Correlation Analyses of the Aqueous-phase Acidities of Alcohols and *gem*-Diols, and of Carbonyl Hydration Equilibria using Electronic and Structural Parameters

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Parameters which have been used successfully to quantify gas-phase proton- and hydride-transfer reactions have now been found to be applicable to reactions in aqueous solution. These parameters can be readily derived for all species. Residual electronegativity correlates directly with pK_a values of most polar-substituted alcohols in aqueous solution. A further empirical parameter is necessary to allow alcohols substituted at the methylol carbon by simple non-polar groups, such as methyl or phenyl, to be included. It is believed that this term is related to entropy effects in solution. A few alcohols substituted by CXY_2 groups (X = H, Cl, Br; Y = Cl, Br) also deviate. In this case, the polarisability due to these large groups is believed to be a further means of stabilisation of the negative charge in the solvated anion, just as in the gas phase. *gem*-Diol pK_a values fit a similar model. The hydration equilibria of ketones and aldehydes can be quantified by the same residual electronegativity parameter along with a hyperconjunction term. These latter two reaction series permit estimation of influences which determine the addition of aqueous OH^- to the C=O group, the results of which have been compared with H^- addition to C=O in the gas phase.

In the course of developing physical models as background work for the reaction and synthesis design program, EROS,[1] we have shown how quantitative gas-phase measurements can be accurately described by new, readily calculated parameters.[2–5] These parameters include residual electronegativity, which reflects the ability of atoms to stabilise charge by inductive effects,[3] and effective polarisability,[2] which reflects stabilisation through induced dipole interactions. Linear equations have been constructed which describe the enthalpies associated with gas-phase proton and hydride-ion addition reactions of a variety of systems. Initial work was concentrated on data measured in the gas phase, where solvent influences are non-existent, thus allowing intrinsic effects of substituents to be studied.

However, since the majority of reactions of interest take place in the condensed phase, it became increasingly important to investigate how far our empirical parameters could be applied to reactions in solution. We anticipated that deviations from gas-phase behaviour could lead to an understanding of the influence of the solvent. In this paper, we describe the results of correlation analyses of three aqueous-phase systems. The first is chosen to parallel as closely as possible one of the gas-phase reactions we have already analysed, that of alcohol acidity [reactions (1) and (2)].[4,5] Not only does this reaction have a good gas-phase analogy, but it is also free of effects due to electron delocalisation, and there is a suitably large amount of relatively precise data. The second system is an extension of the first, and concerns the aqueous-phase acidity of *gem*-diols [reaction (3)]. This connects with the third reaction series, which is the aqueous-phase hydration equilibria of aldehydes and ketones to give *gem*-diols [reaction (4)]. These data, in conjunction with *gem*-diol acidity measurements, lead to a reaction cycle which can give information on the addition of hydroxide anion to the carbonyl group [reaction (5); Scheme]. Such a reaction is a prototype of the important class of nucleophilic carbonyl addition reactions. It also has a gas-phase counterpart in the hydride ion affinity of carbonyl compounds [reaction (6)] which we have already discussed.[5]

Methods

Experimental data were taken from the literature and are recorded in Tables 1—3. The method adopted has been to carry out correlation analyses between the experimental data and parameters which describe quantitatively the various physical effects. As a starting point, these were precisely those that had already been found to be significant in correlation analyses of the gas-phase reactions.

$$ROH(g) \longrightarrow RO^-(g) + H^+(g) \qquad \text{Gas-phase acidity} = \Delta H_r(1) \qquad (1)$$

$$ROH(aq) \rightleftharpoons RO^-(aq) + H^+(aq) \qquad pK_a(ROH) = -\log[RO^-][H^+]/[ROH] \qquad (2)$$

$$\begin{tikzcd} R^1R^2C(OH)_2(aq) \arrow[rr] & & R^1R^2C(OH)O^-(aq) + H^+(aq) \quad (3) \\ & R^1R^2C{=}O(aq) \arrow[ul, "+H_2O", "(4)"'] \arrow[ur, "(5)", "+OH^-"'] & \end{tikzcd}$$

$$K_{hyd}(R^1R^2C{=}O) = [\text{diol}]/[\text{carbonyl}]$$

$$R^1R^2C{=}O(g) + H^-(g) \longrightarrow R^1R^2CHO^-(g) \qquad (6)$$

Scheme.

Table 1. Aqueous acidity[a] of alcohols $R^1R^2R^3COH$ and empirical parameters[b]

