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Ring Substituent Effects on Acetophenone Dimethyl Acetal Formation. 2. Dual-Parameter Treatment of Kinetic Data for Acid-Catalyzed Acetal Formation and Hydrolysis in Methanol Containing Small Amounts of Water[1]

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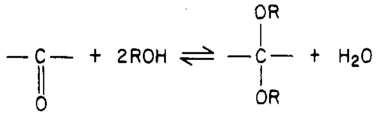
The rates of formation and hydrolysis of para- and meta-substituted acetophenone dimethyl acetals have been measured, by a water-concentration method, in methanol containing HBr and small amounts of water. The rate coefficients for pure anhydrous methanol have been extrapolated. Acid and water-concentration effects are consistent with the usual mechanism for acetal hydrolysis in water, but the rate-limiting step in the hydrolysis direction corresponds to water addition to the hemiacetal-yielding oxocarbenium ion. Substituent effects on both extrapolated rate coefficients fit the Young–Jencks-modified Yukawa–Tsuno equation. The validity of this equation and its usefulness for separating polar and conjugative effects are discussed.

Although there is a great deal of work on acetal hydrolysis in water or in media in which water is one of the major components,[2] there is little work on the kinetics of acetal–carbonyl compound interconversion in alcohols (eq 1), i.e., under conditions corresponding to the formation



$$-\overset{\displaystyle O}{\overset{\|}{C}}- + 2ROH \rightleftharpoons -\underset{OR}{\overset{OR}{C}}- + H_2O \qquad (1)$$

of fairly stable acetals. Only Davis et al.[3] have studied benzaldehyde dimethyl acetal formation and hydrolysis in a 95% methanol–water mixture. We recently[1] reported that a water-concentration jump method is highly useful for determining ketone-to-acetal equilibrium constants in methanol, because it avoids the determination of the small amounts of water at equilibrium. The same jump procedure can also be used for measuring the rates of acid-catalyzed interconversion of ketone and acetal. In this context, its main advantage lies in the fact that the exact concentrations of water can be derived, thereby making it possible to examine the reaction mechanism in pure methanolic conditions. We report here the results obtained for substituted acetophenones in methanol.

Kinetic data on the acetophenone–acetophenone dimethyl acetal system are of great interest as regards to the appropriateness and the usefulness of free energy relationships for the separation of polar and conjugative effects. This system is a good reaction model for studying substituent effects on the ground states and on the transition state, because the forward and reverse rate constants can be determined with accuracy.

Results

Acetal formation in methanol and partial acetal hydrolysis, due to the addition of small amounts of water, were studied by monitoring UV absorbance variations. As described previously,[1] two sets of kinetic curves, corresponding to absorbance decrease and absorbance increase, respectively, were observed. The absorbance values at equilibrium before, $(A_\infty)_1$, and after, $(A_\infty)_2$, the water-concentration jump make it possible to determine the water concentration very accurately.

A significant advantage of the procedure is that, due to their large absorptivities, only very small concentrations of acetophenones are needed. Consequently, the changes in water concentrations during the runs are negligible, and the rates are first order for direct and reverse reactions. It follows that eq 2 and 3, corresponding to the first and

$$\ln [A_t - (A_\infty)_1] = -(k_F + k_H)t + \ln [A_o - (A_\infty)_1] \qquad (2)$$

$$\ln [(A_\infty)_2 - A_t] = -(k_F + k_H)t + \ln [(A_\infty)_2 - (A_\infty)_1] \qquad (3)$$

second run, respectively, can be derived directly by assuming that the absorbance at time t can be written as

$$A_t = \epsilon_{ke}[ke]_t + \epsilon_{ac}[ac]_t$$

where ϵ_{ke} and ϵ_{ac} are the molar absorption coefficients of ketone and acetal, respectively, and where bracketed symbols correspond to concentrations. In eq 2 and 3, k_F and k_H are the pseudo-first-order rate coefficients for the forward and reverse (hydrolysis) processes; they are related to concentration equilibrium constants K_c by eq 4. The

$$k_F/k_H = K_c a_{MeOH}^2/[H_2O] \qquad (4)$$

$k_F + k_H$ sums have been determined for different water concentrations, and the k_F and k_H values are calculated by means of eq 5 and 6. Typical data for 3-nitroacetophenone at constant acid concentration are listed in Table I. Water concentrations therein are those calculated by eq 7 from the absorbances $(A_\infty)_1$ and $(A_\infty)_2$ at equilibrium

$$k_F = (k_F + k_H)/(1 + [H_2O]/K_c a_{MeOH}^2) \qquad (5)$$

$$k_H = (k_F + k_H)/(1 + K_c a_{MeOH}^2/[H_2O]) \qquad (6)$$

$$[H_2O] = K_c a_{MeOH}^2 (A_\infty - c\epsilon_{ac})/(c\epsilon_{ke} - A_\infty) \qquad (7)$$

(c is the stoichiometric ketone concentration: c = [ke] + [ac]). It can be noted that the water concentrations calculated in this way do not include water engaged in H_3O^+ which is in equilibrium with lyonium ion $CH_3OH_2^+$ (eq 8).

$$CH_3OH_2^+ + H_2O \overset{K_r}{\rightleftharpoons} CH_3OH + H_3O^+ \qquad (8)$$

Data in Table I show that k_F and k_H at constant stoi-

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(1) Part 1: Toullec, J.; El-Alaoui, M.; Kleffert, P. *J. Org. Chem.* **1983**, *48*, 4808–4816.

