the unsubstituted ester series.<sup>3</sup> This is in accord with the enhanced reac-

tivity of the  $\alpha$ - and  $\beta$ -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<sup>17</sup> and lead to an easier nucleophilic attack by  $Y_1$  upon  $\beta$ -hydrogen,  $H_6$ . We also note that the extents to which ( $Y_1-C_2$ )  $\pi$ -HOMO is raised and ( $C_5-H_6$ )  $\sigma^*$ -LUMO is lowered are invariably greater with the  $\alpha$ - compared to the  $\beta$ -methylated series, which is again in line with the greater reactivity of the  $\alpha$ -compared to the  $\beta$ -methylated series.

Thus the activation enthalpies,  $\Delta H^*$ , are lowered and hence the reactivities are increased as the  $\pi$ -HOMO<sub>S</sub> of the ( $Y_1-C_2$ ) fragment are elevated and the  $\sigma^*$ -LUMO<sub>S</sub> of the ( $C_5-H_6$ ) fragment are depressed. This is accompanied by the decrease in the  $C_5-H_6$  bond polarization ( $\Delta q$ ) and the degree of bond breaking ( $\Delta d$ ) in the TS (Table 3). Thus as the  $\sigma^*$ -LUMO of ( $C_5-H_6$ ) gets higher, bond polarization ( $\Delta q$ ) and the degree of bond cleavage ( $\Delta d$ ) of the  $C_5-H_6$  bond in the TS increases and the reactivity of the pyrolysis decreases ( $\Delta H^*$  increase). This is in line with the principle of narrowing of inter-frontier level separation,<sup>18</sup> 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,  $\Delta E_{\sigma} = H_{ij}^2 / \Delta \epsilon$ , where  $\Delta \epsilon$  is the inter-frontier energy gap and  $H_{ij}$  is the interaction matrix between the two FMO<sub>S</sub>. The total energy of the reaction system rises however until the TS is reached so that  $\Delta H^*$  becomes higher as the reaction progresses further along the reaction coordinate. These trends apply equally to the  $\sigma^*$ -LUMO of ( $C_5-H_6$ ) of both the  $\alpha$ - and  $\beta$ -methylated series. In between the two series, however,  $\Delta q$  and  $\Delta d$  for ( $C_5-H_6$ ) together with  $\Delta H^*$  are always greater with the less reactive (higher  $\Delta H^*$ )  $\beta$ -methylated series, which is also in accord with the principle of inter-frontier level gap narrowing.

Inspection of Table 3 shows that polarization ( $\Delta q$ ) and the degree of bond cleavage ( $\Delta d$ ) 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  $\alpha$ - or  $\beta$ -methylation, with the more reactive  $\alpha$ -methylated series having, in all cases, the greater  $\Delta d$  and  $\Delta q$  values compared to  $\beta$ -methylated series. This order is in fact in line with the degree of carbonium ion stabilization at  $C_4$ ; due to the  $p$ - $\pi$  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  $\Delta H^*$  values, *i.e.*, less reactivity,<sup>19</sup> 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<sup>24</sup> 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  $p$ - $\pi$  conjugation, (3), in the ground state. Once the  $X_3-C_4$  bond starts to cleave, the electrons will be transferred to  $\beta$ -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 ( $\Delta q$ ) (and bond cleavage ( $\Delta d$ )) 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  $\Delta q$  or  $\Delta d$  of one bond, *e.g.*  $X_3-C_4$ , is shown to give a smaller  $\Delta q$  or  $\Delta d$  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 successive stages according to the sequence as numbered in (1). This interpretation can, of course, accommodate a large  $C_5$ -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  $\beta$ -methylation partially contributes to long range stabilization of the incipient carbonium ion at the  $\alpha$ -carbon ( $C_4$ ). However this seems unlikely since the long range  $\alpha$ -carbonium ion stabilization should lead to a greater bond polarization ( $\Delta q$ ) and bond cleavage ( $\Delta d$ ) of the  $X_3-C_4$  bond for the  $\beta$ -methylated rather than for the unsubstituted ethyl formates obtained in Table 3.

We conclude that a methyl group, being a  $\sigma$ - as well as  $\pi$ -donor, substituted at either  $\alpha$ - or  $\beta$ -carbon elevates the  $\pi$ -HOMO of the donor ( $Y_1-C_2$ ) and depresses the  $\sigma^*$ -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  $\alpha$ -methyl group, since  $C_2$  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.<sup>20</sup>

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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), surfactant 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.<sup>1</sup> Recently, the micellar chemical and photochemical reactions.<sup>1</sup> Recently, the micellar systems have also been employed to modify and improve many analytical schemes.<sup>2</sup>

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.<sup>3-5</sup> Absorption<sup>6</sup> and fluorescence<sup>7-10</sup> 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.<sup>7-10</sup> Also studies on the kinetics of hydrolysis<sup>11</sup> and solubilization<sup>12</sup> 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,<sup>2b</sup> 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