Kinetics and Thermodynamics of Keto–Enol Tautomerism of Simple Carbonyl Compounds: An Approach Based on a Kinetic Study of Halogenation at Low Halogen Concentrations[1]

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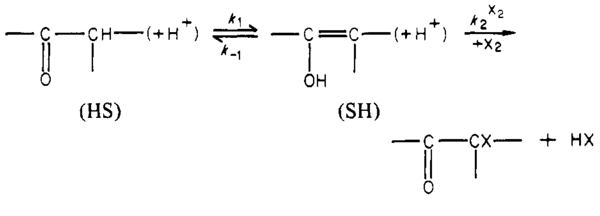
Abstract: Kinetic data for bromination and/or iodination of cycloalkanones and aryl-substituted acetophenones in water, using very low halogen concentrations (10^{-7}–10^{-5} M) (i.e., when the rate-limiting step is not enolization but partly halogen addition to enol) provide the hydronium-catalyzed enolization rate coefficients (k_1) and the apparent second-order rate coefficients $k_{\mathrm{II}} = K_{\mathrm{HS}}^{\mathrm{SH}} k_2$ (where $K_{\mathrm{HS}}^{\mathrm{SH}}$ is the keto–enol equilibrium constant and k_2 the enol halogenation rate constant). As previously suggested, the rate of enol halogenation is usually encounter controlled. This makes it possible to estimate k_2 and to calculate $K_{\mathrm{HS}}^{\mathrm{SH}}$ from data on k_{II}. The enol ketonization rate coefficients are deduced and compared with those for methyl and ethyl enol ether hydrolysis. It is shown that the ratio enol ketonization/enol ether hydrolysis of parent compounds varies in the range 15–150 and depends on enol structure. For the different rate and equilibrium coefficients which intervene in the two-step mechanism of keto–enol interconversion of acetophenones, a variety of linear free-energy relationships are established, using the Young–Jencks modified Yukawa–Tsuno equation. A Brønsted relation is observed by plotting the rate constants for enol formation from the conjugated acids of acetophenones vs. the CH acidity constants of these ions. The Brønsted exponent, $\alpha = 0.4$, is in agreement with a transition state model in which the proton is less than half-transferred. Data on enthalpy and entropy of activation for enolization of cycloalkanones, compared with those for keto–enol equilibrium, are also in favor with an early transition state.

The equilibrium between a simple aldehyde, or a simple ketone, and its corresponding enol tautomeric form is usually so displaced toward the keto form that the amount of enol at equilibrium can neither be detected nor measured by using spectroscopic methods. On the other hand, the halogen titration method,[2-7] which works well for multifunctional compounds, becomes very difficult to apply when the enol content is less than 1 ppm and leads to ambiguous results. Indeed, several authors have reported results[8] which differ from each other and are not in agreement with indirect estimations.[9-13] Even the most sensitive form of the halogen titration method,[7] which avoids errors resulting from impurities, has given results, especially for cyclohexanone and cyclopentanone, which are in disagreement with estimations based on thermodynamic determination of Gibbs free energy for enol ether formation.[9,10]

Recent estimations of the enol content of simple carbonyl compounds in water have been reported by Guthrie.[10-12] First, enol formation equilibrium constants have been deduced from the measurements of the heat of formation of the related methyl ether (relative to the parent carbonyl compound), and from estimates of the entropy terms and of the Gibbs free energy differences between enols and ethers. Secondly, the ketonization rate constants were estimated as being equal to the rate constants for hydrolysis of the corresponding methyl enol ethers; the equilibrium constants were then calculated as the ratios between hydronium-catalyzed enolization and hydronium-catalyzed hydrolysis rate constants. However, although these two independent methods of estimation have led to concordant results, usually corresponding to a much lower enol content than that obtained by halogen titration, a number of problems were not solved. In particular, it is dubious to assume that the enol ketonization rate constants are equal to those for enol ether hydrolysis. It must be noted that this assumption is supported only by a comparison between 1-methoxycylohexene hydrolysis and 1-hydroxycyclohexene ketonization,[14] and the rate constant used for the latter was deduced using the questionable equilibrium data obtained by bromine titration. On the other hand, the thermodynamic method has the disadvantage of being imprecise and needing an indirect estimation of the equilibrium constant for the methyl transfer reaction, corresponding to the formation of enol ether from enol.

We previously proposed another approach[13] which is based on kinetic measurements of acid-catalyzed ketone halogenation at very low halogen concentrations, i.e., when the rate-limiting step is not just the usual enolization, since the rate is affected also by the step of halogen addition to enol (eq 1). We have shown (a)



(HS) (SH)

$$-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{|}{\mathrm{CH}}-(+\mathrm{H}^+) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} -\underset{\substack{|\\ \mathrm{OH}}}{\mathrm{C}}=\underset{|}{\mathrm{C}}-(+\mathrm{H}^+) \xrightarrow[+\mathrm{X}_2]{k_2^{\mathrm{X}_2}} -\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{|}{\mathrm{CX}}- + \mathrm{HX} \quad (1)$$

that under these conditions the rate fits eq 2, which includes the

$$-\frac{\mathrm{d}[\mathrm{X}_2]}{\mathrm{d}t} = \frac{[\mathrm{X}_2]}{\dfrac{1}{k_{\mathrm{II}}^{\mathrm{X}_2}[\mathrm{HS}]} + \dfrac{[\mathrm{X}_2]}{k_1[\mathrm{H}^+][\mathrm{HS}]}} \qquad (2)$$

enolization rate coefficient, k_1, and the apparent second-order rate coefficient, $k_{\mathrm{II}}^{\mathrm{X}_2}$ [the product of the keto–enol equilibrium constant,

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[1] Abstracted in part (data on bromination and iodination of substituted acetophenones) from the "Doctorat ês-Sciences Physiques" of Mohiedine El-Alaoui, University of Paris VII, Paris, 1979.

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K_{HS}^{SH}, and of the elementary rate coefficient for halogen addition, $k_2^{X_2}$ (eq 3)],[15,16] *and* (b) *that* $k_2^{X_2}$ is independent *of the* halogen,

$$k_{II}^{X_2} = K_{HS}^{SH} \times k_2^{X_2} \text{ with } K_{HS}^{SH} = k_1/k_{-1} \tag{3}$$

chlorine, bromine, or iodine.[13] The latter observation was explained as being the result of the encounter control of halogen addition to *simple enols*. We *therefore pointed out that* $k_2^{X_2}$ must be approximately independent of enol structure and, consequently, that the experimental k_{II} coefficient is proportional to K_{HS}^{SH}. Furthermore, since the encounter-controlled rate coefficient can be estimated from the encounter frequency, the tautomerism equilibrium constants K_{HS}^{SH} can be deduced. This paper deals with the application of this experimental procedure to the determination of K_{HS}^{SH} for cycloalkanones and ring-substituted acetophenones. Since data are available for acid-catalyzed hydrolysis of the corresponding methyl and ethyl enol ethers,[17-19] the discussion of the results will be focused on a comparison between enol ketonization and enol ether hydrolysis rate constants.

Results

Kinetic Data. Kinetic data for acid-catalyzed iodination and/or bromination of cycloalkanones [$C_nH_{2n-2}O$ with n = 5 (**1**), 6 (**2**), 7 (**3**), 8 (**4**), and 9 (**5**)] and of ring-substituted acetophenones [$XC_6H_4COCH_3$ with X = 4-OCH_3 (**6**), 4-CH_3 (**7**), H (**8**), 4-Cl (**9**), 3-Cl (**10**), 3-CF_3 (**11**), 3-NO_2 (**12**), and 4-NO_2 (**13**)] were deduced from studies carried out in water with a large excess of the ketone and sodium bromide or iodide, by following the decrease of the halogen concentration using the couloamperometric method.[13,15,20] The initial halogen concentrations were always very low ($<10^{-5}$M) and depended on the ketone, temperature, and halide concentrations. Under these conditions, eq 2 (which corresponds to the case where enol ketonization and halogen addition to enol have comparable rates, and which includes the steady-state approximation) is valid. However, as bromide or iodide ions were in excess, and as we must take into account the intrinsic reactivities of X_2 (X = Br or I) and X_3^-, the elementary $k_2^{X_2}$ constants and the apparent $k_{II}^{X_2}$ coefficients must be replaced by $(k_2^{X_2})_g$ and $(k_{II}^{X_2})_g$, respectively, which can be defined in terms of the stoichiometric halogen concentration ($[X_2]_a = [X_2] + [X_3^-]$), and are related by eq 4 and 5 to k_2 and k_{II} for X_2 and X_3^-.

$$(k_2^{X_2})_g\{1 + K_{X_3^-}[X^-]\} = k_2^{X_2} + k_2^{X_3^-}K_{X_3^-}[X^-] \tag{4}$$

$$(k_{II}^{X_2})_g\{1 + K_{X_3^-}[X^-]\} = k_{II}^{X_2} + k_{II}^{X_3^-}K_{X_3^-}[X^-] \tag{5}$$

($K_{X_3^-}$, equilibrium constant for the formation of X_3^- and corresponding to $X_2 + X^- \rightleftharpoons X_3^-$).[21,22]