(2) For a recent review, see: Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1–77.

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Table I. Typical Kinetic Data for 3-Nitroacetophenone–3-Nitroacetophenone Dimethyl Acetal Interconversion at Constant Stoichiometric Acid Concentration[a,b]

$10^2[H_2O]$,[c] M	$10^2(k_H + k_F)$,[d] s^{-1}	10^2k_F,[e] s^{-1}	10^4k_H,[f] s^{-1}	$10^2[CH_3OH_2^+]$,[g] M	k_f,[h] M^{-1} s^{-1}	k_h,[i] M^{-2} s^{-1}
			From First Equilibration[j]			
1.01	1.17	1.12	4.69	9.09	0.124	0.511
1.02	1.19	1.14	4.81	9.13	0.125	0.518
1.07	1.19	1.14	5.03	9.11	0.125	0.517
1.09	1.18	1.13	5.09	9.06	0.125	0.515
1.12	1.18	1.13	5.22	9.04	0.125	0.515
1.16	1.19	1.14	5.36	9.07	0.125	0.510
1.19	1.19	1.13	5.57	9.07	0.125	0.517
1.20	1.20	1.11	5.67	9.04	0.123	0.522
1.30	1.19	1.13	6.07	8.92	0.127	0.523
1.35	1.17	1.11	6.19	8.89	0.125	0.516
1.37	1.17	1.11	6.27	8.88	0.125	0.515
			From Second Equilibration[k]			
2.05	1.16	1.07	9.08	8.50	0.126	0.521
2.39	1.20	1.09	10.8	8.33	0.131	0.542
2.54	1.18	1.07	11.2	8.44	0.126	0.523
3.22	1.19	1.05	14.0	8.15	0.129	0.533
4.32	1.20	1.02	18.2	7.74	0.133	0.544
4.32	1.14	0.967	17.3	7.82	0.124	0.511
6.01	1.15	0.921	22.9	7.29	0.126	0.523
9.00	1.11	0.880	30.1	6.48	0.123	0.517
9.41	1.16	0.834	32.5	6.41	0.130	0.540
20.3	1.13	0.613	51.7	4.65	0.132	0.548
32.2	1.11	0.473	63.6	3.64	0.130	0.543

[a] At 25 ± 0.05 °C. [b] Due to small volume variations when water is added, $[H^+]_{st}$ is not rigorously constant ([HBr] = 9.34–9.60 × 10^{-2} M). [c] Calculated from eq 7 and corrected by taking into account small variations due to acetal formation (water formation) or hydrolysis (water consumption); listed values are those calculated after 1 half-life. [d] Calculated from absorbance–time curves (eq 2 and 3). [e] Calculated from $(k_H + k_F)$ values (eq 5). Calculated from $(k_H + k_F)$ values (eq 6). [g] From eq 9. [h] $k_f = k_F/[CH_3OH_2^+]$. [i] $k_h = k_H/[CH_3OH_2^+][H_2O]$. [j] From kinetic runs corresponding to acetal formation in "dry methanol". [k] From kinetic runs after the water-concentration jumps.

chiometric HBr concentration ($[H^+]_{st} = [CH_3OH_2^+] + [H_3O^+]$) are neither independent of nor proportional to water concentration, but that, if $[CH_3OH_2^+]$ is calculated by eq 9 (K_r = 4.94 M^{-1}),[5] the catalytic constants for $CH_3OH_2^+$, $k_F/[CH_3OH_2^+]$ and $k_H/[CH_3OH_2^+]$, are independent of and proportional to water concentration, respectively (Table I, Figure 1).

