A Quantitative Description of Fundamental Polar Reaction Types. Proton- and Hydride-transfer Reactions connecting Alcohols and Carbonyl Compounds in the Gas Phase

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Four simple but fundamental gas-phase reactions involving proton and hydride additions or extrusions, and comprising a complete thermochemical cycle, have been studied by correlation analyses. The species of interest were alcohols (proton and hydride extrusions, to alkoxide anion and hydroxycarbenium ion, respectively), and aldehydes and ketones (proton and hydride additions, to give the same ionic products as formed from the alcohols). The heats of these reactions can be described accurately by linear two- or three-parameter equations. Residual electronegativity is a readily calculated property which reflects the ease of stabilisation of charge by inductive–field effects. Effective polarisability quantifies the intramolecular stabilisation of charge by interaction between the charge centre and induced dipoles in the substituents. The third parameter reflects hyperconjugation influences by C–H and C–C bonds. The statistical models are internally consistent among the four reactions in reflecting the various physical influences on the reaction enthalpies. Electronegativity is responsible for roughly the same amount of stabilisation in all four reactions. Substituent polarisability is more effective at stabilising positive charge than negative. This generalisation applies to saturated and unsaturated cations (protonated alcohols–ethers, and protonated ketones–aldehydes, respectively). The analyses also reflect the degree to which bonds hyperconjugate with the C=O bond, as well as with adjacent charged, unsaturated centres.

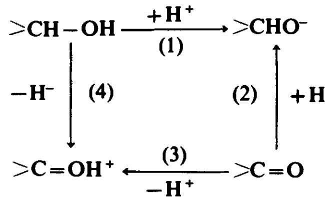
Computer-assisted methods for designing organic chemical syntheses and predicting reactions between organic molecules are of considerable current interest. Several computer programs have been described which are based on built-in libraries of known reactions.[1] However, our approach to this general problem is fundamentally different. Instead of extracting reactions from a data bank, the program EROS (Elaboration of Reactions for Organic Synthesis) generates them in a formal manner as bond-breaking and -making processes, thus giving access to reactions, both known and unknown.[2] A major aspect of program development is the introduction of methods to distinguish automatically between, on the one hand, those reactions which are merely formally conceivable, and, on the other hand, those which are chemically realistic. Initially the quantitative evaluation of reactions in EROS was based on thermochemical criteria.[3] More recent developments are aimed at introducing further chemical effects, especially electronic factors, into EROS. A new reaction prediction version of the program which is based on these concepts has recently been implemented.[4] It is the purpose of this paper to describe a study of some fundamental heterolytic processes using the quantitative models upon which the new EROS version is based.

Faced with the problem of defining the reactivity of a compound, the organic chemist conventionally looks for the functional groups in the structure. This approach has condensed a lot of empirical observations in a concise manner, but its qualitative nature leaves outstanding the problem of differentiating quantitatively between the reactivities of various functional groups. The approach used in EROS by-passes the concept of functional groups, and attempts to quantify the reactivity of *each* bond in a molecule, thus answering two basic questions: where is the reaction site, and how is the relative reactivity of a given site modified by structural variations?

It was decided at an early stage that quantum mechanical methods for describing reactivity would be inappropriate, given the complexity and number of molecules likely to be encountered in a synthesis tree. Instead we have modelled reactivity by linear combinations of readily calculated values for various chemical effects. This treatment is related to the use of substituent constants in a conventional linear free energy relationship (l.f.e.r.) approach, whilst overcoming some of the deficiencies inherent in the latter. Thus, calculations for each system should account for strong interactions between the various structural entities which are present, eliminate the necessity of distinguishing between reaction site, skeleton, and substituent, and also allow treatment of systems for which no substituent constant data are available.

Models which quantify some of the effects of interest have already been described. The PEOE procedure[5] gives a rapid access to atomic charge and residual electronegativity (χ) values, the latter providing a quantitative measure of the inductive effect (by which we mean non-π effects, operating by field and/or through-bond mechanisms).[6] Two procedures enable calculation of effective substituent polarisability (α_d, N_c).[7] These all take account of the important fact that structural features closest to the particular bond under consideration are more influential than those which are more remote.

