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Ring Substitutent Effects on Acetophenone Dimethyl Acetal Formation. 1. Dual-Parameter Treatment of Equilibrium Data in Methanol, Water, and Dodecane[1-3]

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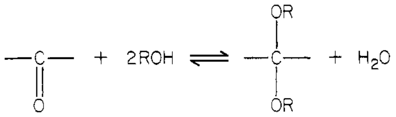
For substituted acetophenones, the ketone to acetal equilibrium constants, K_x, measured by a water concentration jump method, are reported. Ketone and acetal partition coefficients, P, for the water–dodecane and methanol–dodecane solvent systems provide Gibbs free energies of transfer from methanol to dodecane and from methanol to water. Both sets of results make it possible to calculate K_x values in water and dodecane; these values are compared with those directly measured in methanol and with equilibrium constants reported for other reactions involving the trigonal to tetrahedral conversion of the carbonyl carbon atom. Substituent effects for the three solvents are examined by means of the usual dual-parameter Gibbs free energy relationships. The Young–Jencks modified Yukawa–Tsuno equation, $\log K_x = \rho^n\sigma^n + \rho^r(\sigma^+ - \sigma^n) + i$, gives $\rho^n = 1.73$, 1.81, and 0.99 for methanol, dodecane, and water, respectively, but $\rho^r \approx 1$ whatever the solvent. It is concluded that the through-ring conjugation effects are solvent independent. In contrast, the Taft–Lewis equation, $\log K_x = \rho_I\sigma_I + \rho_R^+\sigma_R^+ + i$, gives ρ_I and ρ_R^+ values that are both solvent dependent. The substituent effects on relative solubilities in methanol, dodecane, and water are examined by means of the equation $\Pi_{X(Y)} = \log P_{X(Y)} - \log P_{H(Y)}$ where Y is the carbonyl or the acetal group and X is the substituent. It is shown that $\log P_{X(Y)}$ deviates from additivity ($\Pi_{X(Y)} \neq \Pi_{X(H)}$ and is Y dependent) because of the effects of X on carbonyl and acetal solvation. These effects are particularly large for solvation of acetals by water molecules. Therefore, substituent effects on K_x are interpreted as being mainly due to (a) an inductive effect of the substituted ring on ketone stability, (b) a solvent-independent through-ring conjugation effect within the ketone, and (c) a specific inhibition of acetal solvation by water molecules.

Reactions involving the trigonal to tetrahedral conversion of the carbonyl carbon atom have been extensively studied because they are initiated by one of the most important elementary processes of organic chemistry, namely the nucleophilic attack of the carbonyl group, and because the resulting chemical species are often unstable intermediates in the course of many organic and bioorganic transformations.[4] Although acetal formation (eq 1) in



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

alcohols is one of the simplest examples of this kind of reaction, the related kinetic and thermodynamic data are relatively scarce, probably because the usual shift of the equilibrium towards the keto form makes it necessary to measure the concentration of small amounts of water with accuracy.[5] This is particularly true for acetophenone dimethyl acetal formation which has a very low equilibrium constant.[6] The data on dimethyl acetal formation from ring-substituted acetophenones reported herein were obtained by an original water concentration jump procedure which avoids the determination of water concentration at equilibrium.

The acetophenone–acetophenone dimethyl acetal system is of great interest when examining ring-substitutent effects in this kind of reactions and, more specifically, when testing the validity and the usefulness of dual-substituent parameter free energy relationships.[7] However, the analysis of the substituent effects and their comparison with those observed for similar reaction is rendered difficult by the difference in solvents. Indeed, data on acetal formation in methanol cannot be compared with data on hydration, cyanhydrin formation, bisulfite addition, etc. usually obtained in water. So, it is of interest to get data on acetal formation in water, a solvent in which direct measurements are usually impossible.

Acetal formation equilibrium constants in water can be calculated from data in methanol provided that the Gibbs free energies of transfer of products and reactants are known.[8] These energies have been obtained by measuring partition coefficients between water and dodecane, and then between dodecane and methanol. This procedure, required by the miscibility of water and methanol, has the advantage of also providing the equilibrium constants in dodecane and of allowing comparisons between free energy relationships in protic solvents and in an aprotic solvent of low dielectric constant.

Results

The Water Concentration Jump Method. The main difficulty in measuring the ketone to acetal equilibrium constants in methanol lies in the determination of the water concentrations at equilibrium. Indeed, since the equilibrium constant usually favors a large prevalence of

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[1] Abstracted from the "Doctorat ès-Sciences Physiques" of M. El-Alaoui, University of Paris VII, Paris, 1979, and from the "Doctorat de Troisième Cycle" of P. Kleffert, University of Paris VII, Paris, 1981.

[2] Preliminary communication: Toullec, J.; Alaya, M. *Tetrahedron Lett.* **1978**, 5207–5211.

[3] The name "acetal" for ketone derivatives has been preferred instead of the more common name "ketal" according to Rule C-331-1 of the IUPAC "Nomenclature of Organic Chemistry", Sect. A–F and H; Pergamon Press: Elmsford, NY, 1979.

[4] Some pertinent recent references are: Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999–7003. Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898–906. Jensen, J. L.; Lenz, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 1291–1293. Finley, R. L.; Kubler, D. J.; McClelland, R. A. *J. Org. Chem.* **1980**, *45*, 644–648. Capon, B.; Grieve, D. M. A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 300–302. McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6912–6915. Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 4884–4890. McClelland, R. A.; Santry, L. J. *Bull. Soc. Chim. Belg.* **1982**, *91*, 392.

[5] For a recent review, see: Toullec J. *Adv. Phys. Org. Chem.* **1982**, 18, 1–77.

[6] Davis, T. S.; Kubler, D. G.; Sartwell, P.; Zepp, R. *J. Org. Chem.* **1965**, *30*, 4284–4292.

[7] For a review, see: Shorter, J. In "Correlation Analysis in Chemistry: Recent Advances", Chapman, N.B., Shorter, J., Eds.; Plenum Press: London, 1978; pp 119–173.

[8] Cf., for example: (a) Buncel, E.; Wilson, H. *Acc. Chem. Res.* **1979**, *12*, 42–48. (b) Kamlet, M. J.; Abboud, J. L. M.; Taft, R. W. *Prog. Phys. Org. Chem.* **1981**, *13*, 485–630.

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Table I. Determination of the Ketone to Acetal Mole Fraction Equilibrium Constant for Acetophenone in Methanol (25 °C)

$10^2[H^+]_{st}$, M[a]	$10^2[H_2O]_1$, M[b]	$10^2\Delta[H_2O]$, M[c]	10^4K_x[d]	n[e]
0.54	0.7	0.8-1.32	6.48 ± 0.14	3
1.02	0.8	0.6-9.72	6.47 ± 0.29	13
2.70	1.3	0.59-8.7	6.21 ± 0.23	12
5.60	1.1	1.17-5.9	6.37 ± 0.18	4
10.0	1.2	1.02-5.0	6.15 ± 0.11	5
			av 6.32 ± 0.11	

[a] Stoichiometric bromohydric acid concentration. [b] Free water concentration before the jump, calculated from absorbance A_1 and the measured K_x value. [c] Range of water concentration jumps for the considered series of measurements. [d] Figures are standard deviations. [e] Number of measurements at constant stoichiometric acid concentration but at different $\Delta[H_2O]$ jumps.

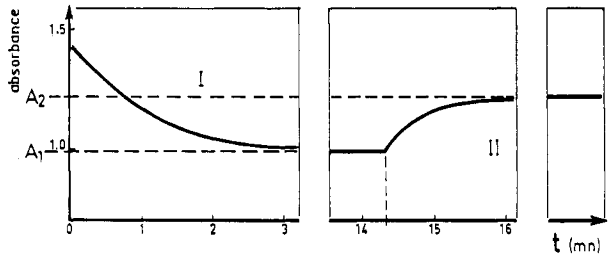

Figure 1. Typical ketone to acetal equilibrium constant determination by the water concentration jump method (4-methoxyacetophenone; [HBr] = 2.16 × 10^{-3} M; stoichiometric ketone concentration = 8.95 × 10^{-5} M; water concentration at the first equilibrium position = 0.413 × 10^{-2} M; water concentration at the second equilibrium position = 1.11 × 10^{-2} M; 25 °C). Curve I corresponds to the first equilibration after ketone addition; curve II corresponds to the second equilibration following the water concentration jump.