$$[CH_3OH_2^+] = [H^+]_{st}a_{MeOH}/(K_r[H_2O] + a_{MeOH}) \quad (9)$$

Similar data were obtained for different substituted acetophenones. However, in some cases, mainly for acetophenone and for acetophenones bearing an electron-releasing substituent, we observed that $k_F/[CH_3OH_2^+]$ is slightly depressed when $[H_2O]$ is increased and that the dependence of $k_H/[CH_3OH_2^+]$ on $[H_2O]$ is not strictly linear. For example, data for 4-methoxyacetophenone show that $k_F/[CH_3OH_2^+]$ decreases by ca. 10% from $[H_2O]$ = 0.0034 M to $[H_2O]$ = 0.048 M. Therefore, catalytic rate constants $(k_f)_m$ and $(k_h)_m$ in *pure anhydrous methanol* have been defined as the limiting values of $k_f = k_F/[CH_3OH_2^+]$ and of $k_h = k_H/[CH_3OH_2^+][H_2O]$, respectively, when the water concentration approaches zero. However, since the small variations of $k_F/[CH_3OH_2^+]$ are not usually linearly related to water concentration, $(k_f)_m$ was calculated as the intercept of the linear plot of $(k_H + k_F)/[CH_3OH_2^+]$ vs. $[H_2O]$ (except for 4-methoxyacetophenone for which the intercept is too small). Moreover, the rate constants determined in this way do not depend on the values attributed to the equilibrium constants. Catalytic rate constants for lyonium ion, $(k_h)_m$, were calculated as $(k_f)_m/K_c a_{MeOH}^2$. Table II lists $(k_f)_m$ and $(k_h)_m$ for meta- and para-substituted acetophenones.

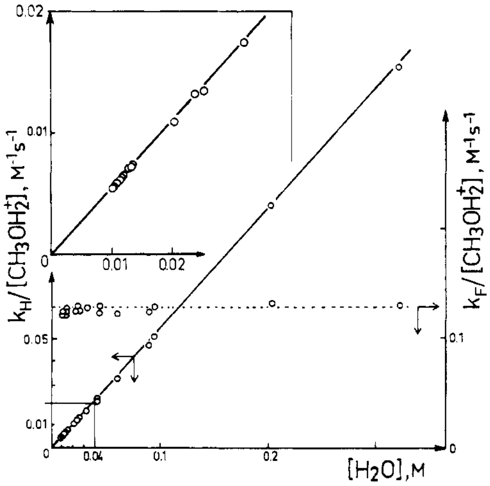
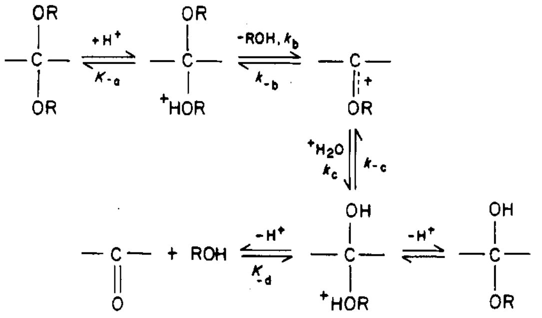


Figure 1. Dependence of the catalytic rate coefficients for 3-nitroacetophenone dimethyl acetal formation and hydrolysis on the concentration of small amounts of water in methanol.

Discussion

Mechanism of Ketone–Acetal Equilibration. A great many studies have been devoted to the mechanism of acid-catalyzed acetal hydrolysis in water and in water–dioxane mixtures. At the beginning of the 1970's, the classical A_1 mechanism (eq 10),[6] corresponding to pree-



(10)

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Table II. Substituent Effects on Forward and Reverse Rate Coefficients for Acetal Formation from Acetophenones[a]

X in $XC_6H_4COCH_3$	$10^2[H^+]_{st}$,[b] M	$10^2[H_2O]$,[c] M	10^3K_c,[d] M	$(k_f)_m$,[e] $M^{-1}\,s^{-1}$	$(k_h)_m$,[f] $M^{-2}\,s^{-1}$
4-OCH_3	0.20	0.33–4.75	2.16 ± 0.09	2.50 ± 0.18	1160
4-CH_3	1.02	0.29–4.10	5.93 ± 0.42	2.38 ± 0.07	401
H	1.02	0.78–10.5	15.5 ± 0.3	1.41 ± 0.02	91
	2.6	1.23–3.42		1.47 ± 0.02	95
	5.5	1.10–7.0		1.44 ± 0.03	93
	10.0	1.18–6.2		1.39 ± 0.04	90
4-F	2.9	1.90–21.1	16.9 ± 0.9	0.795 ± 0.020	47.0
4-Cl	1.0	0.91–6.4	32.8 ± 1.5	0.604 ± 0.024	18.4
	2.9	0.95–5.9		0.615 ± 0.008	18.7
3-Cl	2.9	1.75–21.1	69.3 ± 0.9	0.394 ± 0.004	5.68
	5.8	0.92–12.0		0.386 ± 0.002	5.57
3-CF_3	2.8	1.05–11.9	107 ± 4	0.236 ± 0.002	2.20
	5.9	0.84–5.4		0.240 ± 0.002	2.24
	9.9	0.83–16.2		0.249 ± 0.003	2.32
3-NO_2	9.6	1.01–32.2	244 ± 14	0.126 ± 0.001	0.516