Various gas-phase processes have been successfully described by these quantities.[6–8] Concentration for the present on the gas phase eliminates the complicating influence of solvent. In particular, a recent paper describes the treatment of proton affinities of alcohols and ethers, and gas-phase acidity of alcohols.[8] This latter reaction (1) is the starting point of the subject of the current paper. An alkoxide anion can also be derived from the corresponding aldehyde or ketone by attack of a hydride anion [reaction (2)]. Furthermore, the alcohol→carbonyl connection can also be made by an alternative sequence of hydride and proton additions [reactions (3) and (4)]. These reactions constitute a thermochemical cycle (Scheme) which has particular significance in the present context. Thus, it comprises all possible fundamental types of heterolytic reactions: neutral molecule plus a positive ion [reaction (3)]; neutral molecule plus a negative ion [reaction (2)]; dissociation of a neutral molecule to two ions [reactions (1) and (4)]; and combination of two ions to give a neutral molecule [reverse of reactions (1) and (4)].



Scheme.

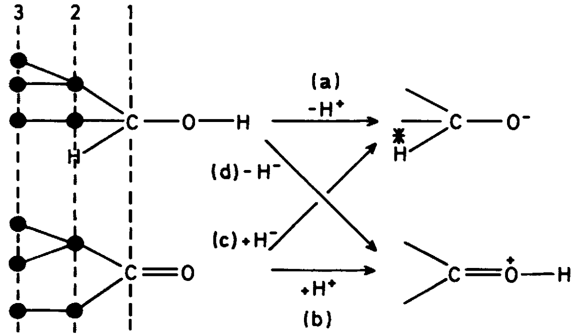


Figure 1. Definition of neighbour spheres for the calculation of residual electronegativities and effective substituent polarisabilities in alcohols and ketones

Furthermore, the reactions described in the Scheme are significant for additional reasons. Reactions (2) and (4) involve a change in hybridisation between sp^2 and sp^3 carbon, with consequences both for the electronic interaction between substituent and reaction site, and also for possible steric interactions between substituents.

Details of the procedure for calculating effective substituent polarisability have been given in full elsewhere.[7] In summary, two different models lead to α_d and N_c values, as in equations (i)

$$\alpha_d = 4(\sum_i d^{n_i - 1}\cdot\tau_i)^2/N \qquad \text{(i)}$$

[where α_d = effective substituent polarisability; N = total number of electrons in system; d = damping factor (=0.75); τ_i = polarisability contribution for each atom, i; n_i = number of bonds between atom i and the charged reaction centre = neighbour sphere (see Figure 1)][7] and (ii) (where N_c is a

$$N_c = \sum_n b_n(0.5)^{n-1} \qquad \text{(ii)}$$

connectivity number which models effective substituent polarisability, and b_n is the number of bonds in the nth neighbour sphere).[7]

The PEOE procedure for calculating charges (q) and residual electronegativities (χ) for atoms in a molecule has also been discussed in detail in previous papers.[5,9] Unique and characteristic values for both q and χ are derived for each atom, in each case the calculated values also reflecting the influence of remote atoms in the molecule. A χ value is taken as a measure of the remaining potential of the atom in its molecular environment to attract electron density to itself, and in this way is related conceptually to the conventional inductive effect.

Although direct calculation of these parameters is possible for all species involved in the reaction cycle, including ions (Scheme), it has always been our intention to study reactivity using data derived for the neutral molecules. To describe the enthalpy differences between the neutral species and the ions involved in the four reactions, the input parameters have been derived from data on the alcohols and carbonyl compounds as follows, with reference to Figure 1. For the alcohol acidity, first sphere influences correspond to those for the carbon attached directly to oxygen, second and further spheres being as indicated in Figure 1a. Thus, in calculating α_d, the n_i term in equation (i) is equal to these neighbour spheres. Since the hydroxy hydrogen plays no part in stabilisation of the derived alkoxide anion charge, it is omitted from consideration. The case of carbonyl proton affinity is analogous (Figure 1b). Addition of hydride to carbonyl (Figure 1c) gives the same anion as acid ionisation, but in this case any particular influence due to the C-H* present in the product (Figure 1) is ignored since this is not present in the neutral precursor. Finally, for consistency throughout the four reactions, the spheres of neighbour atoms for alcohols losing hydride are defined as in Figure 1d.