Table II. Cumulative Data for Substituent Effects on the Ketone to Acetal Equilibrium Constant in the Acetophenone Series (25 °C)

X in XC_6H_5-$COCH_3$	10^4K_x		
	methanol[a]	dodecane[b]	water[b]
4-OCH_3	0.882 ± 0.039	0.396	0.0783
4-CH_3	2.42 ± 0.17	1.15	0.187
H	6.32 ± 0.11	3.28	0.438
4-F	6.91 ± 0.37	3.74	0.266
4-Cl	13.4 ± 0.6	6.83	0.569
3-Cl	28.3 ± 0.4	15.5	0.780
3-CF_3	43.8 ± 1.5		
3-NO_2	99.7 ± 5.6	44.2	1.92
4-NO_2	147 ± 13	104	2.30

[a] Measured by the water concentration jump method. Figures are standard deviations. [b] Calculated by eq 12 with data on equilibrium constants in methanol and data on Gibbs free energy of transfer (cf. Table III).

the keto form, the amount of water must be kept so low that it is difficult to control it with accuracy. To avoid this problem, Garrett and Kubler[9] and, more recently, Wiberg and Squires[10] used very large concentrations of ketones. So, the amount of water formed by the reaction was large and the initial residual water concentration in methanol could be neglected. The experimental methods were UV spectroscopy in Garrett–Kubler's work and ^1H NMR spectroscopy in Wiberg–Squires'. However, this procedure has two major disadvantages: (i) The apparent equilibrium constants would differ from the true thermodynamic constants (because the ketone–acetal concentrations are high, their activities should deviate from the concentrations). (ii) The UV spectroscopy option cannot be used for high absorptivity compounds.

The method we used entails following the variations of absorbance when the ketone to acetal equilibrium in acidic methanol is shifted by the addition of a small but known amount of water, and measuring absorbance before (A_1) and after (A_2) the jump (Figure 1). Indeed, the equilibrium constant with respect to mole fractions, K_x (eq 2)

$$K_x = \frac{(a_m)_{ac}(a_m)_w}{(a_m)_{ke}(a_m)^2_m} \tag{2}$$

[$(a_m)_{ac}$, $(a_m)_{ke}$, $(a_m)_w$, and $(a_m)_m$ are the rational activities of acetal, ketone, water, and methanol, respectively, with methanol containing the other components at infinite dilution as the reference state], can be expressed as

$$(K_x)_m = \frac{\Delta x_w (x_{ac})_1 (x_{ac})_2}{(x_{ke})_2 (x_{ac})_1 (x_m)_2{}^2 - (x_{ke})_1 (x_{ac})_2 (x_m)_1{}^2} \tag{3}$$

when the activity coefficients are set equal to unity.[11] (In this equation Δx_w is the jump in the mole fraction of water, x_m, x_{ke}, and x_{ac} are the equilibrium mole fractions of methanol, ketone, and acetal, respectively, and subscripts 1 and 2 refer to the first and second equilibrium positions.) Since the acetal and ketone molarities are related to absorbances A_j, to the stoichiometric ketone concentrations (c_j = [ketone]$_j$ + [acetal]$_j$), and to the molar absorption coefficients (ϵ_{ac} and ϵ_{ke} for acetal and ketone, respectively) (eq 4 and 5), eq 3 can be expressed as in eq 6 where V^*_m

$$[\text{acetal}]_j = (c_j\epsilon_{ke} - A_j)/(\epsilon_{ke} - \epsilon_{ac}) \tag{4}$$

$$[\text{ketone}]_j = (A_j - c_j\epsilon_{ac})/(\epsilon_{ke} - \epsilon_{ac}) \tag{5}$$

$$(K_x)_m = \Delta[H_2O](c_2\epsilon_{ke} - A_2)(c_1\epsilon_{ke} - A_1)/\{V^*_m[(A_2 - c_2\epsilon_{ac})(c_1\epsilon_{ke} - A_1)[\text{MeOH}]_2{}^2 - (A_1 - c_1\epsilon_{ac})(c_2\epsilon_{ke} - A_2)[\text{MeOH}]_1{}^2]\} \tag{6}$$

is the mole volume of methanol in pure solvent. When the variations of the volume and of the methanol concentration are negligible, the latter equation can be reduced to eq 7.

$$(K_x)_m = \Delta[H_2O](c\epsilon_{ke} - A_2)(c\epsilon_{ke} - A_1)/V^*_m[c(\epsilon_{ke} - \epsilon_{ac}) \times (A_2 - A_1)[\text{MeOH}]^2] \tag{7}$$

The jump in water concentration can be calculated by eq 8, where $\Delta[H_2O]_{add}$ is the amount of added water per

$$\Delta[H_2O] = \Delta[H_2O]_{add} - \Delta[\text{ketone}] - \Delta[H_3O^+] \tag{8}$$

volume, Δ[ketone] is the difference in ketone concentration, and $\Delta[H_3O^+]$ is the variation of hydronium ion con-

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(9) Garrett, R.; Kubler, D. G. *J. Org. Chem.* **1966**, *31*, 2665–2667.

(10) Wiberg, K. B.; Squires, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 5512–5515.

(11) This assumption is fully justified for acetals and ketones which are always at very low concentrations (≃10^{-4} M). For water concentrations ranging from ca. 3 × 10^{-3} M to ca. 0.1 M, it is also appropriate to neglect the deviations of the activity coefficient from unity. Indeed, data on pressure–composition diagrams for the water–methanol system (cf., e.g., ref 21) exhibit relatively small deviations from ideality. Likewise, since activity coefficients are taken with respect to pure methanol, the activity coefficient of methanol containing small amounts of water should not differ from 1.

centration which can be calculated by considering the $CH_3OH_2^+$–H_3O^+ equilibrium (eq 9).[12,13] Indeed, a part of

$$CH_3OH_2^+ + H_2O \rightleftharpoons CH_3OH + H_3O^+ \qquad (9)$$

added water is engaged in the hydronium ion and should not be included in the actual water concentration change.[14] Typical results for unsubstituted acetophenone are listed in Table I. Equations 6 and 7 were tested at different bromohydric acid concentrations.[15] Cumulative data for substituted acetophenones are listed in Table II.

Partition Coefficients of Ketones and Acetals for the Dodecane–Water and Methanol–Dodecane Solvent Systems. Because of its insolubility in water[16] and its low solubility in methanol,[17] dodecane was used as a counter solvent to measure the Gibbs energies of transfer of ketones and acetals from methanol to water. Partition coefficients between water and dodecane and between methanol and dodecane were determined from UV spectroscopy measurements of the concentrations of ketones and acetals in both sets of phases;[18,19] they are listed in

Table III. Partition of Substituted Acetophenones and of the Parent Dimethyl Acetals between Methanol and Dodecane and between Water and Dodecane: Methanol to Water Gibbs Free Energies of Transfer[a]

	acetophenones					acetophenone dimethyl acetals				
X[b]	$\log P_{m\to d}$	$\Delta G°_{m\to d}$, cal mol^{-1} [c]	$\log P_{d\to w}$	$\Delta G°_{d\to w}$, cal mol^{-1} [c]	$\Delta G°_{m\to w}$, cal mol^{-1} [d]	$\log P_{m\to d}$	$\Delta G°_{m\to d}$, cal mol^{-1} [c]	$\log P_{d\to w}$	$\Delta G°_{d\to w}$, cal mol^{-1} [c]	$\Delta G°_{m\to w}$, cal mol^{-1} [d]
4-OCH_3	−0.501 ± 0.022	−337 ± 30	−0.895 ± 0.005	2727 ± 7	2390	0.318 ± 0.005	−1455 ± 7	−2.319 ± 0.009	4670 ± 12	3215
4-CH_3	−0.599 ± 0.011	−203 ± 15	−1.626 ± 0.005	3724 ± 7	3521	0.201 ± 0.005	−1295 ± 7	−3.091 ± 0.050	5723 ± 68	4428
3-CH_3	−0.554 ± 0.009	−265 ± 12	−1.723 ± 0.005	3856 ± 7	3591	0.174 ± 0.001	−1258 ± 2	−3.117 ± 0.050	5758 ± 68	4500
H	−0.689 ± 0.002	81 ± 3	−1.121 ± 0.005	3035 ± 7	2954	0.073 ± 0.009	−1120 ± 12	−2.595 ± 0.030	5046 ± 40	3926
4-F	−0.792 ± 0.009	60 ± 12	−1.200 ± 0.010	3143 ± 14	3203	−0.049 ± 0.003	−954 ± 4	−2.911 ± 0.040	5477 ± 55	4523
4-Cl	−0.573 ± 0.006	−239 ± 8	−1.848 ± 0.005	4027 ± 7	3788	0.196 ± 0.005	−1288 ± 7	−3.542 ± 0.040	6338 ± 55	5050
3-Cl	−0.664 ± 0.009	−115 ± 12	−2.006 ± 0.005	4243 ± 7	4128	0.075 ± 0.001	−1123 ± 2	−3.858 ± 0.010	6769 ± 14	5646
3-CF_3	−0.840 ± 0.013	125 ± 18	−2.082 ± 0.010	4346 ± 14	4371					
3-NO_2	−1.209 ± 0.048	629 ± 65	−0.535 ± 0.025	2236 ± 35	2865	−0.379 ± 0.001	−504 ± 2	−2.635 ± 0.037	5101 ± 50	4597
4-NO_2	−0.927 ± 0.017	244 ± 23	−0.695 ± 0.005	2454 ± 7	2698	−0.301 ± 0.005	−610 ± 7	−2.680 ± 0.005	5162 ± 7	4552

[a] At 25 °C. [b] X in $XC_6H_4COCH_3$ or in $XC_6H_4C(OCH_3)_2CH_3$. [c] Calculated with eq 10. [d] Calculated with eq 11.