[a] At 25 ± 0.05 °C; errors are standard deviations. [b] Stoichiometric HBr concentration. [c] Range of water concentrations. [d] K_c = [acetal][H_2O]/[ketone]a_{MeOH}^2, calculated from data of ref 1, (a_{MeOH} = 1 in pure anhydrous methanol). [e] Lyonium ion catalytic coefficient for acetal formation, extrapolated to pure methanol. [f] Lyonium ion catalytic rate coefficient for acetal hydrolysis, extrapolated to pure methanol.

quilibrium formation of the acetal conjugated acid, followed by alcohol detachment, hemiacetal formation, and hemiacetal cleavage, appeared to be well-established. However, recent data have shown that this reaction can exhibit a more complicated behavior regarding the timing of the different chemical events (proton transfers, C–O bond dissociation, molecular entity separation, and hemiacetal cleavage). (i) A concerted mechanism has been shown to be valid when the leaving alcohol is an excellent leaving group or when the oxocarbenium ion is a fairly stable reaction intermediate.[7] (ii) Rate-limiting diffusional separation was suggested to account for unexpected general-acid catalysis.[8] (iii) Significant hemiacetal buildup has been observed in some cases, showing that hemiacetal breakdown is not always as fast as assumed.[9]

Whatever the actual mechanism of acetal hydrolysis, it is always taken for granted that oxocarbenium ion formation is slow compared to oxocarbenium ion hydration. This is ascribed to the following inequality (eq 11) which

$$k_c[H_2O] \gg k_{-b}[ROH] \qquad (11)$$

means that the oxocarbenium ion is more easily trapped by bulk water than by the small amounts of alcohol. This inequality is consistent with studies by Cordes and Wenthe[6a,b,10] on 2,2-dimethoxypropane hydrolysis in an equimolecular mixture of D_2O and CD_3OD. These authors showed that the OCD_3/OCH_3 group exchange occurs roughly at the same rate as acetone formation by hydrolysis and concluded that methanol attachment to the oxocarbenium ion is about as fast as water attachment.[11] It follows that the reverse inequality (eq 12) should be valid

$$k_c[H_2O] \ll k_{-b}[CH_3OH] \qquad (12)$$

in methanol containing only small amounts of water. Hence, since it can be assumed that the ketone–hemiacetal interconversion is fast (vide infra), the pseudo-first-order rate constants k_F and k_H for acetal formation and acetal hydrolysis can be expressed by eq 13 and 14. These

$$k_F = k_{-c}[CH_3OH][CH_3OH_2^+]/K_d \qquad (13)$$

$$k_H = k_b k_c[H_2O][CH_3OH_2^+]/K_{-a}k_{-b}[CH_3OH] \qquad (14)$$

equations account for the specific catalytic effect of the lyonium ion $CH_3OH_2^+$ and indicate that k_F and k_H should be independent of and proportional to water concentration, respectively. (In eq 13 and 14, discrete formation of the acetal conjugate acids is assumed. However, other equations containing similar terms for water and lyonium ion concentrations can be derived for concerted mechanisms.)

The fact that specific acid catalysis by lyonium ions is observed is consistent with a reaction mechanism involving, as shown in eq 10, discrete formation of hemiacetal conjugate acids. (Direct oxocarbenium ion–hemiacetal interconversion via a mechanism involving concerted C–OH and O–H bond cleavage or formation would probably have resulted in general acid catalysis, i.e., in a rate equation containing a term corresponding to H_3O^+ acid catalysis). This is also in keeping with a class e mechanism for hemiacetal breakdown and formation, for which Funderburk et al. found support in their study of formaldehyde hemiacetal hydrolysis.[12]

The facts that $k_F/[CH_3OH_2^+]$ is independent of [H_2O] and that $k_H/[CH_3OH_2^+]$ linearly depends on [H_2O], as observed for 3-nitroacetophenone (Figure 1) and most other cases, show that the inequality of eq 12 is usually valid. The slight deviations from eq 13 and 14, observed mainly for acetophenones bearing electron-releasing substituents, might indicate that this inequality is not always valid over the whole range of water concentrations, especially when a stabilizing substituent increases the water-

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(11) However, Schubert and Brownawell (Schubert, W. M.; Brownawel, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 3487–3490) observed significant OCD_3/OCH_3 group exchange during the hydrolysis of methylal despite the fact that water was by far the most abundant nucleophile present. This means that inequality of eq 11 could not be valid in some cases.

(12) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459.