The integrated form (eq 6), derived from eq 2 ([HS] is considered to be constant), was verified over the whole range of ketone and halogen concentrations and made it possible to calculate the rate coefficients k_I ($=k_1[H^+]$) and $(k_{II}^{X_2})_g$.

$$\frac{t' - t}{[X_2]_a^t - [X_2]_a^{t'}} = \frac{1}{(k_{II}^{X_2})_g[HS]}\,\frac{\ln[X_2]_a^t - \ln[X_2]_a^{t'}}{[X_2]_a^t - [X_2]_a^{t'}} + \frac{1}{k_I[HS]} \tag{6}$$

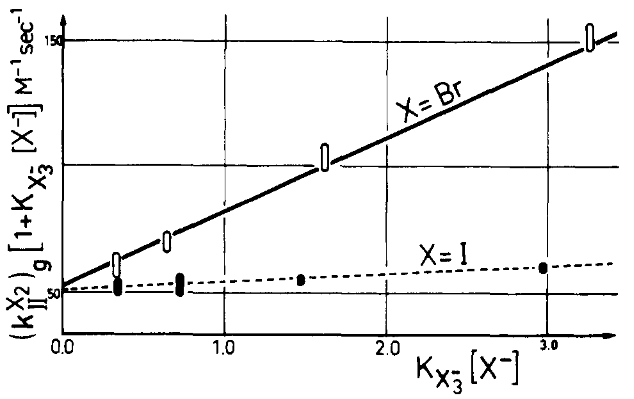

Figure 1. Bromide and iodide concentration effects on the second-order rate constants for cyclopentanone bromination and iodination. The slope corresponds to $k_{II}^{X_3^-}$ and the intercept to $k_{II}^{X_2}$ (see eq 5) (25 °C).

($[X_2]_a^t$ and $[X_2]_a^{t'}$ = analytical iodine and bromine concentrations at times t and t').

For bromination of compounds **1**–**5**, measurements were performed at [H_2SO_4] = 0.25 M and at different NaBr concentrations [0.2, 0.1, 0.04, 0.01 (or 0.02) M], at 5, 15, 25, and 35 °C. For iodination of the same compounds we observed that the reactions reach equilibrium at high iodide concentrations. So, in order to avoid the reverse reactions, only small iodide concentrations were used ([NaI] × 10^3 = 4, 2, 1, and 0.5 M, except for **2**: [NaI] × 10^3 = 0.5 and 0.25 M). The iodination measurements were carried out only at 25 °C.

Since bromination of **6** exhibited a more complex kinetic behavior due to competitive bromination of the nucleus and of the side chain, bromination rate constants were only measured for compounds **7**–**13**. When possible, measurements at different sulfuric acid concentrations were done (e.g., in the 0.1–0.5 M range for **7**). For iodination of acetophenones, it was observed that the reverse reaction is of great importance, especially for acetophenones bearing an electron-withdrawing substituent. So, accurate iodination measurements were only performed for X = 4-OCH_3 and 4-CH_3. By contrast to cycloalkanones, temperature influence was not studied for acetophenones.

The kinetic results for bromination and iodination of compounds **1**–**13** are provided in Tables S1–S4 as supplementary material.[23] In these tables, each k_I and k_{II} value is the average of about 10 measurements carried out repeatedly for the same ketone concentration, but using different initial halogen concentrations chosen in order to verify eq 6.

Figure 1 shows that eq 5 is valid for both halogens. The second-order rate coefficients $k_{II}^{X_2}$ correspond to the intercepts of the observed linear relationships, and $k_{II}^{X_3^-}$ to the slopes.

The results listed in Tables S1–S4 show no significant variation of k_I with bromide and iodide concentrations. Furthermore, the k_I values for bromination and iodination studies are equal as expected. This confirms the validity of the kinetic treatment which includes the steady-state approximation.

From similar measurements for acetone,[13,15] we observed that k_I is proportional to H_2SO_4 concentration, from 0.05 to 0.5 M. The same result is obtained here for **7**. Therefore, one can define an apparent catalytic enolization rate coefficient k_{1a} (Table I), expressed by $k_{1a} = k_I/[H^+]_a$, where $[H^+]_a$ is twice the molarity of sulfuric acid. Since sulfuric acid is not fully dissociated in the experimental conditions, it must be noted that k_{1a} differs slightly from hydronium catalytic rate coefficient. However, a comparison of the k_{1a} value for acetone (2.45 × 10^{-5} M^{-1} s^{-1})[13,15,24] with accurate data reported in literature (2.84 × 10^{-5} M^{-1} s^{-1})[24,25] shows that a ratio of 1.15 must be allowed for correcting k_{1a} in order to obtain the true hydronium catalytic rate coefficients k_1 (Table II).[26]

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[22] 20 (5 °C), 18 (15 °C), 16.3 (25 °C), and 14.9 M^{-1} (35 °C) were chosen as the $K_{Br_3^-}$. The value 16.3 M^{-1} at 25 °C was measured (Dubois, J. E.; Garnier, F. *Bull. Soc. Chim. Fr.* **1965**, 1715–1718). The other values were calculated by taking into account the observed $\Delta H°$ (Scaife, D. B.; Tyrrell, H. J. V. *J. Chem. Soc.* **1958**, 386–392).

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Table I. Cumulative Kinetic Data for the Bromination and the Iodination of Cycloalkanones ($C_nH_{2n-2}O$) and Acetophenones ($XC_6H_4COCH_3$)[a]

n in $C_nH_{2n-2}O$ or X in XC_6H_4-$COCH_3$	temp,[b] °C	bromination			iodination		
		$10^5 k_{1a}$,[c] $M^{-1}\,s^{-1}$	$k_{II}^{Br_2}$,[d] $M^{-1}\,s^{-1}$	$k_{II}^{Br_2}/k_{II}^{Br_3^-}$ [e]	$10^5 k_{1a}$,[c] $M^{-1}\,s^{-1}$	$k_{II}^{I_2}$,[f] $M^{-1}\,s^{-1}$	$k_{II}^{I_2}/k_{II}^{I_3^-}$ [g]
5	5	0.616 ± 0.008	8.43 ± 0.07	1.4 ± 0.1			
	15	1.96 ± 0.04	21.8 ± 0.2	1.5 ± 0.1			
	25	6.15 ± 0.10	50.3 ± 0.8	1.6 ± 0.1	6.00 ± 0.15	50.7 ± 0.7	16.7 ± 2.0
	35	16.45 ± 0.25	127 ± 1	1.9 ± 0.1			
6	5	2.06 ± 0.08	255 ± 8	1.8 ± 0.2			
	15	6.56 ± 0.18	613 ± 5	2.0 ± 0.1			
	25	20.2 ± 0.02	1152 ± 50	1.8 ± 0.4	20.5 ± 0.3	1080 ± 50	
	35	56.6 ± 3.06	2530 ± 33	2.4 ± 0.3			
7	5	0.383 ± 0.013	7.57 ± 0.17	1.8 ± 0.2			
	15	1.18 ± 0.03	17.70 ± 0.05	1.7 ± 0.1			
	25	3.67 ± 0.10	40.0 ± 0.7	1.8 ± 0.1	3.67 ± 0.08	36.5 ± 0.5	17.4 ± 2.4
	35	10.0 ± 0.3	92.8 ± 0.5	2.0 ± 0.1			
8	5	2.43 ± 0.07	25.8 ± 0.5	1.7 ± 0.1			
	15	7.63 ± 0.06	61.5 ± 0.7	1.7 ± 0.1			
	25	23.0 ± 0.6	141 ± 1	2.0 ± 0.1	22.8 ± 0.7	130 ± 1.5	28.4 ± 5.5
	35	61.1 ± 1.5	302 ± 3	2.0 ± 0.1			
9	5	0.95 ± 0.02	23.3 ± 0.25	1.8 ± 0.1			
	15	3.02 ± 0.07	56.5 ± 0.3	2.2 ± 0.1			
	25	9.07 ± 0.23	106.8 ± 1.0	1.9 ± 0.1	9.04 ± 0.20	99.0 ± 1.2	18.6 ± 2.0
	35	25.9 ± 0.6	263 ± 3	2.4 ± 0.2			
4-OCH_3	25				1.24 ± 0.01	6.28 ± 0.10	
4-CH_3	25	1.19 ± 0.05	17.3 ± 0.5	2.2 ± 0.1	1.22 ± 0.07	16.20 ± 0.04	
H	25	1.06 ± 0.04	35.2 ± 1.4	2.0 ± 0.2			
4-Cl	25	0.91 ± 0.01	48.5 ± 1.5	1.8 ± 0.1			
3-Cl	25	0.795 ± 0.010	79.1 ± 0.9	2.1 ± 0.1			
3-CF_3	25	0.762 ± 0.010	82.2 ± 3.5	2.2 ± 0.2			
3-NO_2	25	0.530 ± 0.005	213 ± 8	3.9 ± 0.5			
4-NO_2	25	0.610 ± 0.005	331 ± 6	2.5 ± 0.1			

[a] Figures are standard deviations. [b] ±0.1 °C. [c] Catalytic enolization rate coefficient defined by the equation $k_{1a} = k_I/[H^+]_a$, where $[H^+]_a$ is the analytical proton concentration. [d] Apparent second-order rate coefficient for enol bromination, relative to free bromine (see eq 5). [e] Ratio of the second-order bromination rate coefficients associated to free bromine and tribromide ion, respectively. [f] Apparent second-order rate coefficient for enol iodination, relative to free iodine (see eq 5). [g] Ratio of the second-order iodination rate coefficients associated to free iodine and triiodide ion, respectively.