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[12] Small changes in volume due to the added water were accounted for. Volumes were always considered as additive.

[13] The molarities of H_3O^+ and $CH_3OH_2^+$ at the two equilibrium positions were calculated by means of the following equations,

$$[H_3O^+] = [H^+]_{st}K_r[H_2O]/(K_r[H_2O] + [CH_3OH])$$

$$[CH_3OH_2^+] = [H^+]_{st}[CH_3OH]/(K_r[H_2O] + [CH_3OH])$$

where K_r is the equilibrium constant for proton distribution between water and methanol ($K_r = [CH_3OH][H_3O^+]/[CH_3OH_2^+][H_2O]$)($K_r = 121$ at 25 °C; de Lisi, R.; Goffredi, M.; Turco Liveri, V. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 1096–1111) and where $[H^+]_{st}$ is the stoichiometric acid concentration. Since $[H_2O]$ is unknown in these equations, iterative calculations were done.

[14] Calculations performed without taking into account $[H_3O^+]$ variations provided apparent K_x values which depended on water concentration.

[15] The experiments also provided kinetic parameters which will be reported and discussed in a sequel.

[16] The solubility of dodecane in water is 4.9 × 10^{-8} M (Franks, F. *Nature (London)* **1966**, *210*, 87–88). That of water in dodecane was reported as 65 ppm (2.7 × 10^{-3} M) (Schatzberg, P. *J. Phys. Chem.* **1963**, *67*, 776–779).

[17] GLC measurements were performed to determine the composition of the two phases of the equilibrated dodecane–methanol system. The amount of methanol in dodecane was measured to be less than 0.5%, in agreement with a calculated estimation (cf. ref 22) (~0.3%), whereas the amount of dodecane in the methanolic phase was measured as 8% (w/w). This latter value would make it necessary to correct partition coefficients in order to get Gibbs transfer energies between pure solvents (cf. ref 19).

[18] Since ketone and acetal concentrations were always low (<10^{-2} M) and very different from limit solubilities in each phase, it can be assumed that the activity coefficients do not differ from unity. This assumption was checked in the case of the 4-nitroacetophenone partition between methanol and dodecane. It was observed that the measured partition coefficient was concentration-independent when the concentrations of ketone in the methanol and dodecane phases were varied in the 2.45 × 10^{-3} to 3.86 × 10^{-2} and 3.01 × 10^{-4} to 4.7 × 10^{-3} M ranges, respectively.

[19] Strictly speaking, partition coefficients and Gibbs energies correspond to the transfer of ketones and acetals from dodecane to dodecane 8%–methanol and not to the transfer between pure solvents. In order to estimate errors due to the dodecane content in the methanolic phase, solubilities in pure methanol and in methanol containing 8% (w/w) dodecane were measured for 4-nitroacetophenone and the related acetal (similar measurements were not possible in most cases because the ketone and acetal solubilities were too large). For 4-nitroacetophenone, the limit solubility was almost unchanged (0.393 M in dodecane 8%–methanol, instead of 0.395 M in pure methanol), whereas a more significant difference was observed for the acetal (0.925 M in methanol and 1.065 M in the mixed solvent). The latter result shows that there may be some errors on the methanol to dodecane Gibbs free energies of transfer due to the presence of 8% dodecane in the methanolic phase. However, since, as shown below, the difference in the acetal and ketone Gibbs free energies of transfer from methanol to dodecane is fairly substituent independent, such errors (corresponding to significant Gibbs free energies of transfer of ketones and acetals from methanol containing 8% dodecane to pure methanol) might only be significant on the absolute $(K_x)_d$ and $(K_x)_w$ data, but should not have any influence on the relative ketone to acetal equilibrium constants on going from one substituted acetophenone to another. Furthermore, a direct determination of Gibbs energies of transfer from data on limit solubilities in water and methanol (cf. ref 20) shows that the errors are certainly very small.

Table III, as well as the Gibbs free energies of transfer calculated by eq 10, in which $V^*_{S_1}$ and $V^*_{S_2}$ are the mole

$$\Delta G^\circ_{S_1\to S_2} = -RT \ln [P_{S_1\to S_2}(V^*_{S_2}/V^*_{S_1})] \qquad (10)$$

volumes of the solvents (these are introduced to convert molecularities into mole fractions).

Gibbs free energies for the transfer of substituted acetophenones and of the parent dimethyl acetals from methanol to water were calculated by means of eq 11 and are also listed in Table III.[20]

$$\Delta G^\circ_{m\to w} = \Delta G^\circ_{m\to d} + \Delta G^\circ_{d\to w} \qquad (11)$$

Ketone to Acetal Equilibrium Constants in Water and Dodecane. Data on Gibbs free energies of transfer for acetophenones and the corresponding dimethyl acetals make it possible to calculate the ketone to acetal equilibrium constants with water and dodecane as reference states (Table II). Indeed, the standard Gibbs free energy increment for the ketone to acetal equilibrium in a solvent S (water or dodecane) can be expressed[8] by

$$\Delta G^\circ_S = \Delta G^\circ_m + (\Delta G^\circ_{m\to S})_{ac} - (\Delta G^\circ_{m\to S})_{ke} + (\Delta G^\circ_{m\to S})_w - 2(\Delta G^\circ_{m\to S})_m \qquad (12)$$

as a function of ΔG°_m,

$$\Delta G^\circ_m = -RT \ln (K_x)_m \qquad (13)$$

the standard Gibbs free energy increment for the reaction in methanol, and of $(\Delta G^\circ_{m\to S})_{ac}$, $(\Delta G^\circ_{m\to S})_{ke}$, $(\Delta G^\circ_{m\to S})_w$, and $(\Delta G^\circ_{m\to S})_m$, the Gibbs free energies of transfer for acetal, ketone, water, and methanol, respectively.

The Gibbs energy of transfer of methanol from pure methanol to pure water can be calculated as the difference in the standard Gibbs free energies when activities are defined with pure methanol or pure water as reference states. By definition, this difference is expressed as a function of the Henry coefficient for methanol in methanol–water mixtures, $(k_w)_m$, and of the vapor pressure of methanol, p°_m (eq 14).[21]

$$(\Delta G^\circ_{m\to w})_m = (G^\circ{}_w{}^\infty)_m - (G^\circ{}_m{}^*)_m = -RT \ln \frac{p^\circ_m}{(k_w)_m} = 0.19 \text{ kcal mol}^{-1} \qquad (14)$$

Likewise,

$$(\Delta G^\circ_{m\to w})_w = (G^\circ{}_w{}^*)_w - (G^\circ{}_m{}^\infty)_w = RT \ln \frac{p^\circ_w}{(k_m)_w} = -0.23 \text{ kcal mol}^{-1} \qquad (15)$$

where p°_w is the vapor pressure of water and $(k_m)_w$ is the Henry coefficient of water in methanol–water mixtures.