Table III. Regression Parameters[a]

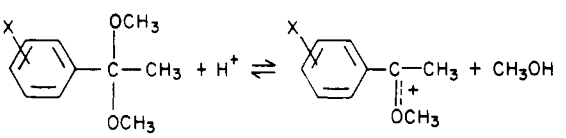
substitnt parameters[b,c]	ρ^n or ρ°	ρ^r	ρ_I	ρ_R° or ρ_R^+	$\mathcal{R}^2$	s	F	pF
			Acetal Formation Rate Coefficients					
σ^n	-1.58 ± 0.05				0.994	0.037	1117	
σ°	-1.54 ± 0.03				0.998	0.023	2820	
σ^n, $\Delta\sigma_n^+$	-1.52 ± 0.04	-0.13 ± 0.06			0.997	0.027	970	5.4
σ°, $\Delta\sigma_o^+$	-1.54 ± 0.04	-0.01 ± 0.03			0.998	0.025	1180	0.0
σ_I, σ_R°			-1.51 ± 0.04	-1.46 ± 0.05	0.998	0.023	1418	958
σ_I, σ_R^+			-1.45 ± 0.11	-0.71 ± 0.07	0.983	0.070	151	99
σ_I, σ_R°, $\Delta\sigma_o^+$		-0.09 ± 0.08	-1.50 ± 0.04	-1.37 ± 0.09	0.998	0.022	1024	1.4
			Acetal Hydrolysis Rate Coefficients					
σ^n	-3.78 ± 0.09				0.965	0.227	168	
σ°	-3.72 ± 0.20				0.982	0.163	312	
σ^n, $\Delta\sigma_n^+$	-3.26 ± 0.06	-1.11 ± 0.07			0.999	0.035	3692	250
σ°, $\Delta\sigma_o^+$	-3.30 ± 0.04	-0.90 ± 0.06			0.999	0.026	6680	233
σ_I, σ_R°			-3.32 ± 0.21	-4.04 ± 0.28	0.989	0.136	239	212
σ_I, σ_R^+			-3.17 ± 0.13	-2.02 ± 0.07	0.996	0.083	635	567
σ_I, σ_R°, $\Delta\sigma_o^+$		-1.04 ± 0.11	-3.22 ± 0.05	-3.04 ± 0.12	0.999	0.031	3139	93

[a] For the meaning of the statistical terms, see ref 18. [b] See ref 20–23. [c] $\Delta\sigma_n^+ = \sigma^+ - \sigma^n$; $\Delta\sigma_o^+ = \sigma^+ - \sigma^\circ$.

to-methanol selectivity of the oxocarbenium ion (for example, a ratio of ca. 25 for k_c/k_{-b} can be calculated in the case of 4-methoxyacetophenone). However, this explanation is not in agreement with data on the relative reactivities of D_2O and CD_3OD with $CH_3C({=}OMe)CH_3^+$ [6a,b,10] and with data on competing α-methoxystyrene hydrolysis and methanol addition (leading to ketones and acetals, respectively).[13] Even in the case of 4-methoxyacetophenone derivatives, the oxocarbenium ion formed by proton addition is exclusively trapped by methanol when the water content is fairly low. It seems, therefore, unlikely that the small deviations from eq 13 and 14 are related to a partial change in the rate-limiting step.

The change in the rate-limiting step on going from water (eq 11) to methanol (eq 12) should result in a decrease in the rate constant for hemiacetal formation from acetal (because of the limitation of the rate by the water attachment step). Therefore, since the rate of hemiacetal breakdown in water usually exceeds that of hemiacetal formation (with only a slight buildup in the most favorable cases)[9] it is more than likely that hemiacetal–ketone interconversion is sufficiently fast as not to control the rate of the overall reaction.

It is noteworthy that the order of magnitude of the hydrolysis rate coefficients in methanol is that expected from the reported data on equilibrium constants for the acetal-to-oxocarbenium ion process (eq 15)[14] and on rate constants for the addition of water to the ions. Indeed, if these equilibrium and rate constants are assumed to be identical in methanol and water, $(k_h)_m$ calculated for unsubstituted acetophenone, 65 M^{-1} s^{-1}, fully agrees with the experimental datum ($(k_h)_m = 92.5$ M^{-1} s^{-1}). Although such an estimation is questionable in many respects, it shows that the hydrolysis rate constants in methanol are consistent with those observed in water when one assumes the same mechanism with a change in the rate-limiting step only.



$$X\text{-}C_6H_4\text{-}C(OCH_3)_2CH_3 + H^+ \rightleftarrows X\text{-}C_6H_4\text{-}C(=\overset{+}{O}CH_3)CH_3 + CH_3OH \quad (15)$$