Encounter Control of Enol Halogenation Rate Constants.[27] Our previous conclusion that halogen addition to simple enols is encounter controlled in water was reached by taking into account the fact that the k_{II} values observed for the chlorination, bromination, and iodination of acetone and of 3-pentanone are identical.[13] At about the same time this latter work was published, Deno and Fishbein[28] claimed that chlorine reacts with 2-butanone enols six times faster than bromine does. This disturbing result was obtained by following the ratio of the formed 1-X and 3-X halo isomers as a function of sulfuric acid concentration in very concentrated media. They observed that the 1-X/3-X ratio depends on X with inflection points around 35 and 45% H_2SO_4 for chlorination and bromination, respectively. These results were ascribed to the different reactivities of chlorine and bromine which make the change in the rate-limiting step, from rate-limiting enolization to rate-limiting halogen addition, dependent on acidity. The factor of 6 was then estimated by assuming that the enolization rates are proportional to the H_0 acidity function. Unfortunately, previously published data on acid concentration effects on enolization had shown that this hypothesis is not true. Indeed, data for acetone[29] and for 3-pentanone[30] exhibit bell-shaped curves with maxima around 40 or 60% H_2SO_4 and only very small increases of the enolization rate constant in passing from 35 to 45% H_2SO_4. This means that the increase of the enolization rate constant of 2-butanone in passing from 35 to 45% H_2SO_4 is certainly far smaller than 6 and, consequently, that the difference in reactivity between chlorine and bromine is, in fact, very slim.

Further evidence in favor of encounter control has been obtained more recently in our laboratory from a study of acetone and acetophenone iodination in basic buffered solutions.[31,32] It was observed that the variations of the second-order rate constant k_{II} vs. pH and iodide ion concentration are exactly those expected if it is assumed that the reactions of enol with I_2 and IOH, and of enolate with I_2, IOH, I_2OH^-, and I_3^-, are all encounter controlled. Moreover, these data yield a value of the acidity constant of acetophenone enol ($pK_a = 10.4$) which is fully in agreement with that published recently by Haspra et al. (10.34).[33]

Similar k_{II} values are observed here for free halogen iodination and bromination of cycloalkanones, whatever the ring size, and for 4-methylacetophenone. So, it can be considered that enol iodination and enol bromination are both encounter controlled for these compounds. Similarly, since 4-methoxyacetophenone enol is certainly intrinsically more reactive than 4-methylacetophenone enol,[34] the encounter-control property is surely also valid

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(26) The hydronium-catalyzed enolization rate constant for cyclohexanone is in perfect agreement with the data reported in literature: 23 × 10^{-5} $M^{-1}\,s^{-1}$ (ref 14), (21–23) × 10^{-5} $M^{-1}\,s^{-1}$ (Audsley, A. J.; Quicq, G. R.; Littler, J. S. *J. Chem. Soc., Perkin Trans. 2.* **1980**, 557–560). Relative values as a function of ring size from cyclopentanone to cyclooctanone (1, 3.3, 0.60, and 3.7) are comparable with those observed in acetic acid–water solutions (90:10), at 29.9 °C: 1,5.3, 0.68, and 4.0) (Shechter, H.; Collis, M. J.; Dessy, R.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905–2910).

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Table II. Rate and Equilibrium Constants for the Enolization of Aliphatic, Alicyclic, and Aromatic Ketones at 25 °C in Aqueous Solution

ketone	$10^8 K_{HS}^{SH}$ [a]	$10^5 k_1$, M^{-1} s^{-1} [b]
aliphatic		
acetone	0.35[c]	2.84[c]
pentanone-3	2.1[c]	2.76[c]
2,4-dimethyl-3-pentanone	0.91[c]	0.17[c]
alicyclic		
cyclopentanone	1.01	6.9
cyclohexanone	23.0	23.3
cycloheptanone	0.80	4.18
cyclooctanone	2.8	26.1
cyclononanone	2.1	10.3
acetophenones ($XC_6H_4COCH_3$)		
X = 4-OCH_3	0.135	1.43
X = 4-CH_3	0.34	1.41
X = H	0.70	1.22
X = 4-Cl	0.97	1.05
X = 3-Cl	1.58	0.915
X = 3-CF_3	1.65	0.870
X = 3-NO_2	4.3	0.610
X = 4-NO_2	6.6	0.700

[a] Keto-enol equilibrium constant calculated from $k_{II}^{Br_2}$ data (Table I) (except for **6**) by taking into account a value of 5 × 10^9 M^{-1} s^{-1} for the addition of bromine to enol. For **6** (4-methoxyacetophenone) K_{HS}^{SH} is deduced from the kinetic data for iodination; a factor of 1.08 is accounted for the small differences between second-order rate constants for bromination and iodination, as observed for **7** and most of other ketones. [b] Hydronium-catalyzed enolization rate constant deduced from the sulfuric acid-catalyzed rate constant (listed in Table I) by taking into account a factor of 1.15 as observed previously for acetone (see ref 24). [c] Calculated from $k_{II}^{Br_2}$ data from ref 13. These values differ from those given in this reference since K_{HS}^{SH} was previously calculated by using a value of 10^9 M^{-1} s^{-1} for the addition of bromine to enols.

for this compound. In contrast, extension to other substituted acetophenone enols (for which comparisons between iodination and bromination have not been made) is less certain since they are intrinsically less reactive. However, it can be noted from results in Table I that the ratio $k_{II}^{Br_2}/k_{II}^{Br_3^-}$, which is equivalent to $k_2^{Br_2}/k_2^{Br_3^-}$, is small (≈2) and almost the same for reactive enols (for which the diffusion control seems certain) as for intrinsically less reactive enols. This probably means, as shall be assumed below, that the encounter-control property is valid for bromination whatever the ring substituent. It can be noted that this does not imply that enol iodination is necessarily diffusion controlled for all the substituents on which iodination experiments were not performed.

Unlike Br_3^-, the reactivity of which is only half of that of molecular bromine, I_3^- reacts more slowly with enols; this means that triiodide ion reactivity is not encounter controlled although it does not depend markedly on ring size in the cycloalkanone series.

When encounter controlled, the rate constants of halogen addition on enols can be estimated by means of the Smoluchowski equation[35]

$$k_2^{X_2} = \frac{4\pi N_A \sigma}{1000}(D_{X_2} + D_{SH}) \qquad (7)$$

where D_{X_2} and D_{SH} are the diffusion coefficients of halogen and of enol, respectively. For enol bromination, if one takes D_{SH} = 10^{-5} cm^2 s^{-1} (which is about the diffusion coefficient of solvent hydrogen-bonded compounds, such as carboxylic acids)[36] and σ = 5 Å, as the closest approach distance, $k_2^{Br_2}$ can be calculated to be 10^{10} M^{-1} s^{-1}, if the diffusion coefficient of bromine (1.49 × 10^{-5} cm^2 s^{-1})[37] is allowed for.[38] However, on glancing through the literature, it appears that the rate constants of encounter-controlled processes are often smaller by a factor of 2–3 than those calculated from the Smoluchowski equation.[39] In the following we shall admit 5 × 10^9 M^{-1} s^{-1} as the most probable value for the halogen addition rate constant. It can be assumed that this parameter is known within a factor of 2.

Table III. Thermodynamic and Extrathermodynamic Parameters for the Enolization of Cycloalkanones[a]

n in $C_nH_{2n-2}O$	$\Delta H^{\ddagger}_1$, kcal mol^{-1} [b]	$\Delta S^{\ddagger}_1$, cal mol^{-1} K^{-1} [b]	$\Delta H°$, kcal mol^{-1} [c]	$\Delta S°$, cal mol^{-1} K^{-1} [d]
5	18.14 ± 0.20	−16.7 ± 0.7	10.44 ± 0.34	−1.3 ± 1.2
6	18.22 ± 0.08	−14.0 ± 0.3	8.02 ± 0.43	−3.3 ± 1.5
7	17.99 ± 0.12	−18.2 ± 0.6	9.39 ± 0.29	−5.5 ± 1.0
8	17.75 ± 0.12	−15.3 ± 0.4	9.18 ± 0.05	−3.7 ± 0.2
9	18.13 ± 0.09	−16.1 ± 0.3	8.71 ± 0.50	−5.6 ± 1.8

[a] Figures are standard deviations. [b] Enthalpy and entropy of activation for enolization, calculated by plotting ln k_1 − ln T vs. $1/T$. [c] Standard enthalpy difference between ketone and enol (298 K), calculated from the variations with temperature of the apparent second-order rate constant by application of the equation $\Delta H° = \Delta H^{\ddagger}_{II} - B$. B(= 4.23 kcal mol^{-1}) is the temperature coefficient of the viscosity variations (see eq 9). [c] Standard entropy difference between ketone and enol (298 K); $\Delta S°$ is considered to be equal to the apparent entropy of activation $\Delta S^{\ddagger}_{II}$ which is determined from the variations with temperature of the second-order rate constant for bromination.