R^1	R^2	R^3	pK_a	$\bar{\chi}_{12}$	*np*	α_d
Set A: polar substituents apart from CCl_3, $CHCl_2$, CBr_3, and $CHBr_2$						
CF_3	CF_3	CF_3	5.20[c]	7.259	0	3.434
CF_3	CF_3	CF_2Cl	5.30[c]	7.139	0	4.032
CF_3	CF_3	$COH(CF_3)_2$	5.95[c]	6.941	0	4.215
H	CF_3	CF_3	9.30	6.511	0	2.686
H	H	$C_2F_4CH_2OH$	12.10[d]	5.622	0	2.497
H	H	$C_4F_8CH_2OH$	12.10[d]	5.624	0	2.292
H	H	CF_3	12.37	5.781	0	1.976
H	H	CF_2CHF_2	12.74	5.618	0	2.244
H	H	CHF_2	13.30	5.547	0	2.027
H	H	CH_2CN	14.03	5.236	0	2.698
H	H	$C(CH_2OH)_3$	14.10	5.234	0	3.596
H	H	CH_2F	14.20	5.332	0	2.163
H	H	CH_2Cl	14.31	5.235	0	2.850
H	H	CH_2Br	14.38	5.209	0	3.040
H	H	CH_2I	14.56	5.204	0	3.757
H	H	$C_2H_4OCH_3$	14.82	5.292	0	2.630
H	H	C_2H_4OH	15.07	5.289	0	2.492
H	H	C_3H_6OH	15.10[e]	5.161	0	2.706
H	H	CH_2OPh	15.10	5.297	0	2.644
H	H	$C_2H_4OC_2H_5$	15.12	5.292	0	2.630
H	H	H	15.49	5.079	0	1.779
Set B: alcohols containing unsubstituted alkyl or phenyl groups						
CH_3	CF_3	CF_3	9.60[c]	6.558	1	3.374
Ph	H	CF_3	11.90[e]	6.012	1	4.123
CH_3	CH_3	CF_3	12.70	5.873	2	3.469
CH_3	H	CF_3	13.08	5.827	1	2.714
$C{\equiv}CH$	H	H	13.55	5.516	1	1.644
$C{\equiv}CPh$	H	H	13.87	5.522	1	2.631
$C{\equiv}CCH_3$	H	H	14.16	5.519	1	2.716
Ph	H	H	15.40	5.300	1	3.506
CH_2Ph	H	H	15.48	5.171	1	3.191
$CH{=}CH_2$	H	H	15.52	5.248	1	2.896
$CH{=}CHPh$	H	H	15.62	5.254	1	2.841
$CH{=}CHCH_3$	H	H	15.80	5.251	1	2.963
CH_3	H	H	15.90	5.124	1	2.509
$C(CH_3)_3$	H	H	16.04	5.171	1	3.644
CH_2CH_3	H	H	16.10	5.140	1	2.841
$CH(CH_3)_2$	H	H	16.10	5.156	1	3.231
CH_3	CH_3	H	16.57	5.169	2	3.284
CH_3	CH_3	CH_3	16.84	5.214	3	4.071
Set C: alcohols containing CCl_3, $CHCl_2$, CBr_3, or $CHBr_2$ groups						
CCl_3	CF_3	CF_3	5.10[c]	6.916	0	5.255
CCl_3	CCl_3	H	10.30	5.847	0	6.511
CCl_3	H	H	12.24	5.461	0	3.956
CBr_3	H	H	12.70	5.381	0	4.959
$CHCl_2$	H	H	12.89	5.347	0	3.379
$CHBr_2$	H	H	13.29	5.294	0	3.971

[a] Unless otherwise stated, data from the compilation in ref. 13. Some extrapolated values are included. [b] $\bar{\chi}_{12}$ is the residual electronegativity parameter; *np* reflects the number of non-polar groups attached to the methylol carbon; α_d is the effective polarisability. [c] R. Filler and R. M. Schure, *J. Org.* 1967, **32**, 1217. [d] C. H. Rochester, in 'The Chemistry of the Hydroxy Group,' ed. S. Patai, Interscience: London, 1971, Part 1, p. 327. [e] J. Murto, note *d*, Part 2, p. 1087.

The background to the empirical residual electronegativity ($\bar{\chi}_{12}$), polarisability (α_d), and hyperconjugation parameters (*Hyp*) has been presented in detail in earlier papers,[2–7] including the accompanying paper.[5] Relevant values are recorded in Tables 1—3. Correlation analyses were performed using multilinear regression techniques,[8] to give linear models of the form (i). where c_n are the regression coefficients

$$pK_a \text{ or } \log K = c_0 + c_1\cdot\text{parameter } 1 + c_2\cdot\text{parameter } 2 \ldots \quad \text{(i)}$$

where c_n are the regression coefficients determined by a least determined by a least-squares criterion. Regression results are recorded in Table 4. General checks on the statistics and data have been described elsewhere.[5] Of particular relevance is the fact that all regression coefficients (c_1, c_2, ...) have signs consistent with physical intuition.

Results and Discussion

Aqueous-phase Acidity of Alcohols.—One of the most significant results to emanate from recent quantitative work on gas-phase proton-transfer equilibria was the order of stabilisation of unsolvated alkoxide anion (RO^-), R = Me < Et <

Table 2. Aqueous pK_a values[a] for *gem*-diols $R^1R^2C(OH)_2$ and empirical parameters

R^1	R^2	pK_a	$\bar{\chi}_{12}$	*np*	α_d
$CFCl_2$	$CFCl_2$	6.42	6.747	0	3.949
$CFCl_2$	CF_2Cl	6.48	6.859	0	3.576
CF_3	CF_3	6.58	7.221	0	2.472
CF_2Cl	CF_2Cl	6.67	6.972	0	3.205
CF_3	$CHBr_2$	7.69	6.687	0	3.593
CHF_2	CF_2Cl	7.90	6.840	0	2.864
CHF_2	CHF_2	8.79	6.709	0	2.529
CCl_3	H	10.04	6.107	0	3.296
CF_3	H	10.20[b]	6.450	0	2.389
$C{\equiv}CPh$	H	11.80[b]	6.195	1	3.041
H	H	13.27	5.702	0	2.115
CH_3	H	13.57	5.751	1	2.550
$CH(CH_3)_2$	H	13.77	5.784	1	2.956
CH_3	CH_3	*c*	5.799	2	3.586

[a] Unless otherwise stated, data from C. H. Rochester, in 'The Chemistry of the Hydroxy Group,' Part 1, ed. S. Patai, Interscience, London, 1971, p. 327. [b] Ref. 15. [c] Not available. Values of parameters given are used to calculate effects reported in Table 5.