Ring-Substituent Effects. Substituent effects on the forward and reverse rate constants for ketone–acetal interconversion can be analyzed by the Young and Jencks correlation procedure,[14,15] based on a separation of the resonance and polar terms that contribute to the observed Gibbs energy of activation. According to these authors, log k variations can be written as in eq 16, where σ^n and

$$\log k = \rho^n\sigma^n + \rho^r(\sigma^+ - \sigma^n) + i \qquad (16)$$

σ^+ are the Wepster[16] and Brown[17] parameters, respectively. In this equation, derived from the Yukawa–Tsuno–Sawada (YTS) equation,[18] $\rho^n\sigma^n$ represents the polar effect of the substituted ring and $\rho^r(\sigma^+ - \sigma^n)$ the effect resulting from conjugation between the reaction center and the ring. The main advantage of eq 16 over the YTS equation lies in the fact that ρ^n and ρ^r are additive parameters, within experimental error, according to the relationship $\rho_{eq}^i = \rho_f^i - \rho_r^i$. As stressed by Young and Jencks, "the parameter ρ^r is a measure of the amount that resonance contributes to the stabilization of the transition state or product of a reaction", whereas the YTS parameter r^+ only expresses "the relative importance of polar and resonance contributions to the free energy relationship under consideration". When eq 16 is applied to the lyonium catalytic rate constants $(k_f)_m$ and $(k_h)_m$, excellent relationships are found with $\rho^n = -1.52 \pm 0.04$ and -3.25 ± 0.05 and with $\rho^r = -0.13 \pm 0.06$ and -1.11 ± 0.07, respectively (Table III).[19-21] The differences between the ρ^i values for

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(19) In the regression equations, figures after the sign ± are the standard deviations of the regressions coefficients; $\mathcal{R}$ is the simple or multiple correlation coefficients for linear or multiple regression; s is the standard deviation for regression; F and pF (partial F for the last cited variable) are as defined by Draper, N. R.; Smith, H. "Applied Regression Analysis"; Wiley: New York, 1966.

(20) The σ^n values are those given in ref 15: −0.111 (4-OCH_3), −0.129 (4-CH_3), 0.168 (4-F), 0.238 (4-Cl), 0.373 (3-Cl), 0.467 (3-CF_3), and 0.674 (3-NO_2).

(21) The σ^+ values are those given in ref 17: −0.778 (4-OCH_3), −0.311 (4-CH_3), −0.073 (4-F), 0.114 (4-Cl), 0.399 (3-Cl), 0.520 (3-CF_3), and 0.674 (3-NO_2).

(22) The σ_I, σ_R° and σ_R^+ values are those given in ref 25b. For meta substituents σ_R° values were multiplied by the factor 0.5, the extent of communication of resonance effects to the meta position, and σ_R° values were taken instead of σ_R^+ values for DSP correlations using σ_I and σ_R^+.

(23) The σ° values are those compiled by Exner, O. In "Advances in Free Energy Relationships"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London, 1972; pp 1–69.

the forward and reverse reactions correspond to the ρ^n and ρ^r values observed for equilibrium (1.73 and 1.01, respectively).[1]

As pointed out previously,[24] eq 16 can be considered as a simplified three-parameter equation (eq 17), in which the contributions of (i) resonance *within* the ring and of (ii) the *substituent polar effect contribution to the overall polar effect of the substituted ring* (accounted for by the σ° or σ^n parameters) are separated according to Taft and Lewis's proposals.[25] (In keeping with the Taft–Lewis

$$\log k = \rho_I\sigma_I + \rho_R{}^\circ\sigma_R{}^\circ + \rho^r(\sigma^+ - \sigma^\circ) + i \qquad (17)$$

formulation, σ° parameters are used instead of σ^n in eq 17, but both sets of parameters designate the same thing, and the values for most substituents are nearly identical.) It follows that the Young–Jencks equation, as well as the YTS equation, is valid only if ρ_I and $\rho_R{}^\circ$ are of similar magnitude. Although its precision is lowered because there are few points, eq 17 was used to calculate ρ data listed in Table III. These data show that $\rho_I/\rho_R{}^\circ$ is close to unity and that use of an "encompassing" parameter, σ° or σ^n, is permissible.

The validity of the YTS equation and, consequently, of the derived formulations has however been questioned.[26] Most significantly, it can be noted that, when these equations are used, it is implicitly assumed that the resonance-induced polar effect of the substituted ring is independent of the conjugation between the functional reacting group and the ring. Usually, this should not be true; Taft et al.[27] recently showed that in 1,4-disubstituted benzenes (XYC_6H_4) conjugation between X and the benzene ring depends on Y and that $\sigma_R{}^\circ$ parameters should be altered by taking into account a ϵ parameter which depend on the electron demand of the Y-substituted carbon atom. However, the fact that the substituent effects on the rates of acetophenone dimethyl acetal interconversion fit the Young–Jencks equation indicates that the deviations from the $\sigma_R{}^\circ$ scale are in this case of minor importance and, therefore, that the resonance-induced polar effects of the substituted ring are accounted for by a $\rho_R{}^\circ\sigma_R{}^\circ$ term with $\rho_R{}^\circ \approx \rho_I$.