The relative variations of $k_2^{Br_2}$ with temperature can be calculated by means of eq 8, which is established from eq 7 and from the classical Stokes–Einstein equation.[35]

$$(k_2^{Br_2})_{T_2}/(k_2^{Br_2})_{T_1} = \eta_{T_1}T_2/\eta_{T_2}T_1 \qquad (8)$$

where (T_1 and T_2 = two experimental absolute temperatures; η_{T_1} and η_{T_2} = the corresponding viscosities of water.

This equation means that the bromine addition rate constant is inversely proportional to the viscosity of the medium. On the other hand, it can be established that η fits the following empirical equation in the 5–35° range (b and B are adjustable parameters).

$$\eta = be^{B/RT} \qquad (9)$$

Therefore, the apparent enthalpy of activation of the encounter-controlled bromine addition rate constant is B (=4.23 kcal mol^{-1})[40] and, if one considers the estimated rate constant at 25 °C (5 × 10^9 M^{-1} s^{-1}, to which corresponds ΔG^{*} = 4.22 kcal mol^{-1}), the apparent entropy of activation is nearly zero. As we shall see below, these remarks will be useful for estimating the standard entropy and enthalpy data for keto–enol equilibrium.

Keto–Enol Equilibrium Constants. Since the diffusion coefficients of enols are not expected to depend markedly on ring size and on substituent, and since their variations are compensated by variations of the σ term in eq 7,[41] diffusion-controlled rate

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(35) (a) Moelwyn-Hughes, E. A. "The Chemical Statics and Dynamics of Solutions", Academic Press: London, 1971; pp 98–113. (b) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1–49.

(36) Albery, W. J.; Hitchman, M. L.; Ulstrup, J. *Trans. Faraday Soc.* **1968**, *64*, 2831–2840.

(37) Albery, W. J.; Greenwood, A. R.; Kibble, R. F. *Trans. Faraday Soc.* **1967**, *63*, 360–368.

(38) A value of 10^9 M^{-1} s^{-1} has been erroneously derived in ref 13. This makes the deduced keto–enol equilibrium constants underestimated.

(39) Some examples of diffusion-controlled reactions implying halogens have been reported: a rate constant of 6.2 × 10^9 M^{-1} s^{-1} (25 °C) was measured for complexation of iodine to triiodide ion whereas calculations gives 1.5 × 10^{10} M^{-1} s^{-1} (Turner, D. H.; Flynn, G. W.; Sutin, N.; Beitz, J. V. *J. Am. Chem. Soc.* **1972**, *94*, 1554–1559); the rate constants for bromine addition to the anions of uracil and 1-methyluracil are 6 × 10^9 and 7.9 × 10^9 M^{-1} s^{-1} (30 °C), respectively (Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830–835).

(40) The value of B, 4.23 kcal mol^{-1}, was obtained by plotting ln η against $1/T$ for 5, 15, 25, and 35 °C, and using the least-squares treatment (data from "CRC Handbook of Chemistry and Physics", 59th ed.; CRC Press: West Palm Beach, Fl., 1970; p F51).

(41) The encounter-controlled rate constant for halogen addition to enols is proportional to $(r_{SH} + r_{X_2})^2/r_{SH}r_{X_2}$, as the result of combining eq 7 with the Stokes–Einstein equation which expresses that the diffusion constants are inversely proportional to radii (r_{SH} and r_{X_2}, radii of enol and halogen molecules, respectively). As emphasized in ref 13, the rate constant is, therefore, approximately independent of radii for small molecules, since the variations of the square term are roughly compensated by those of the product term.

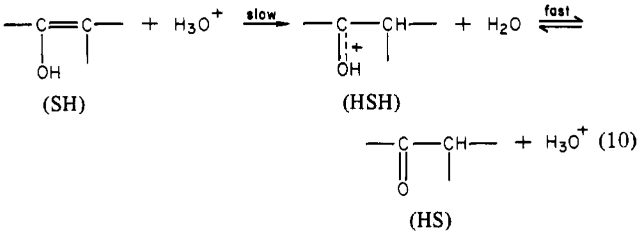
constants for halogen addition to enol must be approximately enol independent. The enolization equilibrium constants are therefore determined by taking into account the estimated rate constant for addition. Such calculated values are listed in Table II. It should be stressed that these results depend on the value attributed to $k_2^{Br_2}$ (or $k_2^{I_2}$). Since the uncertainty in the encounter-controlled rate constant is estimated to be about 2, the uncertainty in log K_{HS}^{SH} is about 0.3 unit.

Temperature Effects. From the kinetic data for cycloalkanones, the least-squares treatment of the linear relationship observed by plotting ($\ln k_1 - \ln T$) and ($\ln k_{II}^{Br_2} - \ln T$) vs. $1/T$ leads to apparent $\Delta H^{\ddagger}{}_{I}$, $\Delta S^{\ddagger}{}_{I}$, $\Delta H^{\ddagger}{}_{II}$, and $\Delta S^{\ddagger}{}_{II}$ extrathermodynamic parameters. It was assumed that the ratio k_{1a}/k_1 is independent of temperature.

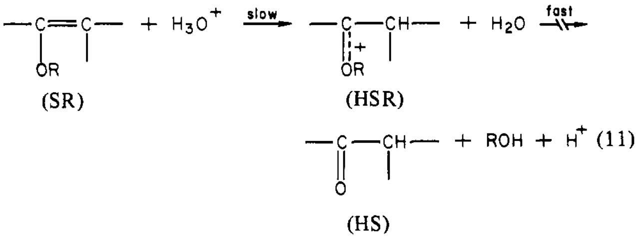
By using the conclusion that the variations of the encounter-controlled rate constant for halogen addition to enols depend only on viscosity variations [corresponding to an apparent enthalpy of activation of 4.23 kcal mol^{-1} and to a negligible entropy of activation (see above)], the $\Delta H°$ and $\Delta S°$ values for keto–enol equilibria can be calculated as $\Delta H° = \Delta H^{\ddagger}{}_{II} - 4.23$ and $\Delta S° = \Delta S^{\ddagger}{}_{II}$. The results are listed in Table III.

Discussion

Ketonization Rate Constants vs. Enol Ether Hydrolysis Rate Constants. Comparisons between α Brønsted exponents for general acid catalysis (similar α values),[14] as well as between isotope effects[24] (similar solvent isotope effects on the hydronium catalytic rate constants), have led to the conclusion that there are important similarities between the mechanism of enol ketonization and that of enol ether hydrolysis. The rate-limiting step of the two reactions is proton attachment to the double bond with formation either of a hydroxycarbenium–alkylidene oxonium mesomeric ion (HSH) (eq 10) or of an alkoxycarbenium–alkyl alkylidene oxonium mesomeric ion (HSR) (eq 11), respectively.



(SH) (HSH) (HS) (10)



(SR) (HSR) (HS) (11)

It can therefore be expected that the ratio of the enol ketonization and enol ether hydrolysis rate constants depends on the relative abilities of the OH and OR groups to delocalize the formed positive charge. Recently, Tidwell and his collaborators[42] established that the rate constants for proton addition to a double bond conjugated with different substituents Y fit a linear free-energy relationship when the $(\sigma_p{}^+)_Y$ parameters are used (eq 12).

$$\log (k_{H^+})_Y = -10.5(\sigma_p{}^+)_Y - 8.92 \qquad (12)$$

Therefore, if one takes into account the $\sigma_p{}^+$ values of the OR [$(\sigma_p{}^+)_{OEt} = -0.83$,[42b] $(\sigma_p{}^+)_{OMe} = -0.78$[43]] groups and of the OH group (−0.92[43]), the ratios between the hydronium-catalyzed rate constants for enol ketonization (k_{-1}) and the hydronium-catalyzed rate constants for hydrolysis of methyl and ethyl enol ether derivatives, $(k_{hyd})_{Me}$ and $(k_{hyd})_{Et}$, respectively, can be evaluated as $k_{-1}/(k_{hyd})_{Me} = 30$ and $k_{-1}/(k_{hyd})_{Et} = 9$, although these values are only approximate since the Tidwell relationship is rough and does not allow for small substituent effects.