In previous work[6,8] it has been found advantageous to use a composite electronegativity term, $\bar{\chi}_{12}$ [equation (iii)], and again

$$\bar{\chi}_{12} = 0.5\,(\chi_1 + 0.25\bar{\chi}_2) \qquad \text{(iii)}$$

for consistency this parameter has been used in the current study. However, in all four reactions of the Scheme it is found that χ_1 alone is highly correlated with $\bar{\chi}_{12}$ (correlation coefficient $r > 0.99$), so it makes little difference which is actually used in the analyses. Both χ_1 and $\bar{\chi}_{12}$ can be taken as measures of the inductive effect. [We also find that the $\bar{\chi}_{12}$ values derived for the different systems (Figure 1) are also highly correlated.]

As will become apparent, a third parameter, which describes hyperconjugation influences, is also necessary in the analyses. Relevant data are also included in Table 1, further discussion being deferred to the next section.

The thermochemical parameters which are of interest are defined for reactions (1) and (4) as follows. The gas-phase acidity [reaction (1)] is given by the enthalpy of the reaction as drawn [equation (iv)]. Since the reaction is endothermic, the quantities are always positive.

$$\text{Acidity(ROH)} = \Delta H_r\,(1) \qquad \text{(iv)}$$

The hydride ion affinity (HIA) of carbonyl compounds [reaction (2)], and the corresponding proton affinity (PA) [reaction (3)], are each conventionally given by the negatives of the respective enthalpies of reaction, and since each reaction is exothermic, the HIA and PA values are both also positive [equations (v) and (vi)].

$$\text{HIA}(>\text{C=O}) = -\Delta H_r\,(2) \qquad \text{(v)}$$

$$\text{PA}(>\text{C=O}) = -\Delta H_r\,(3) \qquad \text{(vi)}$$

Finally, for consistency the thermochemistry of reaction (4) is given by the heat of reaction as drawn, *i.e.* a positive quantity since the reaction is endothermic [equation (vii)]. In this way, ΔH_r (4) is identical to the HIA of the hydroxycarbenium ion.

$$\text{HIA}(>\text{COH}^+) = \Delta H_r\,(4) \qquad \text{(vii)}$$

High quality, precise data are available in the literature for reactions (1) and (3), derived from ion cyclotron resonance measurements. However, no direct measurements are available for the hydride-transfer reactions (2) and (4), but values can be derived if heats of formation for the relevant alcohols and carbonyl compounds, as well as proton affinities and acidities, are available [equations (viii) and (ix)].

$$\text{HIA}(>\text{C=O}) = -\Delta H_r\,(2) = \Delta H_f(>\text{C=O}) - \Delta H_f(>\text{CHOH}) - \Delta H_r\,(1) + \Delta H_f(\text{H}^+) + \Delta H_f(\text{H}^-) \qquad \text{(viii)}$$

Table 1. Molecular parameters[a] for modelling electronic effects in R^1R^2CHOH and R^1R^2CO

		Alcohols				Carbonyl compounds						
R^1	R^2	χ_1	$\bar{\chi}_{12}$	α_d	N_c	χ_1	$\bar{\chi}_{12}$	α_d	N_c	*Hyp*	*HypH*	*HypC*
H	H	8.285	5.079	1.779	2.5	9.805	5.875	1.803	2.0	0	0	0
Me	H	8.363	5.124	2.509	3.25	9.903	5.933	2.503	3.5	3	3	0
Et	H	8.387	5.14	2.841	3.625	9.930	5.952	2.819	4.25	3	2	1
Pr^n	H	8.389	5.142	2.941	3.813	9.933	5.955	2.909	4.625	3	2	1
Pr^i	H	8.411	5.156	3.231	4.0	9.957	5.970	3.202	5.0	3	1	2
Bu^n	H	8.389	5.142	2.908	3.906	9.933	5.955	2.870	4.813	3	2	1
Bu^t	H	8.435	5.171	3.644	4.375	9.98	5.987	3.612	5.75	3	0	3
$MeOCH_2$	H	8.609	5.292	2.630	3.563	10.18	6.138	2.596	4.125	2	2	0
CHF_2	H	8.960	5.547	2.027	3.25							
CF_3	H	9.294	5.782	1.976	3.25	10.939	6.740	1.935	3.5	0	0	0
Me	Me	8.440	5.169	3.284	4.0	10.000	5.990	3.269	5.0	6	6	0
Et	Me	8.464	5.185	3.231	4.375	10.027	6.009	3.615	5.75	6	5	1
Et	Et	8.49	5.202	4.031	4.750	10.054	6.028	4.002	6.5	6	4	2
Pr^i	Me	8.49	5.202	4.031	4.750	10.054	6.028	4.002	6.5	6	4	2
Bu^t	Me	8.512	5.216	4.442	5.125	10.081	6.047	4.410	7.25	6	3	3
Bu^t	Et	8.536	5.232	4.863	5.5	10.11	6.066	4.830	8.0	6	2	4
Pr^i	Pr^i	8.54	5.233	4.863	5.5	10.11	6.066	4.830	8.0	6	2	4
Bu^t	Pr^i	8.56	5.247	5.292	5.875	10.14	6.086	5.258	8.75	6	1	5
Bu^t	Bu^t	8.584	5.263	5.726	6.25	10.16	6.101	5.690	9.5	6	0	6
$-(CH_2)_4-$		8.49	5.203			10.059	6.034	3.867	6.25	6	4	2
$-(CH_2)_5-$		8.49	5.230			10.059	6.034	4.028	6.75	6	4	2
cyclo-C_6H_{11}	Me					10.06	6.034	4.242	7.375	6	4	2
CH_2F	Me					10.33	6.373	2.929	5.0	5	5	0
CH_2F	CH_2F					10.66	6.505	2.759	5.0	4	4	0
CF_3	Me	9.37	5.827		4.0	11.037	6.80	2.673	5.0	3	3	0
CHF_2	CHF_2					11.35	7.04	2.637	5.0	2	2	0
CF_3	CHF_2					11.72	7.329	2.630	5.0	1	1	0
CF_3	CF_3	10.345	6.511	2.686	4.0	12.106	7.628	2.644	5.0	0	0	0