For the methanol to dodecane transfer, $(\Delta G^\circ_{m\to d})_m$ and $(\Delta G^\circ_{m\to d})_w$ can be estimated from the limit solubilities of methanol $(x_d{}^{max})_m$[22] and water $(x_d{}^{max})_w$[16] in dodecane and from the above data for the methanol to water transfer (eq 16 and 17).

$$(\Delta G^\circ_{m\to d})_m = -RT \ln (x_d{}^{max})_m = 2.4 \text{ kcal mol}^{-1} \qquad (16)$$[23]

$$(\Delta G^\circ_{m\to d})_w = (\Delta G^\circ_{m\to w})_w - RT \ln (x_d{}^{max})_w = 4.15 \text{ kcal mol}^{-1} \qquad (17)$$

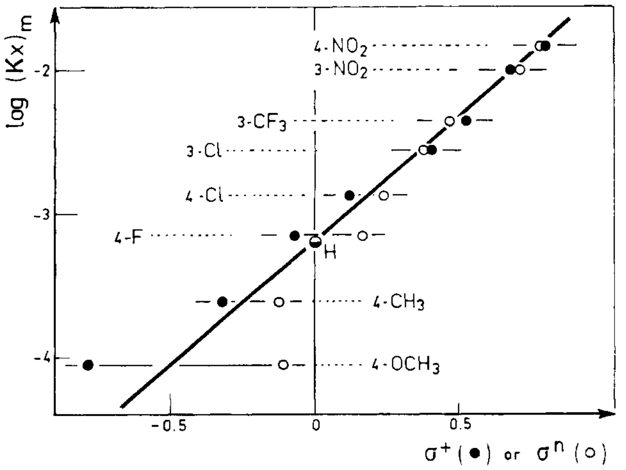

Figure 2. Hammett–Wepster and Brown plots for the ketone to acetal equilibrium constants in methanol for the ring-substituted acetophenone series.

Discussion

Dual-Substituent Parameter Treatment. In Figure 2, the logarithms of ketone to acetal equilibrium constants in methanol are plotted against the Wepster σ^n[24] and the Brown–Okamoto σ^+ parameters.[25] It is clear that neither the σ^n nor the σ^+ scale give satisfactory relationships. Since σ^n is believed to measure the polar interactions between the reacting side chain and the substituted ring in the absence of through-ring conjugation between electron-donating substituents and a reaction center of low π electronic density,[26] it follows that through conjugation would occur but to a lesser extent than for the reaction used as a standard for the definition of the σ^+ parameters (rate for hydrolysis of substituted phenyldimethylcarbinyl chlorides in 90% aqueous acetone at 25 °C).

An equation which caters to this kind of situation was proposed by Yukawa and Tsuno,[27] and later by Yukawa,

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(20) To test the validity of the procedure, the Gibbs energies of transfer of 4-nitroacetophenone and the related acetal from methanol to water were also determined from the limit solubilities in the two solvents (0.395 M and 8.8×10^{-3} M for the ketone, 0.925 M and 9.84×10^{-4} M for the acetal, in methanol and water, respectively). The results obtained by the equation

$$\Delta G^\circ_{m\to w} = -RT \ln (x_w^{max}/x_m^{max})$$

(where x_w^{max} and x_m^{max} are the limit mole fractions in water and methanol) [$(\Delta G^\circ_{m\to w})_{ke} = 2.74$ kcal mol^{-1}; $(\Delta G^\circ_{m\to w})_{ac} = 4.60$ kcal mol^{-1}] are in agreement with those calculated from the partition coefficients (Table III). It should be noted that the solubility procedure is less reliable than that based on partition coefficients because of the large solubilities in methanol which could make activities different from concentrations.

(21) $p^\circ_m/(k_w)_m$ and $p^\circ_w/(k_m)_w$, the ratios of the vapor pressures and of the Henry coefficients, were calculated from literature data (Butler, J. A. V.; Thomson, D. W.; McLennan, W. H. *J. Chem. Soc.* **1933**, 674–686; Hall, D. J.; Mash, C. J.; Pemberton, R. C. *Natl. Phys. Lab. Div. Chem. Stand. NPL Rep. Chem. (UK)* **1979**, *95*).

(22) As far as we know, there is no quantitative data on the mutual solubilities of dodecane and methanol in the literature. These have been estimated from literature data on the different normal alkane–methanol solvent systems ("Solubilities of Inorganic and Organic Compounds"; Stephen, H., Stephen, T., Eds.; Pergamon Press: London, 1963; Vol. 1, pp 1143–1145. We assumed that the log *P* terms for the partition of methanol and alkane between the two phases are linearly dependent on the number of methylene groups in the alkane, and we extrapolated data for the methanol–heptane, methanol–octane, and methanol–nonane to the methanol–dodecane systems. These estimations provided the following methanol to dodecane w/w ratios: 89.2:10.8 and 0.3:99.7. Direct GLC measurements provided 92:8 and 0:100.

(23) Since, this value is only estimated (cf. ref 22), systematic errors on $(K_x)_d$ can occur. However, it should be stressed that such a systematic error is of no matter for the following discussion which deals mainly with relative variations with substituent.

(24) 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: –0.111 (4-OCH_3), –0.069 (3-CH_3), –0.129 (4-CH_3), 0.168 (4-F), 0.238 (4-Cl), 0.373 (3-Cl), 0.467 (3-CF_3), 0.710 (3-NO_2), 0.778 (4-NO_2).

(25) The σ^+ parameters are those of Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4087: –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), 0.674 (3-NO_2), 0.790 (4-NO_2).

(26) Vorpagel, E. R.; Streitwieser, Jr., A.; Alexandros, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 3777–3781.

(27) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 971–981.

Tsuno, and Sawada (eq 18).[7,28-30] As suggested by Young

$$\log k \text{ (or } K) = \rho[\sigma^n + r(\sigma^+ - \sigma^n)] + i \qquad (18)$$

and Jencks,[31] this equation can also be written as eq 19,

$$\log k \text{ (or } K) = \rho^n\sigma^n + \rho^r(\sigma^+ - \sigma^n) + i \qquad (19)$$

whereby it is possible to separate the polar contribution of the substituted ring from the through-conjugation effect. When applied to acetal formation in methanol, an excellent relationship is observed (eq 20). A similar treatment in

$$\log (K_x)_m = (1.73 \pm 0.086)\sigma^n + (1.01 \pm 0.13)(\sigma^+ - \sigma^n) - (3.19 \pm 0.04)$$

($\mathcal{R} = 0.9993$; $s = 0.032$; $F = 2130$; $pF = 256$; $n = 9$)[24,25,32] (20)

dodecane and water gives eq 21 and 22.

$$\log (K_x)_d = (1.81 \pm 0.18)\sigma^n + (1.06 \pm 0.27)(\sigma^+ - \sigma^n) - (3.49 \pm 0.09)$$

($\mathcal{R} = 0.997$; $s = 0.07$; $F = 512$; $pF = 63$; $n = 8$)[24,25,32] (21)

$$\log (K_x)_w = (0.99 \pm 0.19)\sigma^n + (0.90 \pm 0.29)(\sigma^+ - \sigma^n) - (4.42 \pm 0.10)$$

($\mathcal{R} = 0.993$; $s = 0.07$; $F = 166$; $pF = 38$; $n = 8$)[24,25,32,33] (22)

It is noteworthy that the ρ^n value depends on the solvent (1.73 in methanol, 1.81 in dodecane, and 0.99 in water) and that the ρ^n/ρ^r ratio decreases when going from dodecane or methanol (1.7) to water (1:1). This means that the polar effects are relatively more important in dodecane or methanol than in water.

According to eq 23, deduced from eq 12, the effect of

$$\delta_X \log (K_x)_{S_2} = \delta_X \log (K_x)_{S_1} + \delta_X[(\Delta G^\circ_{S_1 \to S_2})_{ac} - (\Delta G^\circ_{S_1 \to S_2})_{ke}]/RT \qquad (23)$$

a substituent X on log K_x [$\delta_X \log (K_x)_{S_2}$] in a solvent S_2, water or dodecane, can be expressed as a function of the substituent effect in S_1 [$\delta_X \log (K_x)_{S_1}$] and of the substituent effect on the Gibbs free energies of transfer of acetals and ketones. In Figure 3, the differences between the acetal and ketone Gibbs free energies of transfer from methanol or dodecane to water are plotted against the σ^n parameters. The straight lines observed correspond to the following equations:

$$[(\Delta G^\circ_{m \to w})_{ac} - (\Delta G^\circ_{m \to w})_{ke}]/RT = (0.80 \pm 0.11)\sigma^n + 0.75 \quad (r = 0.984;\ s = 0.05;\ F = 219;\ n = 9) \qquad (24)$$

$$[(\Delta G^\circ_{d \to w})_{ac} - (\Delta G^\circ_{d \to w})_{ke}]/RT = (0.73 \pm 0.14)\sigma^n + 1.52 \quad (r = 0.969;\ s = 0.07;\ F = 110;\ n = 9) \qquad (25)$$

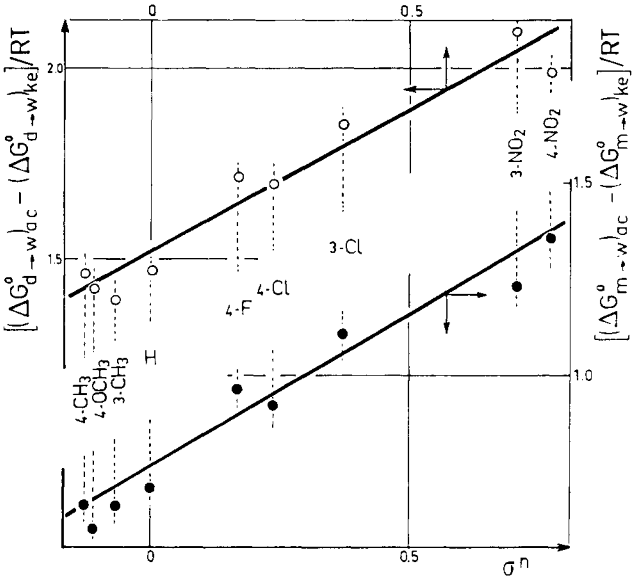

Figure 3. Differences between Gibbs free energies of transfer of acetals and ketones from dodecane to water (open circles) and from methanol to water (closed circles) vs. σ^n normal substituent parameters for the ring-substituted acetophenone series.