In Table IV are shown the calculated rate constants for enol ketonization, deduced from the K_{HS}^{SH} values (Table II) by taking into account the enolization rate coefficients, as well as the rate constants for hydrolysis of the corresponding methyl[44] and ethyl ethers.[18,19] It can be seen that the predicted ratios are roughly in agreement with those obtained. However, the behavior of cycloalkanone derivatives seems different from that of substituted acetophenones; the enol ketonization/enol ether hydrolysis ratio is about independent of ring size, whereas it depends markedly on substituent in the acetophenone series. Moreover, when log k_{-1} is plotted against log $(k_{hyd})_{Et}$, straight lines are observed with slopes close to 1 (1.07 ± 0.11; $r = 0.984$; $s = 0.09$)[45] and to 0.8 (0.76 ± 0.04; $r = 0.991$; $s = 0.09$) for cycloalkanone and acetophenone derivatives, respectively. This means that *ring-size effects are roughly the same* for the two reactions but that *polar and/or conjugative effects are slightly different.*

The following equation has been obtained by application of the Yukawa–Tsuno treatment[46] under the form recently suggested by Young and Jencks.[47]

$$(\log k_{-1})_X = -(1.57 \pm 0.12)\sigma_X{}^n - (0.75 \pm 0.19)(\sigma_X{}^+ - \sigma_X{}^n) + 3.29 \qquad (13)$$

$$(R = 0.992,\ s = 0.10)^{45,48,49}$$

The two parameters ρ^n (−1.57) and ρ^r (−0.75), which correspond to the sensitivity of the reaction rate constant to the polar effects of the substituted ring and to through-conjugation, respectively, can be compared with the same parameters for proton attachment to different substituted olefinic compounds $XC_6H_4CH(Y){=}CH_2$. In Table V it is shown that the ρ^n and ρ^r values roughly decrease with the ability of the Y group to delocalize the positive charge formed in the transition state. Such behavior has been discussed previously[17] and was explained as the result of the competing resonance between Y and the substituted ring. The observation that the ketonization rate constant depends less markedly on substituent X than does the hydrolysis rate constant is therefore perfectly in agreement with what is expected if one considers the resonance abilities of the OH and alkoxy groups.

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(42) (a) Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357–363. (b) Csizmadia, V. M.; Koshy, K. M.; Lau, K. C. M.; McClelland, R. A.; Nowlan, V. J.; Tidwell, T. T. *Ibid.* **1979**, *101*, 974–983.

(43) Brown, H. C.; Okamoto, Y.; *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987.

(44) Rate constants for the hydrolysis of the substituted methyl styryl ethers have been calculated in standard conditions (water; 25 °C) from the data reported by Loudon and Berke (ref 17) (water–dioxane 95:5; 29.9 °C). A temperature correction was allowed for by assuming an enthalpy of activation of 12 kcal mol^{-1} for the unsubstituted compound, as suggested by the data of Sagatys, D. S. (Ph.D. Thesis, Illinois Institute of Technology, Chicago, 1970), for enol ethers of comparable reactivity. For the other compounds, $\Delta H^{\ddagger}$ was calculated from the $\Delta G^{\ddagger}$ variations with substituents by assuming that the reaction is isoentropic. In order to take into account the difference of solvents, it was assumed that the ratio between the calculated constant for ethyl styryl ether in the dioxane–water mixture at 25 °C and that reported by Kresge et al. (ref 18 and 19) is the same for the substituted ethers whatever the substituent.

(45) In the regression equations, figures after the sign ± are the standard deviations of the regression coefficients; *r* and *R* are the sample and multiple correlation coefficients for linear and multiple regression, respectively; *s* is the standard deviation for regression.

(46) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2274–2286.

(47) (a) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8247. (b) *Ibid.* **1979**, *101*, 3288–3294. See also: Young, P. R.; McMahon, P. E. *Ibid.* **1979**, *101*, 4678–4681.

(48) The σ^n values are those of Van Bekkum, H.; Verkade, P. E.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 815–850 [$\sigma^n = -0.111$ (4-OCH_3); −0.129 (4-CH_3); 0.238 (4-Cl); 0.373 (3-Cl); 0.467 (3-CF_3); 0.710 (3-NO_2); 0.778 (4-NO_2)].

(49) The σ^+ parameters are those given in ref 43 [$\sigma^+ = -0.778$ (4-OCH_3); −0.311 (4-CH_3); 0.114 (4-Cl); 0.399 (3-Cl); 0.520 (3-CF_3); 0.674 (3-NO_2); 0.790 (4-NO_2)].

(50) Sollenberger, P. R.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4261–4271.

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(52) Simandoux, J. C.; Torck, B.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1972**, 4402–4409.

(53) Schubert, W. M.; Keeffe, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 559–566.

Table IV. Comparison of the Rate Constants for Hydronium-Catalyzed Ketonization of Simple Enols with Those of Hydrolysis of the Related Methyl and Ethyl Enol Ethers (Water, 25 °C)

ketone	k_{-1}, $M^{-1}\ s^{-1}$ [a]	$(k_{hyd})_{Me}$, $M^{-1}\ s^{-1}$ [b]	$(k_{hyd})_{Et}$, $M^{-1}\ s^{-1}$ [c]	$k_{-1}/(k_{hyd})_{Me}$	$k_{-1}/(k_{hyd})_{Et}$
aliphatic					
acetone	8100	$278^{d,e}$	579^{f}	29.1	14.0
3-pentanone	1310				
2,4-dimethyl-3-pentanone	187				
alicyclic					
cyclopentanone	6950	218^{d}	454^{f}	31.9	15.3
cyclohexanone	985	38.4^{d}	80^{f}	25.7	12.2
cycloheptanone	5250	209^{d}	436^{f}	25.1	12.0
cyclooctanone	9300	299^{d}	623^{f}	31.1	14.9
cyclononanone	4820	130^{d}	271^{f}	37.1	17.8
acetophenones ($XC_6H_4COCH_3$)					
X = 4-OCH_3	11400	385^{g}	645^{h}	29.6	17.7
X = 4-CH_3	4150	124^{g}	277^{h}	33.5	15.0
X = H	1730	53.3^{f}	$118^{f,h}$	32.5	14.7
X = 4-Cl	1085	16.4^{i}	38.1^{i}	66.2	28.5
X = 3-Cl	580	7.51^{i}	17.5^{i}	77.2	33.1
X = 3-CF_3	530	3.63^{i}	9.7^{i}	146	54.6
X = 3-NO_2	143	1.22^{i}	3.64^{i}	117	39.3
X = 4-NO_2	106	0.723^{g}	2.01^{h}	147	53

[a] Hydronium-catalyzed rate constant for enol ketonization, deduced from the data of Table II as the ratios k_1/K_{HS}^{SH}. [b] Rate constant for hydronium-catalyzed hydrolysis of the methyl enol ether related to the specified ketone. [c] Rate constant for hydronium-catalyzed hydrolysis of the ethyl enol ether related to the specified ketone. [d] Calculated from the rate constant for the homologous ethyl ether using a ratio of 0.48, as suggested previously (see ref 11). [e] This datum differs from that reported by Salomaa, P.; Kankaanperä, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801 ($k_{hyd} = 970\ M^{-1}\ s^{-1}$). However, as pointed out by Guthrie (ref 11), this result is questionable since it is based upon experiments conducted in phosphate buffers where the hydronium ion catalyzed reaction provides only a small contribution to the observed rate, and since it contrasts with the usual pattern, namely that methyl enol ethers react about two times slower than the corresponding ones. [f] From ref 19. [g] From ref 17, calculated by taking into account differences in temperature and in solvent (see footnote 44). [h] From ref 18. [i] Intrapolated by using the Yukawa–Tsuno relationship applied to methyl and ethyl enol ether hydrolysis (see Table V).

Table V. Parameters of the Yukawa–Tsuno Equation Applied to the Variations (with X) of the Rate Constant for Proton Transfer to an Olefinic Double Bond Conjugated with Y, for Compounds Having the General Formula $XC_6H_5C(Y)=CH_2$ [a]

Y	$(\sigma_p^+)_Y$	ρ^n	ρ^r	ref
R_2N^b	−1.7	−1.3	feeble	50
OH	−0.92	−1.57	−0.75	this work
OEt	−0.83	−2.14	−0.77	18
OMe	−0.78	−2.33	−0.97	17
Me^c	−0.31	−3.4	−2.4	51
H	0	-4.0^c	-2.8^c	52
		-3.6^d	-3.4^d	53
CF_3	0.61	−4.0	−4.0	42a

[a] Parameters of the equation $\log [k_{H^+}]_X = \rho^n\sigma^n + \rho^r(\sigma_X^+ - \sigma_X^n) + \log [k_{H^+}]_H$ (where k_{H^+} is the hydronium catalytic constant); the ρ^n and ρ^r parameters are calculated from literature data by using the least-squares treatment. [b] R_2N = morpholino; water-promoted reaction. [c] Catalysis by sulfuric acid. [d] Catalysis by perchloric acid.

Table VI. Comparison of Keto–Enol Equilibrium Constants Obtained by Various Methods (in Water, at 25 °C)

	pK_{HS}^{SH} [a]			
ketone	this work[b]	kinetic estimation[c]	thermochemical estimation[d]	halogen titration
acetone	8.46 ± 0.30	7.02	7.2 ± 0.9 (7.8 ± 0.9)	5.60^e $>6^f$
3-pentanone	7.68 ± 0.30		7.8 ± 1.0 (8.4 ± 1.0)	
cyclopentanone	8.00 ± 0.30	6.70	7.2 ± 1.0 (7.8 ± 1.0)	4.9^f
cyclohexanone	6.64 ± 0.30	5.26	5.7 ± 1.1 (6.3 ± 1.1)	5.4^f
acetophenone	8.15 ± 0.30	6.63	6.7 ± 1.0 (7.3 ± 1.0)	4.7^g
4-methoxy acetophenone	8.87 ± 0.30	7.31		
4-nitro acetophenone	7.18 ± 0.30	4.93		

[a] $pK_{HS}^{SH} = -\log K_{HS}^{SH}$. [b] From Table II. [c] Reference 11. [d] Reference 10; values in parentheses are corrected data (see the text). [e] From ref 3. [f] From ref 7. [g] From ref 58.