When applying the Taft's dual-substituent parameter (DSP) procedure[25] to separate polar and resonance effects, it is assumed that the second and third terms of eq 17 can be encompassed and that the overall resonance effect can be accounted for by a $\bar{\sigma}_R$ parameter (eq 18) which depends

$$\log k = \rho_I\sigma_I + \rho_R\bar{\sigma}_R + i \qquad (18)$$

on the electron demand of the reaction center. Although it was recognized that $\bar{\sigma}_R$ was a continuous function, it was decided that a choice of four discrete sets of values [$\sigma_R{}^\circ$, $\sigma_R{}^{BA}$, $\sigma_R{}^+$, and $\sigma_R{}^-$, corresponding to the σ_R components of the four common σ scales (σ°, σ, σ^+, and σ^-)] could be sufficient to deal with different situations. This, however, results in two problems: (i) two different effects are included in the same σ_R parameters, namely, the resonance-induced polar effect of the benzene ring and the resonance effect corresponding to conjugation between the reaction center and the substituted ring [the polar nature of the overall polar effect behind σ^n (or σ°) has been illustrated by ab initio calculations of the energies of interaction between substituted benzene rings and pure point charges, modeling nonbonded reaction centers];[28] (ii) restricting the choice to one of the σ_R scales means that in some cases none is appropriate and could result in not only a poorer fit but also incorrect values of ρ_I and σ_R. Table III also lists the ρ values and the statistical parameters calculated when testing the DSP equation with $\sigma_R{}^\circ$ and $\sigma_R{}^+$ values. For $(k_h)_m$ data, the fit of the results is less satisfactory than that found with eq 16. This clearly stems from the fact that the ratio of the ρ^r and $\rho_R{}^\circ$ values from the three-parameter relationship is neither unity nor zero and that an intermediate scale of σ_R values would be necessary. In contrast, log $(k_f)_m$ vs. σ_I and $\sigma_R{}^\circ$ can be considered equivalent in quality to that obtained by the Young–Jencks approach. This is due to the fact that the $\rho^r(\sigma^+ - \sigma^\circ)$ term is of minor importance and that a one-parameter relationship with only σ° or σ^n gives a satisfactory fitting.

A significant finding when the Young–Jencks approach is used is the small ρ^r value observed for $(k_f)_m$. This means that the conjugation between the ring and the reaction center has almost no influence on the rate coefficient for acetal formation. This property results from parallel effects on ground-state Gibbs energy, i.e., on ketone stability, and on transition state Gibbs free energy. The resonance stabilizing effects of, for example, the methoxy group have roughly the same magnitude on acetophenone and on the transition state which resembles the oxocarbenium ion. This conclusion illustrates the main advantage of eq 16 when compared to the classical form of the Yukawa–Tsuno–Sawada equation, namely, the possibility of an unambiguous separation of the ring-reaction center conjugation effects from the polar effects. The small r^+ value ($r^+ = 0.08$) which would have been found does not mean that the transition-state Gibbs energy is nearly independent of conjugation but that the conjugation effects on the ground state cancel out those on the transition state. A similar explanation holds for the relatively low value for acetal formation; this stems from a compensation of the polar effects on the transition state by the polar effects on the starting material.

The ρ^n and ρ^r values found for acetal hydrolysis in methanol are of the same order of magnitude as those observed for acetophenone dimethyl acetal hydrolysis in water ($\rho^n = -2.0$ and $\rho^r = -0.7$)[14] and for benzaldehyde dimethyl acetal hydrolysis in dioxane–water (50:50)[14] and aqueous methanol (5:95)[3] ($\rho^n = -3.4$ and $\rho^r = -1.8$ in both solvents). When compared to the values estimated for acetal to oxocarbenium ion equilibrium ($\rho^n = -3.6$ and $\rho^r = -2.2$) in water,[14] these results mean that the transition state is probably closer to the oxocarbenium ion in methanol (as expected from the lower stabilities of the ions in a solvent of lower dielectric constant) but that the transition state for the addition of methanol to the ions (acetophenone acetals in methanol and benzaldehyde acetals in aqueous methanol) is similar to that for the addition of water to the same ions (acetophenone dimethyl acetals in water and benzaldehyde dimethyl acetals in aqueous dioxane).

Experimental Section

Materials and UV–vis equipment were as described.[1] Strict first-order behavior was observed for 90% of the reaction. Values

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of $(k_H + k_F)$ coefficients were calculated from eq 2 or 3 by plotting $\ln [A_t - (A_\infty)_1]$ or $\ln [(A_\infty)_2 - A_t]$ vs. time. Standard deviations from the observed straight lines were usually less than 0.5% of the logarithm range. In most cases a slow increase of absorbance was observed before and after the water-concentration jump as the result of a moisture contamination. Appropriate linear corrections were introduced to determine the $(A_\infty)_1$ and $(A_\infty)_2$ values at the water-concentration jump time used in rate-coefficient calculations.