[a] See text for a discussion of the molecular parameters and meanings of symbols.

$$\mathrm{HIA}(>\mathrm{COH}^+) = \Delta H_r\,(4) = \Delta H_f(>\mathrm{C{=}O}) - \Delta H_f(>\mathrm{CHOH}) - \mathrm{PA}(>\mathrm{C{=}O}) + \Delta H_f(\mathrm{H}^+) + \Delta H_f(\mathrm{H}^-) \quad \text{(ix)}$$

Because there are now more sources of experimental error, the HIA data are perforce less precise. Heats of formation (Table 2) were taken where possible from the compilation of Cox and Pilcher, using the selected values where appropriate.[10] In other instances, it has been possible to estimate heats of formation by application of the Benson additivity scheme (see footnotes to Table 2).[11,12] Derived HIA values are listed in Table 3, and constitute the first compilation of such data. Literature data for PA and acidity are also collected in Table 3.

Quantitative models for the various heats of reaction, ΔH_r, based on the calculated molecular parameters (Table 1) were derived by multilinear regression using the commercial SAS

Table 2. Heats of formation of alcohols and carbonyl compounds, in kcal mol^{-1}; estimated values are in parentheses

R^1	R^2	$-\Delta H_f(R^1R^2CHOH)$	$-\Delta H_f(R^1R^2CO)$
H	H	48.07	25.95
Me	H	56.24	39.73
Et	H	61.17	45.45
Pr^n	H	65.79	48.94
Pr^i	H	67.84	52.25
Bu^n	H	70.66	(54.03)
Bu^t	H	(75.74)	(57.74)
$MeOCH_2$	H	(91.3)[a]	(74.25)[b]
CF_3	H	204.4[c]	181.65[d]
Me	Me	65.12	51.90
Et	Me	69.98	57.02
Et	Et	75.21	61.65
Pr^i	Me	75.35	62.76
Bu^t	Me	(83.32)	69.28
Bu^t	Et	(88.27)	74.99
Pr^i	Pr^i	(89.22)	74.40
Bu^t	Pr^i	(94.2)	80.84
Bu^t	Bu^t	(95.48)	82.64
$-(CH_2)_4-$		57.97	46.03
$-(CH_2)_5-$		68.38	54.04
cyclo-C_6H_{11}	Me	(81.83)	(68.03)
CF_3	Me	(213.58)[c]	(194.04)[d]
CF_3	CF_3	(361.9)[c]	336.5[d]