Recently, Capon et al.[54] studied the ketonization of acetaldehyde enol formed in situ by decomposition of an enolic orthoester and found that enol ketonization is about 100-fold faster than the hydrolysis of the corresponding ethyl enol ether in an acetonitrile–water mixture. If one considers that the hydronium-catalyzed hydrolysis of ethyl vinyl ether ($1.8\ M^{-1}\ s^{-1}$)[55,56] in water is close to that of 1-(4-nitrophenyl)-1-ethoxyethylene ($2.01\ M^{-1}\ s^{-1}$), this result is in agreement with that observed here. This means that the estimated enol ketonization/enol ether hydrolysis ratios are reliable. Conversely, *it cannot be assumed that the ketonization rate constants are equal to those for the related methyl ethers.*

Keto–Enol Equilibrium Constants. The keto–enol equilibrium constants reported in this work are much smaller than those obtained by using the titration method as can be seen in Table VI. Moreover, it can be noted that the relative ordering of enol contents for cycloalkanones (cyclohexanone > cyclopentanone) is opposite to that found by Bell and Smith,[7] who reported that cyclopentanone contains more enol than does cyclohexanone in aqueous solutions. By contrast, our results are in agreement with Hine and Arata conlcusions[9] that cyclohexanone solutions must contain more enol than do cyclopentanone ones and with recent ab initio calculations.[57]

The bromine titration method was recently applied to acetophenone by Novak and Loudon who reported $K_{HS}^{SH} = 1.92 \times 10^{-5}$ in 40% *tert*-butyl alcohol–water.[58] This value, which has been considered by the authors to be valid in pure water, can be combined with the recent data on acetophenone enol acidity ($pK_a = 10.34$)[33] to give the acidity constant of acetophenone to enolate.

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(54) Capon, B.; Rycroft, D. S.; Watson, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 724–725.

(55) Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B* **1967**, 58–61.

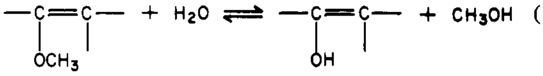
(56) Salomaa, P.; Kankaanperä, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801.

(57) Noack, W. E. *Theor. Chim. Acta* **1979**, *53*, 101–119.

(58) Novak, M.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 2494–2498.

The result obtained this way, $pK_a = 15.05$, is about 3–6 pK units less than the estimated values reported in literature (pK_a = 17.7–21.5).[59–62] On the other hand, the acidity constant deduced from the keto–enol equilibrium constant obtained in this work (pK_a = 18.5) is far more in agreement with that expected.

Comparison with Guthrie's results, obtained from calorimetric data on ketone and methyl enol ether heats of formation[10] (Table VI), shows that our results are about 10-fold smaller. This might arise from a misevaluation of the Gibbs standard free energy for the following equilibrium (eq 14) in the Guthrie procedure. It



$$\underset{\mathrm{OCH_3}}{-\mathrm{C}}=\mathrm{C}- + \mathrm{H_2O} \rightleftharpoons \underset{\mathrm{OH}}{-\mathrm{C}}=\mathrm{C}- + \mathrm{CH_3OH} \qquad (14)$$

was actually assumed that $\Delta G°$ for this equilibrium can be calculated from an experimental equation giving the Gibbs free energy of alcohol–ether equilibria as a function of alcohol acidity constant,[63] by taking into account the pK_a acidity constants of enols. However, since this equation is valid only if resonance does not make an important contribution to acidity, and since this is clearly not the case for enols, the derived keto–enol equilibrium constants might be slightly erroneous. An alternative procedure would be to assume that $\Delta G°$ for acetophenone enol–methyl styryl ether equilibrium is identical with that measured for the phenol–anisole equilibrium ($\Delta G° = 0.81$ kcal mol^{-1}).[64] It should indeed be noted (a) that the acidity constant of acetophenone enol (10.34)[33] is close to that of phenol, (b) that the resonance contributions to acidities (conjugation of a double bond with the charged oxygen atom) are probably about the same, and (c) that the steric changes in going from enol to methyl ether and from phenol to methyl anisole are comparable.[65] According to this hypothesis, log K_{HS}^{SH} for acetophenone can be calculated to be −7.3 instead of −6.7 as reported by Guthrie.[10] This means that the Guthrie data on −log K_{HS}^{SH} are probably 0.5–0.6 unit too low. With this correction, there is satisfactory agreement between the data estimated by using the thermodynamic approach and that reported in this work, if the uncertainty limits are allowed for.

The results reported in Table II show that an electron-withdrawing substituent increases the enol content at equilibrium. When log K_{HS}^{SH} is plotted against the Brown–Okamoto σ^+ parameters,[43,49] a good linear relationship is observed (eq 15). The

$$\log (K_{HS}^{SH})_X = (1.02 \pm 0.08)\sigma_X{}^+ - 8.14 \qquad (15)$$

$$(r = 0.983;\ s = 0.11)^{45}$$

Yukawa–Tsuno treatment[46,47] does not improve the correlation very significantly ($\rho^n = 1.20 \pm 0.13$; $\rho^r = 0.73 \pm 0.19$; $R = 0.989$; $s = 0.10$). These substituent effects on the keto–enol equilibrium constant can easily be explained by considering the polar and resonance effects on the stability of the two tautomeric forms. First, since it was observed previously that substituent effects on acetal–enol ether equilibrium in methanol are almost unperceivable for acetophenone derivatives,[66] conjugation between the double bond and the substituted aromatic ring, as well as polar interactions, do not introduce important relative energy variations of the enol form. Secondly, polar and resonance effects on the keto form are known to be large and can be estimated from equilibrium data for nucleophilic additions on benzaldehydes and acetophenones, when the effects can be explained as mainly due to polar and through-resonance interactions in the initial state.[67] Since for such reactions, linear free-energy relationships, with slopes close to unity, are usually observed[68] by plotting equilibrium constants vs. σ^+ parameters, a log K_{HS}^{SH}–$\sigma_X{}^+$ linear plot with slope near 1 is fully in agreement with that expected.

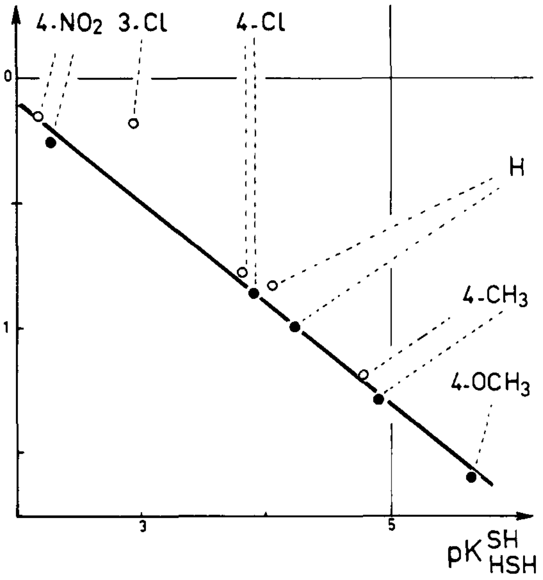
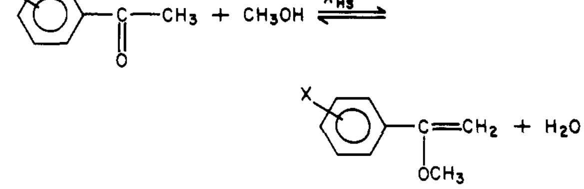


Figure 2. Rate–equilibrium correlation for the rate-limiting step of substituted acetophenone enolization. CH acidity constants (pK_{HSH}^{SH}), which correspond to enol formation from the substituted acetophenone conjugated acids, are deduced from the keto–enol equilibrium constants reported in this work and from literature data (ref 70, open circles; ref 71, closed circles) on OH acidity constants of substituted acetophenone conjugated acids.

The keto–enol equilibrium constants for acetophenones are also in agreement with the data we reported recently for the ketone–enol ether equilibria in methanol (eq 16).[66] For this reaction,



(16)

which is closely analogous to enol formation, it was observed that the equilibrium constants fit the following equation:[69]

$$\log (K_{HS}^{SMe})_X = (1.45 \pm 0.05)\sigma_X{}^n + (0.88 \pm 0.09)(\sigma_X{}^+ - \sigma_X{}^n) - 6.30 \qquad (17)$$

$$(R = 0.997;\ s = 0.05)^{45,48,49}$$

The ρ^r is almost identical with that observed for the keto–enol system (eq 15), whereas the ρ^n is slightly different. This probably results from the solvent influence on the susceptibility to polar interactions and from small variations with X of the energy difference between enol and enol ether, as expected from the Guthrie data on alcohol–ether equilibria.[63]

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[62] (a) Earls, D. W.; Jones, J. R.; Rumney, T. G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 878–880. (b) Kankaanperä, A.; Salomaa, P.; Oinonen, L.; Mattsen, M. *Finn. Chem. Lett.* **1978**, 25–28.