Table 3. Carbonyl hydration equilibrium constants[a] and associated parameters[b] for $R^1R^2C{=}O$

R^1	R^2	$\log K_{hyd}$	$\bar{\chi}_{12}$	*Hyp*	α_d	ΣE_s	$\Sigma\sigma^*$	$\Sigma\sigma_I$	$\Sigma\sigma_R$	Δ	*np*
CH_3	CH_3	−2.700	5.990	6	3.557	0.00	0.00	−0.02	−0.32	0	0
CH_3	CH_2Br	−1.155	6.095	5	4.860	−0.27	1.02	0.19	−0.26	0	0
CH_3	CH_2Cl	−1.041	6.127	5	4.396	−0.24	1.05	0.16	−0.24	0	0
CH_3	CH_2F	−0.777	6.248	5				0.19		0	0
CH_3	CH_2OH	−0.754[c]	6.191	5	3.708	0.03	0.56	0.10	−0.23	0	0
$C(CH_3)_3$	H	−0.629[d]	5.987	3	4.391	−0.30	0.19	−0.01	−0.18	1	3
$n\text{-}C_3H_7$	H	−0.237	5.954	3	3.154	0.88	0.37	−0.01	−0.16	1	1
$CH(CH_3)_2$	H	−0.211[d]	5.970	3	3.610	0.77	0.30	0.01	−0.16	1	2
CH_3	H	0.079	5.932	3	2.143	1.24	0.49	−0.01	−0.16	1	0
CH_2CH_3	H	0.093	5.952	3	3.064	1.07	0.39	−0.01	−0.14	1	1
CH_2Br	CH_2Br	0.267	6.200	4		0.97	2.04	0.40	−0.20	0	0
CH_3	$CHCl_2$	0.447	6.263	4	5.412	−0.15	1.94	0.30	−0.16	0	0
CH_2Cl	CH_2Cl	0.623	6.262	4	5.412	−0.48	2.10	0.34	−0.16	0	0
CH_2OH	H	0.954	6.136	2		1.27	1.05	0.11		1	0
$CH(OH)CH_3$	H	1.362	6.156	2				0.04		1	0
CH_2Cl	H	1.456[c]	6.074	2	3.014	1.00	1.54	0.17	−0.08	1	0
CF_3	CH_3	1.544	6.800	3	3.038	−1.16	2.61	0.39	−0.05	0	0
$CHCl_2$	H	3.170[e]	6.209	1			2.43	0.31	0.00	1	0
H	H	3.403	5.875	0	0.789	2.48	0.98	0.00	0.00	2	0
CCl_3	H	4.456[c]	6.351	0	5.161	−0.82	3.14	0.36	0.08	1	0
CF_3	CF_3	6.079	7.628	0	3.225	−2.32	5.22	0.80	0.22	1	0

[a] Unless otherwise stated, data from H.-J. Buschmann, H.-H. Fuldner, and W. Knoche, *Ber. Bunsenges. Phys. Chem.*, 1980, **84**, 41. [b] See text. [c] P. Le Hénaff, *Bull. Soc. Chim. Fr.*, 1968, 4687. [d] J. P. Guthrie, *Can. J. Chem.*, 1975, **53**, 898. [e] J. P. Guthrie and P. A. Cullimore, *Can. J. Chem.*, 1979, **57**, 240.

$Pr^i < Bu^t$, *exactly opposite* to the order observed for aqueous-phase acidity.[9] Additional effects in solution must therefore be operative in the case of these unsubstituted alkyl derivatives. Since we had already developed satisfactory quantitative explanations for the gas-phase behaviour,[4] we knew that the same relationships could *not* apply to the solution acidities. In particular, we anticipated difficulties with unsubstituted alkyl derivatives. Furthermore, we were aware at the outset that while the gas-phase data of our earlier studies comprised pure enthalpy values, the equilibrium constants which are the data of interest in solution depend on both enthalpy and entropy contributions, *via* the free energy expression (ii).

$$-2.303RT\log K = \Delta G = \Delta H - T\Delta S \qquad \text{(ii)}$$

Figure 1 further emphasises the non-linear relationship between gas- and aqueous-phase acidity for some alcohols (ΔG for each scale).

The data set of pK_a values for 45 alcohols contains compounds of widely varying structure and substitution pattern, and covers a range of *ca.* 12 p*K* units. In anticipation of the difficulties mentioned above, we initially decided to divide the data into two subsets. The first contained all those alcohols which do contain a polar-substituted group on the methylol carbon atom. Those alcohols containing an unsubstituted hydrocarbon group (aryl as well as methyl; 18 molecules) were consigned to Set B (Table 1). In the light of preliminary analyses, it became clear that the acidic behaviour of the polar-substituted alcohols could be better understood if the first set was further subdivided. The six alcohols containing the particularly heavy substituent groups CCl_3, CBr_3, $CHCl_2$, and $CHBr_2$ were put into Set C (Table 1). The remainder comprised Set A, and it is with this series that the discussion begins.