Since the Yukawa–Tsuno treatment does not significantly[34] improve the relationships, this shows that polar interactions are predominant in the transfer energy terms, whereas the through-conjugation effects are negligible. In other words, *these relationships mean that ρ^n in eq 19 decreases from methanol or dodecane to water and that ρ^r can be considered as solvent independent.*

The independence of the Gibbs free energies of transfer from through conjugation is in agreement with what has been established for other series of compounds;[35] it means that through conjugation does not significantly modify the solvation of the carbonyl group. Hence, the resonance energy of acetophenones is not very changed when going from an inert aprotic solvent with a low dielectric constant to more polar protic solvents.

Applying the Young–Jencks form of the Yukawa–Tsuno equation to other reactions involving the trigonal to tetrahedral conversion of the carbonyl carbon atom is interesting. The chosen examples correspond to reactions of benzaldehydes or acetophenones which yield uncharged chemical species, or to reactions which yield products with a negative charge delocalized enough to minimize dipole–charge interactions. For the examples listed in Table IV, it is clear that ρ^r is always close to 1 and roughly solvent

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

(29) Johnson, C. D. "The Hammett Equation"; Cambridge University Press: London, 1973; pp 86–92.

(30) Yukawa, Tsuno, and Sawada (cf. ref 28) used the σ° scale instead of the σ^n scale. Recent ab initio calculations (cf. ref 26) showed that the σ^n parameters are more appropriate.

(31) (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.

(32) In the regression equations, figures after the sign ± are the standard deviations of the regression coefficients; *r* and $\mathcal{R}$ are the sample and multiple correlation coefficients for linear and multiple regression, respectively; *s* is the standard deviation for regression; *F* and p*F* (partial *F* for the latest cited variable) are as defined by Draper, N. R.; Smith, H. "Applied Regression Analysis"; Wiley: New York, 1966; *n* is the number of points.

(33) The one-parameter treatment with the σ^+ scale gives:

$$\log (K_x)_w = (0.95 \pm 0.01)\sigma^+ - 4.41$$

$$(r = 0.992;\ s = 0.07;\ F = 386;\ n = 8)$$

(34) The Yukawa-Tsuno treatment gives:

$$[(\Delta G^\circ_{m \to w})_{ac} - (\Delta G^\circ_{m \to w})_{ke}]/RT = 0.79\ \sigma^n + 0.036(\sigma^+ - \sigma^n) + 0.75$$

$$(\mathcal{R} = 0.985;\ s = 0.08;\ F = 96;\ pF = 0.12;\ n = 9)$$

$$[(\Delta G^\circ_{d \to w})_{ac} - (\Delta G^\circ_{d \to w})_{ke}]/RT = 0.75\ \sigma^n - 0.06(\sigma^+ - \sigma^n) + 1.51$$

$$(\mathcal{R} = 0.970;\ s = 0.10;\ F = 48;\ pF = 0.19;\ n = 9)$$

(35) Hansch, C; Leo A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; John Wiley: New York, 1979; pp 13–43.

(36) Geneste, P.; Lamaty, G.; Roque, J. P. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 188–194.

(37) Ching, W. M.; Kallen, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6119–6124.

(38) Greenzaid, P. *J. Org. Chem.* **1973**, *38*, 3164–3167.

(39) Steward, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399–406.

(40) Davis, T. S.; Feil, P. D.; Kubler, D. G.; Wells, D. J. *J. Org. Chem.* **1975**, *40*, 1478–1482.

(41) Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 185–189.

Table IV. Young-Jencks Modified Yukawa-Tsuno Treatment of Substituent Effects on Equilibrium Constants for Reactions of Benzaldehydes and Acetophenones Involving the Trigonal to Tetrahedral Conversion of the Carbonyl Carbon Atom[a]

reaction	solvent	$\rho^{n\ b,c}$	$\rho^{r\ b,c}$	$\mathcal{R}^c$	s^c	n^c	ref
$ArCOCH_3 + HSO_3^- \rightleftharpoons ArC(OH)(SO_3^-)CH_3$	water	1.11 ± 0.08	0.76 ± 0.21	0.999	0.016	5	31a
$ArCHO + HSO_3^- \rightleftharpoons ArCH(OH)(SO_3^-)$	water	1.17 ± 0.34	1.30 ± 0.25	0.996	0.057	5	36
$ArCHO + HCN \rightleftharpoons ArCH(OH)(CN)$	water	1.00 ± 0.28	1.00 ± 0.19	0.994	0.109	7	37
$ArCHO + H_2O \rightleftharpoons ArCH(OH)_2$	water	1.17	1.06				estimated[d]
$ArCOCH_3 + 2\ CH_3OH \rightleftharpoons ArC(OCH_3)_2CH_3 + H_2O$	water	0.99 ± 0.19	0.90 ± 0.29	0.993	0.072	8	this work
$ArCHO + 2\ CH_3OH \rightleftharpoons ArCH(OCH_3)_2 + H_2O$	methanol 95%	1.58 ± 0.18	1.11 ± 0.13	0.999	0.030	5	40
$ArCHO + CH_3OH \rightleftharpoons ArCH(OH)OCH_3$	methanol	1.97 ± 0.16	0.91 ± 0.25	0.996	0.069	11	41
$ArCOCH_3 + 2\ CH_3OH \rightleftharpoons ArC(OCH_3)_2CH_3 + H_2O$	methanol	1.73 ± 0.09	1.01 ± 0.13	0.999	0.032	9	this work
$ArCOCH_3 + 2\ CH_3OH \rightleftharpoons ArC(OCH_3)_2CH_3 + H_2O$	dodecane	1.81 ± 0.18	1.06 ± 0.27	0.997	0.066	8	this work

[a] At 25 °C. [b] Parameters of eq 19. [c] Cf. ref 32. [d] Treatment of data from ref 38 for hydroxide attachment to substituted benzaldehydes gives $\rho^n = 2.37$ and $\rho^r = 1.06$. The ρ^n value for water addition was calculated as the difference 2.37-1.20, where 1.20 is the ρ^n value for benzaldehyde hydrate dissociation, estimated by analogy with data on trifluoroacetophenone hydrate dissociation (ref 39).

Table V. Taft-Lewis Dual-Parameter Treatment of the Substituent Effects on the Ketone to Acetal Equilibrium Constants for the Acetophenone Series[a]

solvent	substituent parameters	ρ_I	ρ°_R	ρ^+_R	ρ^r	$\mathcal{R}$	s	F	pF
methanol	σ_I, σ°_R [b]	1.75 ± 0.36	2.47 ± 0.45			0.989	0.12	137	118
dodecane		1.82 ± 0.46	2.59 ± 0.60			0.985	0.16	84	73
water		0.94 ± 0.33	1.81 ± 0.44			0.980	0.12	62	68
methanol	σ_I, σ^+_R [c]	1.73 ± 0.11		1.34 ± 0.07		0.999	0.04	1560	1390
dodecane		1.80 ± 0.25		1.40 ± 0.17		0.996	0.09	300	267
water		0.93 ± 0.19		0.98 ± 0.12		0.994	0.06	219	247
methanol	$\sigma_I, \sigma^\circ_R, \sigma^+_R - \sigma^\circ_R$ [d]	1.73 ± 0.09	1.53 ± 0.24		1.13 ± 0.25	0.995	0.03	1359	83
dodecane		1.80 ± 0.26	1.61 ± 0.67		1.18 ± 0.70	0.996	0.09	177	11
water		0.93 ± 0.19	1.11 ± 0.50		0.85 ± 0.52	0.995	0.07	125	10.7

[a] For the meaning of the statistical terms, cf. ref 32. [b] Cf. eq 26. [c] Cf. eq 27. [d] Three-parameter treatment; cf. eq 28 and ref 44.

independent, but that ρ^n is solvent dependent (e.g., ρ^n is 1.97 for the addition of methanol to benzaldehydes, yielding hemiacetal in methanol, whereas it is smaller and equal to 1 for addition of water or HCN in water).