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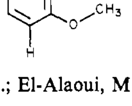
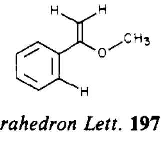
[64] Hine, J.; Weimar, R. D. *J. Am. Chem. Soc.* **1965**, *87*, 3387–3396.

[65] The Guthrie equation (ref 63) which makes it possible to calculate the standard Gibbs free-energy differences for alcohol–methyl ether equilibria includes a term corresponding to the change in strain in going from alcohol to methyl ether. This steric contribution to the acetophenone enol–methyl ether equilibrium constant can be considered to be about equal to the similar term for phenol–anisole equilibrium. Indeed, the methyl–hydrogen cis interactions in methyl α-styryl ether are probably in the same range of magnitude as the methyl–ortho-hydrogen ones in anisole.





[66] Toullec, J.; El-Alaoui, M. *Tetrahedron Lett.* **1979**, 3085–3088.

[67] Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128.

[68] ρ^+ = 1.1 and 1.25 for the addition of HSO_3^- on substituted acetophenones and benzaldehydes, respectively (ref 47a. Geneste, P.; Lamaty, G.; Roque, J. P. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 188–194). ρ^+ = 1.01 for the addition of HCN on substituted benzaldehydes (Ching, W. M.; Kallen, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6119–6124).

[69] Recalculated from the data of ref 66.

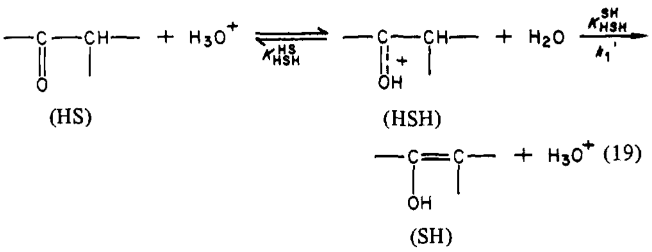
Transition State of Acid-Catalyzed Enolization. By plotting hydronium-catalyzed enolization rate constants vs. σ^n for compounds **6–13**, a good straight line is observed, corresponding to the following equation:

$$\log (k_1)_X = -(0.37 \pm 0.04)\sigma_X^n - 4.90 \qquad (18)$$

$$(r = 0.983;\ s = 0.03)^{45,48}$$

The Yukawa–Tsuno treatment does not improve the relationship ($\rho^n = -0.37 \pm 0.04$; $\rho^r = -0.02 \pm 0.07$; $R = 0.983$; $s = 0.03$). This means that through-resonance effects are not significant as a result of parallel effects on the ketonic ground state and on the transition state.

Recent data on OH acidity constants of the conjugated acids of substituted acetophenones make it possible to calculate the rate constants, k_1' (eq 19), corresponding to proton abstraction from the oxocarbenium ions (HSH), as well as the CH acidity constants of these ions, $K_{\mathrm{HSH}}^{\mathrm{SH}}$. In Figure 2, log k_1' is plotted against p$K_{\mathrm{HSH}}^{\mathrm{SH}}$. Either using the Cox et al. values[70] or those reported by Azzaro et al.[71] for the oxocarbenium to carbonyl compound acidity constants, a straight line, with a slope close to −0.4, is observed.[72] This is in agreement with the α Brønsted exponent observed by varying the catalyst[14,73] (e.g., α = 0.55 and 0.74 for enolization of acetone and cyclohexanone, respectively, catalyzed by carboxylic acids; this means that the rate constants for the base-promoted proton abstraction by carboxylate ions would fit a Brønsted relation with β = 0.45 and 0.26, respectively) and with isotope effects on enolization (for acetone)[24] and ketonization rate constants[24] which are in favor of a transition state model in which a proton is about half-transferred.



$$-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{|}{\mathrm{CH}}- + \mathrm{H_3O^+} \underset{K_{\mathrm{HSH}}^{\mathrm{HS}}}{\rightleftharpoons} -\underset{\underset{\mathrm{OH}}{\|}}{\overset{+}{\mathrm{C}}}-\underset{|}{\mathrm{CH}}- + \mathrm{H_2O} \xrightarrow[k_1']{K_{\mathrm{HSH}}^{\mathrm{SH}}} -\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{H_3O^+} \qquad (19)$$

(HS) (HSH) (SH)

Data on enthalpy and entropy of activation for enolization (Table IV)[74] show that only small variations of $\Delta H^{\ddagger}{}_1$ with ring size are observed, whereas the effects on the enthalpy change in going from ketone to enol are larger. Provided that most of the enthalpy variations result from differences in strain due to the change in carbon atom hybridization, this is in agreement with an early transition state.[75] As a consequence of the small variations of $\Delta H^{\ddagger}{}_1$, ring-size effects on enolization rate coefficients come mainly from $\Delta S^{\ddagger}{}_1$ variations which probably result from the lost of flexibility in going from the initial carbonyl compound to the transition state where the cleaving CH bond must be orthogonal to the carbonyl π nodal plane.[32] It is therefore not surprising that the ordering of enolization rate constants with ring size does not coincide with the ordering of keto–enol equilibrium constants.

Experimental Section

Reagents. All the ketones (**1–13**) are commercially available. Compounds **1–5** and **7–11** were purified by VPC (Varian Aerograph Series 700). The purity was always better than 99.5% and was checked by VPC (Varian Aerograph Series 1200). Compounds **6**, **12**, and **13** were purified by recrystallization in methanol [T = 38–39 °C (**6**), 80–81 °C (**12**), 80 °C (**13**)]. Other reagents were as previously described.[13,15,24]

Kinetic Measurements. The amperometric method for rate determination was similar to that previously described,[13,15,20] except for the use of automatic computer recording.

Ketones were introduced in the cell by using a weighed microsyringe. For **4**, **6**, **12**, and **13** which are solid at room temperature, and for other ketones when the quantity to be introduced was too small, the compound was dissolved in acetic acid. It was verified that acetic acid does not modify the rate constants.

Halogen was produced by halide ion electrolysis (constant current and measure of the electrolysis time) so that the halogen concentration was raised to a value exceeding the chosen $[\mathrm{X_2}]_{\mathrm{a}}^{0}$. The kinetic runs were recorded from $[\mathrm{X_2}]_{\mathrm{a}}^{0}$ up to 80 or 90% of reaction.

Throughout a kinetic run, N points were automatically taken at the rate of one every 0.1 s. A point at time t' was associated to a point at time t, so that $t' - t = \theta$ would be constant and equal to $N \times 0.1/2$ s. The simplest calculations therefore consisted in plotting $\theta/([\mathrm{X_2}]_{\mathrm{a}}^{t} - [\mathrm{X_2}]_{\mathrm{a}}^{t'})$ against $(\ln [\mathrm{X_2}]_{\mathrm{a}}^{t} - \ln [\mathrm{X_2}]_{\mathrm{a}}^{t'})/([\mathrm{X_2}]_{\mathrm{a}}^{t} - [\mathrm{X_2}]_{\mathrm{a}}^{t'})$ and using an ordinary least-squares (OLS) treatment.[76] The slope gave $1/(k_{\mathrm{II}}^{\mathrm{X_2}})_{\mathrm{g}}[\mathrm{HS}]$ and the intercept gave $1/K_{\mathrm{I}}[\mathrm{HS}]$. However, in most cases it was necessary to modify eq 6 in order to introduce two types of corrections: (a) blank reactions of halogen with solvent and (b) slight variations of ketone concentrations. This latter correction was necessary in some cases (mainly for cyclooctanone bromination and iodination) since eq 6 was established by assuming that ketone concentration is constant throughout a run although this was not always so.

To take into account the parallel blank reactions and the ketone concentration variations, eq 2 becomes eq 20, where x is equal to $[\mathrm{X_2}]_{\mathrm{a}}^{t}$,

$$-\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{x}{\dfrac{1}{k_{\mathrm{II}}(a + x)} + \dfrac{x}{k_{\mathrm{I}}(a + x)}} + k_n x^n \qquad (20)$$

a is the ketone concentration *at the end of the run* (it is considered that the ketone concentration at time t is equal to $a + x$ since halogens react stoichiometrically with the ketone), and k_n is the observed n-order rate constant of the blank reaction. By rearranging this equation, it becomes:

$$\left[x + \frac{k_n x^n}{k_{\mathrm{II}}(a + x)} + \frac{k_n x^{n+1}}{k_{\mathrm{I}}(a + x)}\right] \mathrm{d}t = -\left[\frac{1}{k_{\mathrm{II}}(a + x)} + \frac{x}{k_{\mathrm{I}}(a + x)}\right] \mathrm{d}x \qquad (21)$$

Multiplying each member by $(a + x)/x$ and integrating it between t and t' (with $t' - t = \theta$) give eq 22. Equation 23 is then deduced by dividing

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(70) Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2952–2959.