In fact, the experimental pK_a values of the 21 alcohols in Set A were found to correlate very highly with the residual electronegativity parameter, $\bar{\chi}_{12}$ (Table 4, entry 1). Addition of parameters which describe other effects in a multiparameter treatment gave no statistical improvement on this result. That increased substituent electronegativity should lead to enhanced stabilisation of the alkoxide anion, and increase acidity, is wholly in line with chemical intuition, based purely on considerations of an inductive effect. The corresponding *gas-*

Table 4. Correlation analysis results[a]

Entry	n	R^2	s	F	Regression coefficients c_0	 c_1	 c_2	 c_3
					Aqueous acidity of alcohols			
					Set A			
1	21	0.9778	0.51	838	39.74 (±0.94)	$-4.794\,\bar{\chi}_{12}$ (±0.166)		
					Sets A and B			
2	39	0.9448	0.69	633	41.17 (±1.10)	$-4.964\,\bar{\chi}_{12}$ (±0.197)		
3	39	0.9796	0.43	863	39.74 (±0.70)	$-4.785\,\bar{\chi}_{12}$ (±0.123)	$+0.770\,np$ (±0.098)	
					Sets A—C			
4	45	0.9620	0.60	532	39.80 (±0.92)	$-4.843\,\bar{\chi}_{12}$ (±0.162)	$+0.947\,np$ (±0.133)	
5	45	0.9756	0.49	547	39.74 (±0.75)	$-4.609\,\bar{\chi}_{12}$ (±0.140)	$+1.005\,np$ (±0.109)	$-0.404\,\alpha_d$ (±0.084)
					gem-Diol acidity			
6	13	0.9922	0.29	379	39.16 (±1.41)	$-4.023\,\bar{\chi}_{12}$ (±0.224)	$+1.543\,np$ (±0.246)	$-1.361\,\alpha_d$ (±0.163)
					Carbonyl hydration equilibrium			
7	21	0.9495	0.49	169	−8.62 (±1.95)	$+1.964\,\bar{\chi}_{12}$ (±0.302)	$-0.930\,Hyp$ (±0.064)	
8	18	0.5973	1.43	11	−36.89 (±8.54)	$+6.010\,\bar{\chi}_{12}$ (±1.360)	$+1.249\,\Sigma E_s$ (±0.509)	
9	21	0.8327	0.88	45	−32.75 (±3.72)	$+5.163\,\bar{\chi}_{12}$ (±0.583)	$+2.585\,\Delta$ (±0.372)	
10	18	0.7981	1.01	30	−2.05 (±0.46)	$+1.835\,\Sigma\sigma^*$ (±0.250)	$+0.915\,\Sigma E_s$ (±0.296)	
11	19	0.9783	0.33	361	−2.67 (±0.16)	$+1.628\,\Sigma\sigma^*$ (±0.063)	$+2.005\,\Delta$ (±0.135)	
12	21	0.9416	0.52	145	−2.80 (±0.24)	$+10.579\,\Sigma\sigma_I$ (±0.658)	$+2.910\,\Delta$ (±0.226)	
13	18	0.9674	0.41	475	2.83 (±0.13)	$+16.397\,\Sigma\sigma_R$ (±0.752)		
14	20[b]	0.8421	0.85	96	2.40 (±0.25)	$+14.635\,\Sigma\sigma_R$ (±1.493)		
15	20[b]	0.9077	0.65	255	2.66 (±0.17)	$+16.005\,\Sigma\sigma_R{}^+$ (±1.002)		
16	21	0.9716	0.38	194	−6.84 (±1.58)	$+1.708\,\bar{\chi}_{12}$ (±0.243)	$-0.948\,Hyp$ (±0.051)	$-0.402\,np$ (±0.110)

[a] n = number of compounds in the dataset; R^2 = square of the (multiple) correlation coefficient; s = standard deviation; F = Fisher's statistic. [b] Includes two conjugated derivatives (see text).

phase alcohol acidity was found to be dependent not only on $\bar{\chi}_{12}$, but also on the effective polarisability α_d of substituents. This leads to further stabilisation of charge *via* interaction of the induced dipoles with the anion monopole. Although the gas-phase series perforce contained less varied data than the aqueous-phase Set A, the two data sets are roughly comparable. From these data, it therefore appears that the polarisability effect is sufficiently attenuated in solution to be no longer significant (within the limits of the accuracy of the data, our parameters, and the statistical method used). The relative unimportance of this effect in solution has been assumed by many authors. We continue consideration of this point below.

If the pK_a values of the methylated and phenyl alcohols of Set B (Table 1) are now predicted by this model (entry 1, Table 4), using their calculated $\bar{\chi}_{12}$ values, it is found that they deviate in a systematic fashion. The greater the number of hydrocarbon units attached to the methylol carbon atom, the greater the deviation towards higher predicted acidity. In other words, substituents of this kind are in practice causing a relative destabilisation of the alkoxide anion compared with more polar derivatives. Allowance can be made for this *non*polar effect *via* an empirical parameter, *np* (see column 6 in Table 1), which merely records the number of α-hydrocarbon substituents. Inclusion of this parameter in the regression analyses leads to good dual-parameter models, encompassing all 39 of the alcohols in Sets A and B (Table 4, entry 3).