[a] Intramolecular H-bonding enthalpies for 2-oxy derivatives of alcohols were estimated by calculating for suitable analogues the differences between ΔH_f determined experimentally,[10] and those from the additivity scheme.[11,12] In this way, the H-bond increment for $(CH_2OH)_2 = -1.9 \pm 1.5$; $CH_3CH(OH)CH_2OH = -3.45 \pm 0.7$; $(CH_3CHOH)_2 = -4.1 \pm 0.75$; 2-hydroxymethyltetrahydrofuran = -4.95 ± 1.5 kcal mol^{-1}, where the error limits are those quoted[10] for the experimental ΔH_f. A value of -3.4 kcal mol^{-1} was taken as the best value from these data. [b] $[C-(O)(CO)(H)_2] = -11.35$ kcal mol^{-1}; extrapolated from analogous data.[11,12] [c] Group increments for CF_3 alcohols were taken from ref. 11. There could also be some form of weak intramolecular interaction between OH and remote fluorine atoms in the fluoro alcohols. It is more likely electrostatic in nature (dipole–dipole), rather than a formal H-bond. We have made no allowance for its effect since its value is very low (R. J. Krueger and H. D. Mettee, *Can. J. Chem.*, 1964, **42**, 340; M. Partilla, *Spectrochim. Acta*, 1979. **35A**, 585 and previous papers in this series; V. F. Kalasinsky, and H. V. Anjaria, *J. Phys. Chem.*, 1980, **84**, 1940). [d] For $(CF_3)_2CO$, ΔH_f (600 K) = -325.2 kcal mol^{-1} (A. S. Gordon, *Int. J. Chem. Kinet.*, 1972, **4**, 541). ΔH_f (298 K) = -336.5 kcal mol^{-1}, since $\Delta T{\cdot}C_p = -11.3$ kcal mol^{-1}, estimated by an increment scheme.[10,11] Hence, $[C-(F)_3(CO)] = -152.55$ kcal mol^{-1}, based on $[CO-(C)_2] = -31.4$ kcal mol^{-1}.[11,12]

Table 3. Experimental and calculated values for alcohol acidity and carbonyl proton affinity, and derived hydride ion affinities

		Reaction (1)		Reaction (2)		Reaction (3)		Reaction (4)	
R^1	R^2	Expt.	Calc.[a]	Expt.	Calc.[b]	Expt.	Calc.[c]	Expt.	Calc.[d]
H	H	379.2	378.1	43.3	42.7	177.3	179.2	245.2	241.8
Me	H	376.1	375.8	40.8	41.0	187.7	188.4	229.2	229.1
Et	H	374.7	374.8	41.4	42.3	190.7	190.2	225.4	227.0
$\mathrm{Pr^n}$	H	373.7	374.4	43.6	42.8	192.4	191.1	224.9	225.8
$\mathrm{Pr^i}$	H	373.4	373.8	42.6	43.5	193.3	191.9	222.7	224.9
$\mathrm{Bu^n}$	H	372.8	374.2	44.3	43.0	193.3	191.6	223.4	225.2
$\mathrm{Bu^t}$	H	371.8	372.8	46.6	44.7				
$MeOCH_2$	H	372.5	372.2	45.0	46.9				
CHF_2	H	367.0	368.1						
CF_3	H	364.4	363.8	58.8	59.6	170.7	170.6	252.2	252.5
Me	Me	374.1	373.6	39.5	39.3	196.6	197.7	217.0	216.4
Et	Me	372.9	372.5	40.5	40.6	199.7	199.4	213.7	214.3
Et	Et	371.8	371.5	42.2	41.8	201.2	201.2	212.7	212.3
$\mathrm{Pr^i}$	Me	372.0	371.5	41.0	41.8	201.3	201.2	211.7	212.3
$\mathrm{Bu^t}$	Me	370.7	370.5	43.7	43.0	202.3	202.9	210.4	210.9
$\mathrm{Bu^t}$	Et	369.6	369.5	44.1	44.3				
$\mathrm{Pr^i}$	$\mathrm{Pr^i}$	370.2	369.5	45.0	44.3	204.7	204.7	210.5	208.0
$\mathrm{Bu^t}$	$\mathrm{Pr^i}$	368.5	368.5	45.3	45.6				
$\mathrm{Bu^t}$	$\mathrm{Bu^t}$	367.3	367.5	45.9	46.8				
$-(CH_2)_4-$						199.2	200.4	213.2	213.1
$-(CH_2)_5-$						201.7	201.8	212.7	211.5
cyclo-C_6H_{11}	Me					202.3	203.5		
CH_2F	Me					192.7	190.1		
CH_2F	CH_2F					186.2	186.2		
CF_3	Me		361.6[e]	58.4[f]	58.0	179.8	179.8	240.1	239.8
CHF_2	CHF_2					173.8	174.8		
CF_3	CHF_2					167.7	168.1		
CF_3	CF_3		349.1[e]	77.4[f]	76.9	162.0	161.7	263.8	263.8