(71) Azzaro, M.; Gal, J. F.; Garibaldi, S.; Grec-Luciano, A.; Calleri, C. *J. Chem. Res., Miniprint* **1979**, 1478–1493.

(72) In a recent report Cox et al. (ref 70) derived the elementary rate constants for water-promoted abstraction of proton from the oxocarbenium ions HSH related to acetophenones. By plotting the logarithm of these rate constants against −p$K_{\mathrm{HSH}}^{\mathrm{HS}}$, these authors observed a linear relationship with a slope of 0.71. However, it can be noted that such a correlation has no real significance since it refers to two different processes, namely, proton attachment on the carbonyl oxygen atom and proton abstraction from the α position. The larger slope observed results from smaller variations of the p$K_{\mathrm{HSH}}^{\mathrm{HS}}$ acidity constant with substituent, as the result of effects in the same direction on the stability of the carbonyl compound and on that of the oxocarbenium ion.

(73) Bell, R. P.; Lidwell, O. M. *Proc. R. Soc. London, Ser. A* **1940**, *176*, 88–113.

(74) $\Delta S°_{298}$ values close to zero for the keto–enol equilibria are fully in agreement with what predicted from elementary considerations. (Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1–33).

(75) A similar conclusion has been obtained by Werstiuk and Banerjee (Werstiuk, N. H.; Banerjee, S. *Can. J. Chem.* **1977**, *55*, 173–176) who observed that the variations of the acid-catalyzed enolization rate constant are roughly parallel to those of p$K_{\mathrm{HSH}}^{\mathrm{HS}}$ for some cyclic and bicyclic ketones. However, such a conclusion would perhaps not have been made if more recent data on p$K_{\mathrm{HSH}}^{\mathrm{HS}}$ (McClelland, R. A.; Reynolds, W. F. *Can. J. Chem.* **1976**, *54*, 718–725) had been taken into account.

(76) An ordinary least-squares (OLS) treatment of the linear regression between two functions y and x requires that (a) the errors in the dependent variable y predominate over the errors in the independent variable x and that (b) the observations of the dependent variable be of equal weight, corresponding to a constant uncertainty on all values of y. Neither of these conditions is met here, since y and x are two different functions of halogen concentration, the noisy observable. However, we preferred using the OLS treatment instead of the more correct weighted least-squares (WLS) treatment since it is not clear whether the amperometric data are obtained with a constant absolute error or a constant error in percentage. Moreover, weighting factors are usually derived by assuming that the errors on x_i and y_i are uncorrelated. Therefore, since the two functions y and x contain the experimental observable, an exact WLS treatment would require highly complicated calculations. Integration between t and t', separated by a constant time interval θ, makes it possible to reduce the changes in the variance of y_i and x_i throughout a kinetic run; in contrast, with integration between zero time and t, relative errors on $(t - t^0)/([\mathrm{X_2}]_{\mathrm{a}}^{0} - [\mathrm{X_2}]_{\mathrm{a}}^{t})$ and on $(\ln[\mathrm{X_2}]_{\mathrm{a}}^{0} - [\mathrm{X_2}]_{\mathrm{a}}^{t})/([\mathrm{X_2}]_{\mathrm{a}}^{0}) - [\mathrm{X_2}]_{\mathrm{a}}^{t})$ would be far larger for the first points than for the last ones. Another important advantage of this procedure lies in the fact that no special importance is attributed to the first point (t = 0), for which the *uncertainty is similar to that for the other points.*

J. Am. Chem. Soc. **1981**, *103*, 5401-5413

$$a\theta = a\int_t^{t'} x\,\mathrm{d}t + \frac{k_n}{k_{\mathrm{II}}}\int_t^{t'} x^{n-1}\,\mathrm{d}t + \frac{k_n}{k_{\mathrm{I}}}\int_t^{t'} x^n dt = \frac{1}{k_{\mathrm{II}}}(\ln x_t - \ln x_{t'}) + \frac{1}{k_{\mathrm{I}}}(x_t - x_{t'}) \quad (22)$$

$$\frac{a\theta}{x_t - x_{t'}} + \frac{a\int_t^{t'} x\,\mathrm{d}t}{x_t - x_{t'}} + \frac{k_n\int_t^{t'} x^{n-1}\,\mathrm{d}t}{k_{\mathrm{II}}(x_t - x_{t'})} + \frac{k_n\int_t^{t'} x^n\,\mathrm{d}t}{k_{\mathrm{I}}(x_t - x_{t'})} = \frac{1}{k_{\mathrm{I}}} + \frac{1}{k_{\mathrm{II}}}\,\frac{\ln x_t - \ln x_{t'}}{x_t - x_{t'}} \quad (23)$$

each member by $(x_t - x_{t'})$. A comparison with eq 6 shows that this equation contains three correcting terms in which the implicit integrals can be calculated numerically from the experimental curve by using the trapezoidal method. However, since two of these terms include the unknown constants k_{I} and k_{II}, an iterative calculation process must be applied. To initiate this iterative process, a first set of k_{I} and k_{II} values was obtained by neglecting the two terms containing k_{I} and k_{II}. Subsequently, calculations were performed by correcting the left-hand term and by applying a test of convergence of 0.2% to k_{I} and k_{II}. The blank reaction parameters, n and k_n, were determined before each series of runs (n was usually lying between 0.7 and 1.0) and a was estimated from the initial ketone concentration and from the amount of halogen which had reacted with the ketone. All results obtained by using these corrections never deviated more than 10% from uncorrected ones.

We usually prformed several runs on the same ketone and halide solution at different halogen concentrations. We then had to correct halide and ketone concentrations from one run to the next by considering the formation of α-iodo or α-bromo ketone. We then assumed that the halogeno compounds are much less reactive, as was previously observed.[77]

Supplementary Material Available: Tables S1, S2, S3, and S4 of primary kinetic data (10 pages). Ordering information is given on any current masthead page.

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(77) Watson, H. B.; Yates, E. D. *J. Chem. Soc.* **1932**, 1207-1215.

Formation of Stable Bilayer Assemblies in Water from Single-Chain Amphiphiles. Relationship between the Amphiphile Structure and the Aggregate Morphology

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Abstract: The aggregate morphology of 62 single-chain amphiphiles prepared in these laboratories was examined by electron microscopy, and the relationship between the structural elements of the amphiphile and the aggregate morphology was discussed. The aggregate morphology includes globules, multi-, and single-walled vesicles, rods, tubes, and disks. Some of the morphologies are designed as pre-lamella, pre-rod, pre-disk, etc., because of their incomplete assemblage. The basic building block of these morphologies is the bilayer assembly. The structural elements of the amphiphile are conveniently divided into (1) flexible tail, (2) rigid segment, (3) hydrophilic head group, (4) spacer group, and (5) additional interacting group. The first three elements are essential for stable self-assembly, but all five elements affect the aggregate morphology. The flexible tail is linear methylene chains (or their related structures) of C_7 or longer. The rigid segment usually consists of two benzene rings (biphenyl, diphenylazomethine, azobenzene, etc.) and affects the aggregate morphology by its dipolar property and geometry (conformation). The bilayer formation is promoted by dipolar rigid segments and the high-curvature aggregate (rods and tubes) results from bent rigid segments. The disk-shaped aggregate can be obtained from a combination of the extended and bent conformations of a rigid segment. This is supported separately by the morphology change of a two-component system which contains the extended and bent rigid segments. Among the hydrophilic head groups used (trimethylammonium, modified ammonium, phosphate, sulfonate, phosphocholine, and poly(oxyethylene)), the trimethylammonium group appears to be least effective for the molecular alignment. The spacer group is the methylene chain inserted between the rigid segment and the head group. Longer spacers (usually C_{10}) yield well-defined aggregates more effectively than the shorter ones. A most notable example of the additional interacting group is given by the ester group at the tail end, which transforms globular aggregates into vesicles. The aggregation behavior other than the morphology was studied for typical ammonium amphiphiles with different rigid segments. Finally, the light-induced dynamic control of the aggregate morphology was discussed in relation to the static control based on the amphiphile structure. The temperature dependence of the fluorescence intensity of the biphenyl rigid segment was shown to depend on the aggregate morphology.

The biological cell contains many kinds of organelles such as nucleus, mitochondria, ribosome, and the Golgi apparatus. These organelles have characteristic morphologies that are directly related to the respective biological functions.[1] The organelles are self-assembling systems which are composed mostly of proteins and biomembranes. The importance of morphology in relation to the function is obvious in the biological world; however, the morphology-related function is virtually nonexistent in chemistry. If synthetic, self-assembling systems which possess designed morphologies can be developed, a totally new field of chemistry may emerge.

The present study is our initial attempt to this direction. The micellar system and other aqueous aggregates have served this purpose to a certain extent; however, they are usually very fluid and cannot have fixed morphologies.[2] It has been shown since 1977[3,4] that a variety of single-chain and double-chain amphiphiles

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(1) E.g.: Lehninger, A. L. "Biochemistry"; Worth Publishers: New York, 1975.

(2) E.g.: (a) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975. (b) Menger, F. M. *Acc. Chem. Res.* **1979**, *12*, 111-117.

(3) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3860-3861.

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