Presumably the hydration shell will be more tightly bound to the anion than to the non-ionised alcohol, because of the more polar binding site. Furthermore, hydrogen bonds may be formed one bond closer to the substituents in the alkoxide compared with the alcohol. In the presence of the hydrophobic methyl and phenyl substituents, close to the ionic centre, less favourable hydration energies for the anion compared with the neutral alcohol are to be anticipated, compared with the corresponding case of polar alcohol ⟶ polar alkoxide. In the latter case, interaction between water and a larger dipole

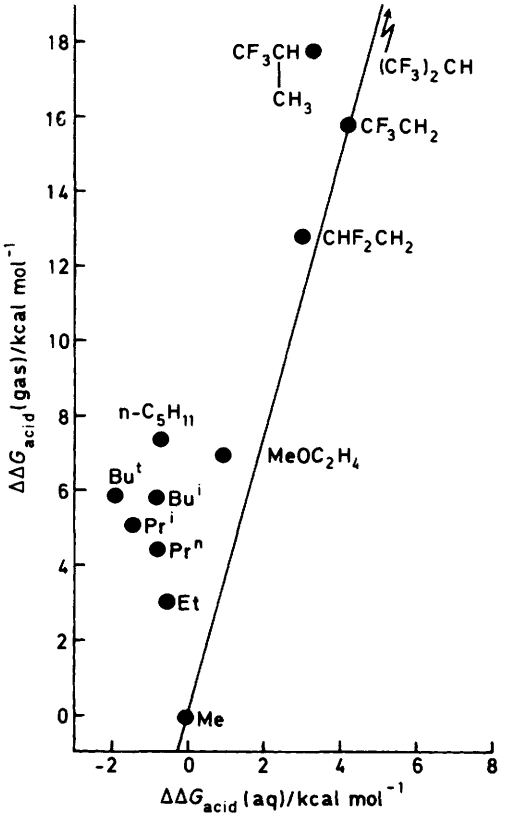


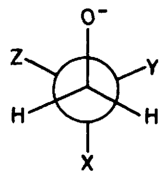
Figure 1. Plot of $\Delta\Delta G$ for acid ionisation of alcohols in the gas phase against aqueous solution values. Note that the scales of both axes are the same

associated with the substituent would alleviate the unfavourable effect of the unsubstituted and therefore hydrophobic alkyl groups.

It is probably here that entropy effects play their major role. The structure, or ordering, of the water around the non-polar alkyl groups will differ from the situation where polar substituents can influence the surrounding water sheath. Variable-temperature pK_a measurements are necessary to confirm this by allowing separation of ΔH and ΔS contributions to ΔG (and pK_a). We are unaware of any such measurements for alcohols. However, the regression equation (Table 4) can be compared with the known situation of analogous carboxylic acid pK_a in aqueous solution.[10,11] The ΔH° and $T\Delta S^\circ$ values for acetic (trimethylacetic) acid dissociation are -0.14 (-0.69) kcal mol^{-1} and -6.57 (-7.54) kcal mol^{-1} at 298 K, respectively. Entropy is clearly considerably more influential in determining ΔG than is enthalpy. Furthermore, the enthalpy difference suggests an acid-*strengthening* effect by the three methyl groups. However, the dominant entropy term negates this enthalpy order, consistent with the observed pK_a values: 4.75 (5.03). Thus, overall the three methyl groups are acid-*weakening*. This behaviour is exactly mirrored by the corresponding alcohol acidities. The electronegativity term in regression equation (3) (Table 4) suggests a weak electron-withdrawing effect by the three methyl groups, leading to acid-strengthening by 0.64 of a pK_a unit (0.9 kcal mol^{-1}).* However, their hydrophobicity influence, as reflected by the *np* term, causes a counteractive and dominant acid-weakening contribution of $+2.4$ pK_a units = 3.3 kcal mol^{-1}.

While it is tempting to draw further quantitative analogies between ΔH and the $\bar{\chi}_{12}$ terms on the one hand, and ΔS and *np* terms on the other, we do not believe that such a comparison is justified in the light of our current limited experience. However, the interpretation that at least part of the *np* term is due to entropy effects is consistent with the known behaviour of analogous carboxylic acids in aqueous solution.

Finally, we consider the case of those alcohols with substituents which contain high proportions of chlorine and bromine atoms (Set C, Table 1). These, too, deviated from the models previously derived (Table 4, entries 1 or 3). In contrast to Set B, though, the deviations were such that their acidities were underestimated by the models, by *ca.* 1 pK_a unit. We believe that in these cases polarisability effects are indeed important. The CCl_3 and CBr_3 groups, and to a lesser extent the $CHCl_2$ and $CHBr_2$ groups, are much bulkier and more polarisable than the other substituents already considered in Sets A and B. Although the negative charge which is generated on acid ionisation [reaction (2)] is dispersed to solvent, particularly through hydrogen-bonding, a concentration of charge will remain in the area of the ion. Here, it can still induce dipoles in particularly polarisable groups, such as CCl_3, *etc.*, which are in the close neighbourhood of the charge centre. A Newman projection (**1**) shows that such is likely to be the case for the di- and tri-chloro and -bromo derivatives. For monohalogeno derivatives, the likely conformation will maintain the halogen relatively remote from the charge centre (**1**; X = Cl, Br, I; Y = Z = H). Introduction of one or more extra halogens means that at least one polarisable atom must be gauche to the charge centre [**1**; X = Y (= Z) = Cl, Br] and therefore more amenable to polarisation by the electric field deriving from the negative charge.