Since the σ^n-type parameters which measure the overall polar effect of the substituted aromatic ring contain resonance contributions due to conjugation of the substituent with the ring, Taft et al.[42] suggested another approach to dual-substituent effects based on a separation of the true *polar effect of the substituent* (characterized by a single set of σ_I parameters) from the resonance contribution. Because resonance with the reaction center depends on the electron demand, these authors suggested distinguishing four different cases with four different σ^+_R sets. The set σ°_R is valid when through conjugation does not occur, and σ_R should be used when conjugation with a center of low electron density occurs (the other two sets, $\sigma_{R,BA}$ and σ^-_R, cater to situations analogous to benzoic acids and when through conjugation with a center of high electron density occurs).

Table V lists the results of the dual-parameter treatment using eq 26 and 27.[43] From these results, it is seen that,

$$\log K_x = \rho_I\sigma_I + \rho^\circ_R\sigma^\circ_R + i \qquad (26)$$

$$\log K_x = \rho_I\sigma_I + \rho^+_R\sigma^+_R + i \qquad (27)$$

as expected, eq 26 does not provide a good fitting of the experimental results, but that eq 27 yields good relationships. However, it can be noted that, in contrast to the Young–Jencks procedure, the ρ^+_R parameter is not constant from one solvent to another. Since the interesting solvent independence of through-conjugation effects cannot be detected with the Taft equation, it is concluded that this equation appears less useful *for this type of study* than the modified Yukawa–Tsuno formulation. This failure results from the fact that the Taft approach does not distinguish the resonance within the aromatic ring (which is partly behind the overall solvent-dependent polar effect of the substituted ring) from the through-conjugation effect.

As pointed out by Nieuwdorp et al.[44] a complete description of substituent effects for this kind of reaction would require a three-parameter relationship (eq 28) but,

$$\log K_x = \rho_I\sigma_I + \rho^\circ_R\sigma^\circ_R + \rho^r(\sigma^+_R - \sigma^\circ_R) + i \qquad (28)$$

as stressed by these authors, the significance of such a three-parameter treatment is questionable for a rather limited number of points. Nevertheless, ρ_I, ρ°_R, and ρ^r have been calculated and the results are also reported in Table V. It can be noted that the ρ_I/ρ°_R ratios are close to unity as required for the validity of the Yukawa–Tsuno treatment.[44,45]

The Origin of the Substituent Effects. As stated above, it is well established that the $\rho^r(\sigma^+ - \sigma^n)$ term in eq

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(42) (a) Taft, R. W.; Lewis, I. C. *J. Am. Chem. Soc.* **1959**, *81*, 5343–5352. Taft, R. W.; Ehrenson, S.; Lewis, I. C.; Glick, R. E. *Ibid.* **1959**, *81*, 5352–5361. (b) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1–80 and references cited therein. (c) Charton, M. *Ibid.* **1981**, *13*, 119–251.

(43) The values of σ_I, σ_R° and σ_R^+ are those given in ref 42b. For meta substituent 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 when testing eq 27.

(44) Nieuwdorp, G. H. E.; de Ligny, C. L; van Houvelingen, H. C. *J. Chem. Soc., Perkin Trans. 2* **1979**, 537–544.

(45) The property that the ρ_I/ρ_R° ratio is roughly equal to unity whatever the solvent is probably only valid within the limits of a first approximation. Taft et al. (Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 4766–4770) reported that the ρ_I/ρ_R° ratio increases with solvent polarity (from 0.16 for cyclohexane to 0.26 for DMSO) when correlating the C-13 chemical shifts in para-substituted benzenes with the σ_I and σ°_R parameters. This "shows that there are relatively greater effects of solvent polarity on the substituent induced polarization of the benzene Π electrons than on Π electron delocalization".

Table VI. Hydrophobic Substituent $\Pi_{X(Y)}$ Parameters for the Dodecane-Water and Methanol-Water Systems

	acetophenones ($Y = COCH_3$)[a]		acetophenone dimethyl acetals ($Y = C(OCH_3)_2CH_3$)[a]		monosubstituted benzenes ($Y = H$)[b]
X	water-dodecane	water-methanol	water-dodecane	water-methanol	water-octanol
4-OCH_3	−0.23	−0.41	−0.28	−0.52	−0.02
4-CH_3	0.51	0.42	0.50	0.37	0.56
3-CH_3	0.60	0.47	0.52	0.42	0.56
4-F	0.08	0.18	0.32	0.44	0.14
4-Cl	0.73	0.61	0.95	0.82	0.71
3-Cl	0.89	0.86	1.26	1.26	0.71
3-NO_2	−0.59	−0.07	0.04	0.49	−0.28
4-NO_2	−0.43	−0.19	0.09	0.46	−0.28

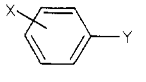
[a] $\Pi_{X(Y)}$ values calculated from data in Table III and defined as $\Pi_{X(Y)} = \log P_{X(Y)} - \log P_{H(Y)}$ (cf. text for the definition of the symbols). [b] $\Pi_{X(H)}$ values from ref 35.

20–22 results from through-conjugation effects within the acetophenone molecular entity.[46] Through conjugation stabilizes the keto form and makes the ketone to acetal equilibrium constant lower. In contrast, the origin of the substituted ring polar effects is not as clear. Do they stem mainly from ketones or from acetals? Are they inductive effects, i.e., through-bond polar effects, or field effects, i.e., through-solvent dipolar interactions?

The variations of Hammett ρ parameters with solvents are usually interpreted in terms of the Kirkwood–Westheimer field effect theory[47,48] whereby field effects, which correspond to dipolar interactions within the reacting molecules or/and within the products, depend on the effective dielectric constant D_E of the solvent cavity where the molecule is located. D_E is a function of the dielectric constant of the bulk solvent and of the shape of the cavity. Poh[48] recently examined the variations of substituted benzoic acid acidity constants as a function of the solvent and tested the Kirkwood–Westheimer approach. He emphasized that D_E variations should be very small for solvents with bulk dielectric constants (D) higher than 20. In view of this, the changes in coulombic dipole interactions in acetal and ketone molecular entities should be very small in going from water ($D = 78$) to methanol ($D = 32$) and large in going from methanol to dodecane ($D = 2$). This clearly runs counter to what is observed for the ketone to acetal equilibrium. Notwithstanding, it can be noted that the dipolar solvent effect difference between water and methanol is usually a little larger than that expected from the D_E approach (e.g., the solvatochromic Taft[49] Π^* parameters are −0.08, 0.60, and 1.09 for dodecane, methanol, and water, respectively) although it is insufficient for making methanol closer to dodecane than to water.

As the variations of the amplitude of the substituent effects with solvents are closely related to the substituent effects on the Gibbs free energies of transfer for ketone and acetal from one solvent to another (eq 23), a study of the effects of X groups on the partition coefficients of ketones and acetals is interesting.

Let us consider the two series of compounds where Y



is $COCH_3$ or $C(CH_3)(OCH_3)_2$ and where X varies. If $(\Delta G^\circ_t)_{X(Y)}$ is the Gibbs free energy of transfer from solvent S_1 to solvent S_2 for a member of these series, $(\Delta G^\circ_t)_{X(Y)}$ can be written as in eq 29, where $(\Delta G^\circ_t)_{H(Y)}$ is the Gibbs

$$(\Delta G^\circ_t)_{X(Y)} = (\Delta G^\circ_t)_{H(Y)} + \delta(\Delta G^\circ_t)_{X(Y)} \qquad (29)$$

free energy of transfer for the unsubstituted compound and where $\delta(\Delta G^\circ_t)_{X(Y)}$ is the increment due to X. This equation can also be written as eq 30, where $\Pi_{X(Y)}$ can be called the

$$\log P_{X(Y)} = \log P_{H(Y)} + \Pi_{X(Y)} \qquad (30)$$

hydrophobic character parameter of X in the presence of Y. It is well established that $\Pi_{X(Y)}$ is roughly equal to $\Pi_{X(H)}$ (monosubstituted compounds) and is independent of Y when Y is an inert substituent or when the electronic and dipolar interactions are of minor importance.[50,51] Therefore, strong deviations of $\Pi_{X(Y)}$ from $\Pi_{X(H)}$ for dipolar substituents, such as halogens, can be characteristic of strong interactions between X and Y.