Registry No. 4-$OCH_3C_6H_4COCH_3$, 100-06-1; 4-$CH_3C_6H_4COCH_3$, 122-00-9; $C_6H_5COCH_3$, 98-86-2; 4-$FC_6H_4COCH_3$, 403-42-9; 4-$ClC_6H_4COCH_3$, 99-91-2; 3-$ClC_6H_4COCH_3$, 99-02-5; 3-$CF_3C_6H_4COCH_3$, 349-76-8; 3-$NO_2C_6H_4COCH_3$, 121-89-1; 4-$OCH_3C_6H_4C(OH)_2CH_3$, 27150-99-8; 4-$CH_3C_6H_4C(OH)_2CH_3$, 53578-01-1; $C_6H_5C(OH)_2CH_3$, 4316-35-2; 4-$FC_6H_4C(OH)_2CH_3$, 73585-52-1; 4-$ClC_6H_4C(OH)_2CH_3$, 72360-69-1; 3-$ClC_6H_4C(OH)_2CH_3$, 73585-53-2; 3-$CF_3C_6H_4C(OH)_2CH_3$, 73589-85-2; 3-$NO_2C_6H_4C(OH)_2CH_3$, 73585-54-3.

Direct Synthesis of Benzo[*c*]phenanthridines and Benzo[*c*]phenanthridones via $S_{RN}1$ Reactions[1]

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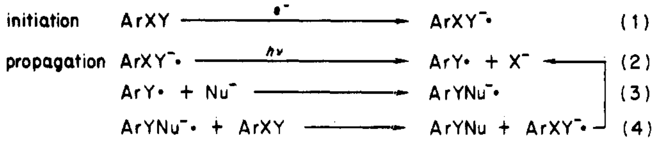
A straightforward and high-yield route to the 11,12-dihydrobenzo[c]phenanthridine (**3**) and 11,12-dihydrobenzo[c]phenanthridone (**14**) ring systems is based upon an $S_{RN}1$ reaction between 2-halobenzylamines **1** or 2-halobenzoic acids **11** and enolates derived from tetralones **2**. The efficient dehydrogenation of **3** or **14** gives the benzo[*c*]phenanthridines **4** or benzo[*c*]phenanthridones **15**. Use of properly substituted reactants leads to nitidine, avicine, and fagaronine and to analogues of those natural products.

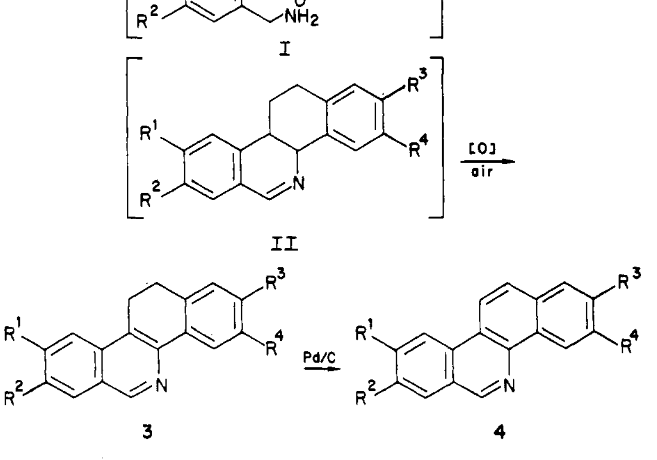
Benzo[*c*]phenanthridines and benzo[*c*]phenanthridones are an important class of the isoquinoline alkaloid family. Synthetic studies started half a century ago,[3a] and since then, workers in this field were very active.[3b–d] In the recent period, targets of special interest were some alkaloids that had shown initial promise as antitumor agents.[4] This fact, together with scarcity from natural source and the need for analogues had led to the synthesis of nitidine,[5–8,24] avicine,[7,9] and fagaronine.[10,11] The multistep syntheses so far reported are of linear type and give overall yields ranging from good to very low. We report now a new and more direct route to these alkaloids and to various analogues.

The extended $S_{RN}1$ reaction (eq 1–4, Scheme I) developed in our laboratory[12] is the key step in the synthesis of isoquinolones[13,14] and isoquinolines[15a,b] from 2-halobenzamides or 2-halobenzylamines and nucleophiles derived from linear ketones (CH_3COR, R = CH_3, i-C_3H_7, t-C_4H_9). We have now applied this method to the synthesis of a series of benzo[*c*]phenanthridines by reaction of substituted iodobenzylamines with substituted tetralones (Scheme II).

Scheme I. The $S_{RN}1$ Extended Reaction



Scheme II. Synthesis of Benzo[*c*]phenanthridines



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