(1)

In fact, the energy associated with a pK_a change of 1 unit, the amount of deviation observed, corresponds to *ca.* 1.3 kcal mol^{-1}, and it is this difference which we are suggesting is due to polarisability. Bordwell and his co-workers recently reached the conclusion that ion-stabilisation *via* polarisability influences is indeed appreciable *even in solution*, and that its magnitude could amount to 3 kcal mol^{-1}.[12] The quantities which concern us are well within the bounds of this possibility.

Our quantitative treatment of gas-phase properties has depended on polarisability influences calculated by an empirical model.[2] While it is unclear whether the same model is appropriate in aqueous solution, we have nevertheless applied it in the current context. Thus, if all the alcohol pK_a data in Sets A—C (Table 1) are regressed against electronegativity, non-polar substituent, and effective polarisability parameters, a good model is now obtained including all data points (entry 5, Table 4). Figure 2 depicts the final correlation.

A previous correlation analysis of primary alcohol acidities related pK_a to the σ^* value of the substituent on the hydroxylated carbon atom.[13] Although good correlations could be obtained for subsets of the whole data set considered, it was found that the data fell on three separate correlation lines. Additionally, secondary and tertiary derivatives could be treated by summing the σ^* contributions of the substituents. No attempts were made to bring these into coincidence, as we have achieved in the above analysis. Any linear free energy

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* For a log K difference of 1 unit, $\Delta G = 2.303RT = 1.38$ kcal mol^{-1} at 298 K.

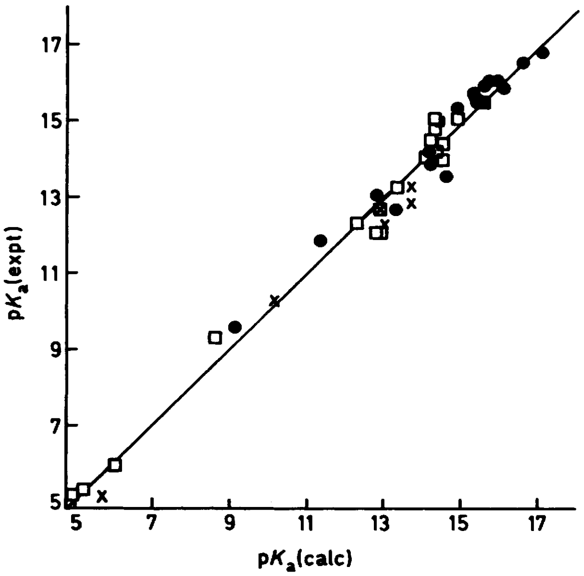

Figure 2. Plot of experimental aqueous alcohol pK_a against values calculated by entry 5, Table 4. □ set A; ● set B; × set C (*cf.* Table 1)

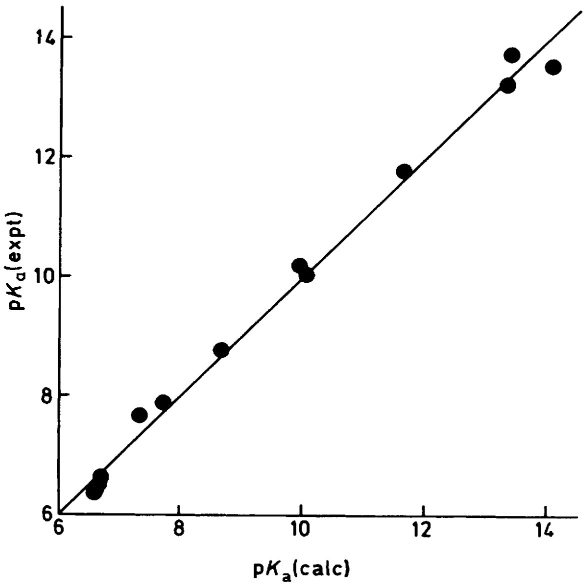

Figure 3. Plot of experimental aqueous *gem*-diol pK_a against values calculated by entry 6, Table 4

relationship (l.f.e.r.) based on σ^* parameters must reflect *inherently* the entropy term, since the σ^* parameters have been determined from equilibrium and rate measurements for aqueous-solution reactions (carboxylic ester hydrolyses and carboxylic acid acidities in this case[13]). Indeed, the mere fact that l.f.e.r.s are found to apply at all depends either on the fact that (i) entropy effects are identical in the systems considered; or (ii) that the combination of ΔH and $T\Delta S$ varies in such a remarkable way that if the $T\Delta S$ term is *not* consistent for different reactions, then the ΔH term compensates. L.f.e.r.s normally give no information on the relative contributions of enthalpy and entropy in a reaction.

The analysis of the solution-phase data may be compared with that of the gas phase. For the purpose of exemplification we consider in more detail the acidity changes induced in methanol on introduction of either two methyl groups (to give propan-2-ol), or two CF_3 groups [$(CF_3)_2CHOH$]. Breakdowns of the contributions of the various effects are given in Table 5. Both the electronegativity and polarisability contributions which are calculated for the gas-phase reaction are found to be about one-third as effective in aqueous solution. However, their relative effects remain about the same. Whereas methyl is overall stabilising in the gas phase, due to both electronegativity and polarisability influences, the additional non-polar effect of methyl in aqueous solution renders methyl overall destabilising toward acid ionisation in this phase (*cf.* Figure 1).