Typical values of $\Pi_{X(H)}$ are given in the literature for the water-octanol solvent system which is usually chosen as a reference in this kind of study.[35,51] In Table VI, values of $(\Pi_{w\to d})_{X(Y)}$ and $(\Pi_{w\to m})_{X(Y)}$, for the water–dodecane and water–methanol systems, respectively, are compared with the standard $(\Pi_{w\to o})_{X(H)}$ values for the water–octanol system.[52] Data for acetophenones show that the Π values for the water–dodecane system are not very different from those for the water–octanol system, and that Π depends only slightly on the meta or para positions of the substituent (e.g., $\Pi_{w\to d}$ is 0.73 for 4-Cl and is 0.88 for 3-Cl, whereas $\Pi_{w\to o}$ is 0.71). This means that the interactions between X and the carbonyl group do affect the respective solvations, but moderately. In contrast, the X–Y interactions effects on solubilities seem quite large for acetals, e.g., $\Pi_{w\to d}$ for the chloro group in the meta position (1.26) differs largely from that for the chloro group in the para position (0.95) and from $\Pi_{w\to o}$ (0.71) for the monosubstituted benzene.[53] These remarks suggest that the X–Y interactions provoke far larger variations of X and Y

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(46) Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128.

(47) (a) Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506–512, 512–517. (b) Westheimer, F. H.; Jones, W. A.; Lad, R. A. *Ibid.* **1942**, *10*, 478–485. (c) Tanford, C. *J. Am. Chem. Soc.* **1957**, *79*, 5348–5352. See also: ref 42c.

(48) Poh, B.-L. *Aust. J. Chem.* **1980**, *33*, 1175–1186.

(49) Chawla, B.; Pollack, S. K.; Lebrilla, C. B.; Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 6924–6930.

(50) Franke, R.; Dove, S.; Kühne, R. *Eur. J. Med. Chim. Ther.* **1979**, *14*, 363–374.

(51) Cf., e.g.: (a) Hansch, C. "Drug Design"; Ariëns, E. J., Ed.; Academic Press: New York and London, 1971; pp 271–342. (b) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–624.

(52) It is well established that the logarithms of the water-octanol partition coefficients are linearly related to the logarithms of the partition coefficients between water and every other organic solvent studied (cf. ref 51). Therefore, since the $\Pi_{X(Y)}$ values are not very different from each other for the methanol-water and dodecane-water systems, when the X group is not too hydrogen bonded to the protic solvents, a direct comparison with $\Pi_{X(H)}$ for the octanol-water system is pertinent.

(53) An interesting comparison can be made with the $[\Pi_{X(Y)}]_{w\to o}$ literature data (ref 50). For X = 3-Cl, Π = 0.76, 0.68, 0.83, 0.61, 1.04, and 0.71 for the Y = OCH_2COOH, CH_2OH, COOH, NH_2, NO_2, OH, and H, respectively. For X = 4-Cl, Π = 0.70, 0.70, 0.87, 0.93, 0.54, 0.93, and 0.71 respectively for the same Y groups. These results show that the Π values for acetals are abnormally large.

solvation in the case of acetals than in the case of ketones.

It is noteworthy that eq 24 and 25 also express that the differences $\Pi_{ac} - \Pi_{ke}$ for the water–dodecane and water–methanol systems vary linearly with σ^n, with slopes equal to 0.80 and 0.73, respectively. Therefore, it is clear that the variations of ρ^n on going from methanol or dodecane to water stem from X and Y mutual effects on respective solvations. Moreover, since $(\Pi_{ac} - \Pi_{ke})$ vs. σ^n slopes are roughly equal for the water–dodecane and water–methanol systems, and since group-interaction effects are much larger for acetals than for ketones, it is likely that *the ρ^n variations stem mainly from substituent effects on acetal group solvation by water molecules.*

It can be emphasized that such a conclusion runs counter to what is expected.

(i) Since the carbonyl group is strongly hydrogen bonded in protic solvents,[54] it is surprising that the field substituent effects on solvation are far larger for acetals than for ketones.

(ii) Although methanol is slightly less able than water to act as a hydrogen-bond donor,[55] hydrogen-bond solvation of acetals by methanol should also occur;[51] it is peculiar that the polar effects of the substituent ring in methanol are similar to those in dodecane but are very different from those in water.

To interpret these points, it can be noted that the partition coefficients of acetals between water and dodecane (log $P = 2.60$) and between water and methanol (log $P_{w\rightarrow d}$ + log $P_{d\rightarrow m} = 2.52$) are abnormally high due to their low solubility in water. Indeed, whereas the partition coefficients observed for unsubstituted acetophenone (log $P_{w\rightarrow d}$ v 1.12 and log $P_{w\rightarrow m} = 1.81$) are in agreement with those reported for other solvent systems (1.68, 1.58, and 1.73 for water–octanol, 1.25 for water–cyclohexane, and 1.08 for water–*n*-heptane)[35] and with that calculated as the sum of the group contributions for the water–octanol system (1.58),[56] the values measured for acetophenone dimethyl acetal deviate largely from that calculated by the additivity rule for the water–octanol system (1.25).[57] This means that hydrogen-bond solvation of acetals by water molecules is strongly inhibited.

Literature data have shown that water to octanol partition coefficients are abnormally increased (i.e., relative solubilities in water are decreased) by a proximity effect when solvated groups are in the benzylic position.[35] For instance, the fragment constants f^{1R} for partition coefficient calculations (fragment method) are 0.48, −1.76, and −1.34 for the benzylic bromo, −N<, and hydroxy groups, respectively, instead of 0.20, −2.18, and −1.64 for normal positions.[35] (In the absence of f^{1R} data for the methoxy group, the usual +0.15 term was assumed in the calculation of log P for acetophenone dimethyl acetal.)[57] In order to explain the low solubility of acetals in water, as well as the large substituent effects on water solvation, it can be suggested that such proximity effects in acetals are far larger than usual, as a consequence of strong hydrophobic or dipole–dipole interactions of the phenyl group with the solvating water molecules. It can be considered that the strongly hydrophobic methyl groups force the solvating water molecules to be in the vicinity of the phenyl group. Therefore, methoxy group solvation would be controlled by the hydrophobic or dipole character of the aryl group which in turn depends on the substituent.

The similarities between substituent effects on ketone to acetal constants in methanol and dodecane, as well as between the Π values for the methanol–water and dodecane–water systems, suggest that hydrogen-bond solvation of acetal molecules by methanol is very weak. This property probably also stems from the oxygen atom–ring interaction which make the hydrogen-bond basicity of acetals far weaker. It can also be asserted that solvation by methanol is a priori due to hydrogen bonding involving the OH group, or to hydrophobic interactions involving the CH_3 group. Therefore, the prevalence of one of the two kinds of interactions depends on the hydrogen-bond basicity of the solute. For weak hydrogen-bond acceptors as aromatic acetals, it is likely that hydrophobic interactions predominate and that the arrangement of the solvent molecules in the cybotactic region favors such a solvation. This would explain why the behavior of acetals in methanol more closely resembles their behavior in hydrocarbons than in water.

Ring–oxygen interactions in acetals are probably not strong enough to explain the 1.7–1.8 ρ^n value in methanol or dodecane, i.e., in the absence of solvation inhibition. Besides these effects, it is likely that usual through-bond solvent-independent polar effects occur. These inductive effects can stem from ketone stability, or from acetal stability, or from both. However, the analogies in ρ^n for different reactions involving the trigonal to tetrahedral conversion of the carbonyl carbon atom and yielding uncharged species (Table V) suggest that the polar substituent effects for all these reactions have the same origin. So, most of the inductive effects are probably related to the influence of X on ketone or aldehyde stability caused by increasing or decreasing the electron density at the positive-charged carbonyl carbon atom.

In summary, three different effects have been considered for interpreting the variations of the ketone to acetal equilibrium constants with substituents in methanol, dodecane, and water: (i) an inductive effect on the stability of the carbonyl compound, (ii) a through-ring conjugation effect between the carbonyl group and the substituent, and (iii) a specific inhibition of acetal solvation.

Experimental Section

Materials. For ketone to acetal equilibrium measurements, methanol (Baker Analyzed Reagent) was distilled with magnesium under nitrogen. The water concentrations (usually less than 30 mg L^{-1}) were checked as described previously[58] and by the Karl Fischer method. Methanolic solutions of hydrobromic acid were prepared by bubbling gaseous HBr (Baker Chemicals) and subsequent dilution. Bulk solutions were stored at −18 °C. Acetophenones were obtained commercially and purified by GLC (Varian Aerograph 1200 instrument, $^3/_8$ in. × 10 ft column packed with 30% Carbowax on Chromosorb W) (except 3-nitroacetophenone and 4-nitroacetophenone which were recrystallized from hot methanol, mp 80–81 °C and 80 °C, respectively). Acetophenone dimethyl acetals were prepared by the reaction of trimethyl orthoformate in methanol with the parent ketone[59] and

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(54) An estimation of the respective abilities of acetophenones and of the parent dimethyl acetals to accept hydrogen bonding is provided by the β scale of solvent HBA (Hydrogen Bond Acceptor) basicities (cf. ref 8b). The reported β values for acetone (0.48) and acetophenone (0.49) are slightly larger than that for dimethoxyethane (0.41).

(55) According to Kamlet, Abboud, and Taft (ref 8b), "the α scale of solvent HBD (Hydrogen Bond Donor) acidities provides a quantitative measure of the ability of a bulk solvent to act as a hydrogen bond donor toward a solute". α values are 1.13, 0.98, and 0 for water, methanol, and dodecane, respectively.

(56) log P for $C_6H_5COCH_3 = f^{\Phi}{}_{C_6H_5} + f_{CO} + f_{CH_3} + (2 - 1)F_b = 1.90 + (-1.09) + 0.89 + (-0.12) = 1.58$ (Symbols are defined in ref 35).

(57) log P for $C_6H_5C(OCH_3)_2CH_3 = f_{C_6H_5} + f_C + f_{CH_3} + 2F_{cBr} + 2f^{1R}_{-O-} + 2f_{CH_3} + (5 - 1)F_b = 1.90 + 0.20 + 0.89 + 2(-0.13) + 2(-1.54 + 0.15) + 2(0.89) + 4(-0.12) = 1.25$. The +0.15 figure in the fifth term allows for the benzylic position of the methoxy groups. Symbols are defined in ref 35.

(58) Toullec, J.; El-Alaoui, M. *Anal. Chim. Acta* **1979**, *109*, 187–190.

(59) Loudon, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 465–479.

Table VII. Observed Molar Extinction Coefficients of Substituted Acetophenones and the Parent Dimethyl Acetals in Methanol[a]

X[b]	λ, nm[c]	ϵ_{ketone}, M^{-1} cm^{-1} [d]	ϵ_{acetal}, M^{-1} cm^{-1} [d]
4-OCH_3	271	16220 ± 60	1480 ± 20
4-CH_3	252	14620 ± 60	190 ± 20
H	241	12300 ± 60	100 ± 10
4-F	243	11650 ± 80	100 ± 10
4-Cl	250	16200 ± 100	0
3-Cl	240	10000 ± 60	0
3-CF_3	235	10440 ± 80	0
3-NO_2	227	22460 ± 25	2800 ± 10
4-NO_2	263	13760 ± 60	10000 ± 80

[a] On a Cary 16 spectrophotometer (1-cm quartz cells, slit width = 0.3 mm and temp = 25 °C). [b] X in $XC_6H_4COCH_3$ or in $XC_6H_4C(OCH_3)_2CH_3$. [c] Acetophenone maximum absorption wavelength. [d] Figures are standard deviations.

distilled. 3-Nitroacetophenone dimethyl acetal and 4-nitroacetophenone dimethyl acetal were recrystallized from hot methanol (mp 44–45.5 and 60–61.5 °C, respectively). The low ketone content was checked by IR spectroscopy. The amount of the parent α-methoxystyrene (due to some methanol elimination) was measured by amperometric titration by using a rotating platinum electrode. The freshly prepared basic (sodium acetate) solution of acetal in methanol was added to an aqueous solution of bromine at low concentration (10^{-6} M); the bromine uptake, due to the fast reaction of the enol ether with the halogen, makes it possible to determine the amount of enol ether in the initial material. Usually, the enol ether content was very low (<0.5%), except for 4-methoxyacetophenone dimethyl acetal which contained 4.6% (w/w) of the corresponding α-methoxystyrene. The UV spectrum of this acetal was corrected by taking into account the absorptivity of the parent enol ether. Other chemicals were reagent grade and used without any purification. Deionized water was distilled.

General Methods. Ketone to Acetal Equilibrium Measurements. UV spectra of acetophenones and of the related dimethyl acetals were recorded on a Varian/Cary 118 spectrophotometer, whereas equilibrium and partition coefficient measurements were performed on a Cary 16 spectrophotometer. Molar extinction coefficients measured at maximum absorption are given in Table VII. For equilibrium measurements, the variations in ketone concentrations were monitored by the absorption at a maximum absorption wavelength. The content of the thermostatted 1-cm cell was stirred by means of a small teflon-coated magnet rotated by a motor located beneath the cell holder. Temperature (25 ± 0.05 °C) was checked in the cell by a Yellow Springs Instrument 45 CU cuvette thermometer (thermistor detector YSI 4502). The cuvette was always filled in a dry box and closed by a soft stopper (silicon elastomer, Rhodorsil CAF 4, Prolabo, France). The small amounts of the methanolic ketone solutions and of water–methanol mixtures were introduced through the stopper by means of microsyringes (20–100 μL). The experimental procedure was as follows: (a) after the two beams were balanced, acetophenone–methanolic solution (weighed) was added to the HBr solution, (b) equilibration absorbance, A_1, was recorded, (c) a weighed amount of pure water or a water–methanol mixture was added to shift the equilibrium, and (d) absorbance A_2 was recorded (cf Figure 1). Usually, a slow increase of absorbance was observed before and after the water concentration jump as the result of a slow moisture contamination. Hence, appropriate corrections were introduced to determine true A_1 and A_2 at the water-jump time.

Partition Experiments. For acetophenone partition coefficient determinations, volumes V_1 (1–10 mL) of dodecane and V_2 (1–10 mL) of methanol or water (the V_1/V_2 ratio depended on the relative solubilities) were stirred at a low enough speed to avoid emulsion formation by a magnetic stirrer in a thermostatted glass vessel at 25 ± 0.1 °C. The acetophenone was introduced in the phase where it is less soluble in order to get low concentrations in the two solvents if compared to limit solubilities. After being allowed to stand for 10 h, small weighed aliquots (20–100 μL) of the two phases were transferred by means of a microsyringe to quartz 1-cm cells containing stirred methanol. Absorbances were recorded, usually at $\lambda_{\max}$. For 3- and 4-nitroacetophenone dimethyl acetals, the same procedure was followed except that the water phase was maintained at alkaline pH (9–10) by sodium carbonate to inhibit acetal hydrolysis. (Sodium carbonate was checked to have no significant effect on the measured partition coefficients). For other acetals, which exhibited small absorptivities at λ > 230 nm, aliquots of the two phases were transferred into $HClO_4$ (0.1 M) methanol–water (90:10) solutions. Under these conditions, acetal hydrolysis was fast and the absorbance due to the parent acetophenone was recorded. Standardization allowed for acetal concentration determination. Usually, partition coefficients were calculated as the ratio of the concentrations in the two equilibrated phases. It was observed that the results were very similar to those calculated from the concentration in only one phase and the total amount in both phases. For 3- and 4-nitroacetophenone dimethyl acetals, the water–dodecane partition coefficients were only determined from the concentrations in dodecane and the initial concentrations. Usually, titration measurements in each phase were repeated 4–5 times and the whole procedure for each partition coefficient determination was repeated a minimum of 4 times with different V_1/V_2 ratios.

Registry No. 4-Methoxyacetophenone, 100-06-1; 4-methylacetophenone, 122-00-9; 3-methylacetophenone, 585-74-0; acetophenone, 98-86-2; 4-fluoroacetophenone, 403-42-9; 4-chloroacetophenone, 99-91-2; 3-chloroacetophenone, 99-02-5; 3-(trifluoromethyl)acetophenone, 349-76-8; 3-nitroacetophenone, 121-89-1; 4-nitroacetophenone, 100-19-6; 4-methoxyacetophenone dimethyl acetal, 27150-99-8; 4-methylacetophenone dimethyl acetal, 53578-01-1; 3-methylacetophenone dimethyl acetal, 87461-62-9; acetophenone dimethyl acetal, 4316-35-2; 4-fluoroacetophenone dimethyl acetal, 73585-52-1; 4-chloroacetophenone dimethyl acetal, 72360-69-1; 3-chloroacetophenone dimethyl acetal, 73585-53-2; 3-nitroacetophenone dimethyl acetal, 73585-54-3; 4-nitrophenone dimethyl acetal, 53577-98-3; methanol, 67-56-1.