Aqueous-phase Acidity of gem-*Diols and Ketone and Aldehyde Hydration Equilibria.*—*gem*-Diol acidity is significant in that it provides an entry into solution-phase carbonyl nucleophilic addition reactions [Scheme, reaction (3)]. Of course, it is also an extension of alcohol acidity, and a similar type of relationship with the empirical parameters might be anticipated. Data for the reaction are recorded in Table 2. In the event, a good three-parameter model could be developed, mirroring closely those obtained for the alcohols (entry 6 in Table 4, and Figure 3). In this case, there is no gas-phase analogue with which the solution data can be compared. However, comparison of the difference between the acidities of the diols $(CF_3)_2C(OH)_2$ and $CH_2(OH)_2$ with the difference for the corresponding alcohols, shows that the electronegativity and polarisability effects contribute about equally to each reaction series (Table 5). There thus appear to be no special differences between the two series. Again, previous correlation analyses have depended on the sum of σ^* constants for the various substituents.[14,15]

Aldehydes and ketones are known to undergo reversible hydration to a lesser or greater extent in aqueous solution, to give *gem*-diols. Although there are considerable data for the equilibrium constants of this reaction, the measurements have been made over several years, in different laboratories under different conditions, and by means of various techniques. Thus, the data are less precise, and less comparable, than the other reaction series. Table 3 lists the experimental data; we have normally selected the most recent determination where more than one measurement has been made. Table 3 also gives literature references, and values of the parameters used in the regression analyses.

The logarithm of the equilibrium constant (log K_{hyd}) does not correlate well with any one of our calculated empirical parameters, but it is found that a two-parameter combination gives a satisfactory model (entry 7, Table 4). This is based on residual electronegativity, a measure of the inductive effect, and a second parameter, *Hyp*, which corresponds to the number of α-H or α-unsubstituted alkyl substituents in the molecule (Table 3). It was found[5] in the cases of several gas-phase proton and hydride-ion addition reactions that it was necessary to include just such a parameter to reflect the hyperconjugating (π-interaction) influence of substituents attached to electron-deficient centres, such as carbenium ions, or the carbon atom of carbonyl groups. It therefore appears that as the substituents become less able to interact with and stabilise the carbonyl group, addition of water becomes more favoured. Increasingly electronegative substituents apparently destabilise the dipole associated with the carbonyl group, and correspondingly favour hydration, which results in decrease of that dipole.

Previous studies of hydration equilibria have also led to derivation of linear relationships. In his excellent review of the subject,[16] Bell has reported a dual-parameter equation in which a component dependent on the inductive effect parameter, σ^*, is combined with a steric term comprising the sum of the E_s steric constants of the substituents. However, consistent with Bell's

Table 5. Comparison of solution and gas-phase effects for R_2CHOH acidity, relative to CH_3OH, and addition of OH^- (solution) and H^- (gas) to R_2CO, relative to H_2CO (kcal mol^{-1})[a]

	Acidity of R_2CHOH				Nucleophile addition to R_2CO				
R	$\bar{\chi}_{12}$	α_d	*np*	Total effect	$\bar{\chi}_{12}$	α_d	*Hyp*	*np*	Total effect
				Aqueous solution					
H	0	0	0	0	0	0	0	0	0
CH_3	−0.6	−0.9	2.9	1.4	−0.8	−2.8	7.8	4.3	8.5[b]
CF_3	−9.0	−0.6	0	−9.6	−13.3	−0.7	0	0	−14.0
				Gas phase[c]					
H	0	0		0	0	0	0		0
CH_3	−1.7	−2.5		−4.3 (−5.1)[d]	−2.1	−3.1	8.8		3.6 (3.8)[d]
CF_3	−27.8	−1.5		−29.3	−32.3	−1.8	0		−34.1 (−34.1)[d]

[a] The signs of the contributions are internally consistent, in the sense that a negative sign indicates stabilisation, for all reaction series in this Table. Solution equilibrium values were converted into kcal mol^{-1}. [b] Based on a calculated *gem*-diol acidity value, *cf.* Table 2. [c] Ref. 5. [d] Experimental values (ref. 5) in parentheses.

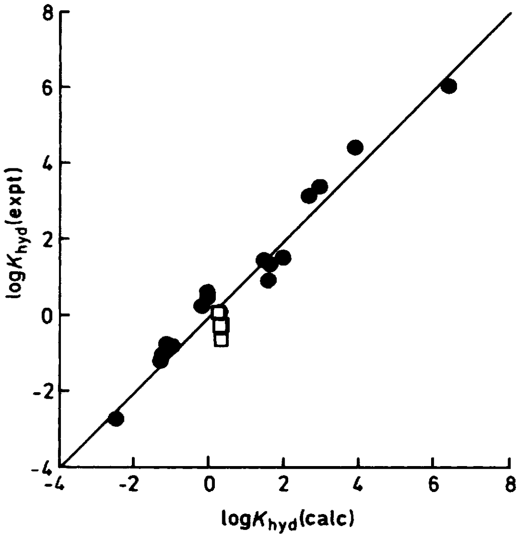

Figure 4. Plot of experimental log K_{hyd} values against values calculated by entry 7, Table 4. The □ symbols represent molecules containing simple, unsubstituted alkyl groups (*cf.* Table 3). Introduction of the *np* parameter brings these points into near concidence with the correlation line (entry 16, Table 4)

own and others' doubts about this procedure, we have found that the latter term is wholly inappropriate in combination with the residual electronegativity parameter (Table 4, entry 8; *cf.* also entry 10). A second equation more related to our own again employs σ^* as the electronegativity term, along with the number of aldehydic hydrogen atoms, Δ, attached to the carbonyl carbon atom (entry 11, Table 4).[17] Again, this latter parameter performs less well in tandem with $\bar{\chi}_{12}$ than our α-substituents indicator, *Hyp*. Consistent with our own interpretation, Δ in entry 11 was taken as a reflection of the π-stabilising ability of the substituents on the carbonyl C–O double bond.[17] A third correlation, derived from the more widely based σ_I inductive effect constant,[18] is inferior to both our own and that based on σ^* (Table 4, entry 12).

If π-effects are indeed important, the pure resonance σ_R constant[18] should correlate directly with log K_{hyd}. In fact, this is found to be the case (Table 4, entry 13). However, when the series is extended to include π-conjugating substituents, such as CH_3CO and RO_2C,* this correlation breaks down (entry 14, Table 4). Application of $\sigma_R{}^+$, which reflects decreased π-interaction of electron-accepting groups with positively charged centres,[18] is somewhat more suitable in this case, judging from the improved correlation (Table 4, entry 15).†

Since σ constants again correlate with the data of this reaction series, and the values of the constants must be reflecting implicitly that part of the free energy due to entropy, as well as enthalpy, it is inevitable that the entropy component of the carbonyl hydration free energy is somehow parallel to that of ester hydrolyses. We might therefore expect that our own correlation (Table 4, entry 7), which makes no explicit allowance for entropy effects, should be deficient in some way. Indeed, it is clear from Figure 4 that it is just those higher alkylated derivatives (Et, Pr^n, Pr^i, Bu^t) that are deviating, in the same way as found in the alcohol acidity study (above). In other words, these non-polar groups are again perturbing the structure of the solvent in a manner different from polar substituted derivatives. The difference in solvation characteristics in going from carbonyl compounds to the *gem*-diol functionality would be expected to parallel the alcohol to alkoxide conversion, in the sense that each involves change from a less to a more hydrophilic functionality. The deviations are consistent with this interpretation. If we make the same empirical allowance through *np* for these groups as in the alcohol series, a statistically significant improvement in the correlation is obtained (Table 4, entry 16).

In combination with the *gem*-diol acidity correlation equation (entry 6, Table 4), the carbonyl hydration equation leads to an expression which quantifies the addition of hydroxide anion to $R_2C{=}O$ (see Scheme).

Although there are no data for the corresponding gas-phase reaction, the data for OH^- addition in solution may be compared with those derived elsewhere[5] for the addition of hydride anion to $R_2C{=}O$ in the gas phase. A breakdown of the various contributions for reactions with $(CH_3)_2CO$ and $(CF_3)_2CO$ is given in Table 5. The electronegativity-dependent

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* Hydration equilibrium data from ref. 17, and σ_R values from ref. 18.

† Using a $\sigma_R{}^+$ value for CO_2CH_3 equal to σ_R, as recommended in ref. 18, still leaves the pyruvate ester deviating substantially from the main trend, although biacetyl fits the line well. Additionally, we have used the original σ_R constants for CF_3 and Bu^t, since it is not clear that their $\sigma_R{}^+$ values are significantly different. Possibly the value of $\sigma_R{}^+$ for CO_2CH_3 should be lower than suggested. Alternatively, the correlation is not valid for π-conjugating substituents.

contribution for OH^- addition in solution is *ca.* 2.5 times less than that for H^- addition in the gas phase. The effect of hyperconjugation is about the same in either phase. Overall, CF_3 stabilises negative charge development in the gas phase, whereas the overall effect of CH_3 is destabilising, largely due to the disruption of hyperconjugative influences in the carbonyl ground state which are removed in the alkoxide product. The overall trend is the same for the addition of OH^- in solution, but here the destabilising influence of methyl is reinforced by the non-polar effect, specific to solution.

Conclusions.—The statistical models which we have described in this paper, based largely on parameters previously applied only to gas-phase reactions, indicate that not only the effects, but also the parameters which quantify them, are common to the two phases. We consider this to be the major point of significance to come from this study. The approach of first investigating inherent substituent effects in the gas phase has been justified, in that further effects in aqueous medium only appear in the light of the prior gas-phase analysis.

The study has also forced us to come face-to-face with the problem of entropy effects in solution, and emphasised that conventional parameters used in free energy relationships are opaque to such matters. While our statistical models have sometimes required more parameters than related σ constant treatments, we believe that the extra information given warrants the approach taken. On the other hand, we do not wish to give the impression that we consider our approach to be the final answer. For instance, we recognise that the *np* parameter is rather simplistic. Nor should it be taken that we are attacking the σ constant concept, which we agree is of immense value in deriving quantitative relationships between chemical data. Rather, we are reiterating an oft neglected point, that free energy means entropy as well as enthalpy, which deserves more attention by those involved in chemical correlation analysis. We hope to develop our own thoughts concerning this problem in future publications.

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