[a] Entry 1 in Table 4. [b] Entry 5. [c] Entry 9. [d] Entry 14. [e] Value extrapolated from the regression expression derived for gas-phase acidity. [f] Calculated from extrapolated gas-phase acidity values.

statistics package,[13] and also a specially designed interactive statistics program.[14] All models take the form of equation (x).

$$\Delta H_r = c_0 + c_1\text{·parameter1} + c_2\text{·parameter2} + \ldots \quad \text{(x)}$$

It is accepted that several physical effects operating simultaneously can be responsible for determining the magnitude of a measured chemical property. It should not be unexpected that *multi*parameter treatments are therefore necessary in analyses of such properties, in the development of models to describe them. Any increase in the number of parameters gives better regression results. However, we took great care to ensure that addition of a new parameter was both chemically and statistically significant. Thus, if sufficient checks of the statistics are built into the study a multiparameter model can be statistically rigorous, and chemically relevant and meaningful. A paper by Mager develops this point.[15] In the present work the following statistics have been routinely calculated. Ehrenson's f value[16] gives the level of significance on going from n-parameter to $(n + 1)$-parameter treatment. Cook's D statistic[17] was used to check for particularly influential points in the data set (which therefore could bias the results due to their experimental error). The correlation matrix revealed no direct correlation between the independent variables (residual electronegativity, polarisability, hyperconjugation). Multicollinearities among the independent variables which could have given rise to unreliable predictions of the regression coefficient were routinely checked by the options present in the SAS procedures.[13]

Results

Our previous studies of gas-phase proton-transfer reactions have been concerned with amine,[7] alcohol–ether, and thiol–sulphide proton affinities,[8] and alcohol acidities.[8] For those reactions the two parameters residual electronegativity ($\bar{\chi}_{12}$) and effective substituent polarisability (α_d or N_c) have sufficed to model the heats of reaction with a good degree of accuracy. For instance, alcohol acidity [reaction (1) in the Scheme] is a component of the current reaction cycle, and the models represented by the parameters given in entries 1 and 2 of Table 4 were satisfactorily derived. This series differs slightly from that studied previously,[8] in that the tertiary alcohol, $\mathrm{Bu^tOH}$, was now excluded (as it cannot be obtained from a carbonyl compound through addition of a hydride anion), but a few more recent data on primary and secondary alcohols have now been included.

It was anticipated that the same parameter combination would be applicable in the other reactions of the Scheme. In fact, when attempts were made to correlate the proton affinity values for aldehyde and ketone protonation [reaction (3), Scheme] directly with the $\bar{\chi}_{12}$ or α_d (or N_c) parameters alone, no satisfactory correlation was found. On the other hand, a reasonable correlation could be obtained by a two-parameter expression based on $\bar{\chi}_{12}$ and α_d (or N_c) (Table 4, entries 7 and 8). However, the deviations between the experimental values and those calculated from the regression equation were far higher than experience had led us to accept. Furthermore, the deviations were quite clearly related to the structures of the carbonyl compounds. Thus unsubstituted aldehydes were grouped separately from unsubstituted ketones, while formaldehyde and the fluorinated derivatives were even more divergent in their behaviour.

The hydroxycarbenium ions which are formed differ from the simpler saturated species such as protonated alcohols and ethers,[8] or amines,[7] in that an *un*saturated ion is formed, *i.e.* one containing an unfilled electron shell. Thus, there is a much

Table 4. Results of regression analyses[a]

Entry	n	R^2	s	F	c_0	Regression coefficients for					
						$\bar{\chi}_{12}$	N_c	α_d	*Hyp*	*HypH*	*HypC*
					Reaction (1) $>CHOH \xrightarrow{-H^+} >CHO^-$						
1	19	0.9624	0.71	204.7	475.58 (±5.50)	−18.24 (±1.03)	−13.93 (±0.17)				
2		0.9493	0.82	149.7	479.36 (±6.50)	−19.42 (±1.21)		−1.69 (±0.17)			
					Reaction (2) $>C{=}O \xrightarrow{+H^-} >CHO^-$						
3	20	0.9585	1.91	196.3	−80.37 (±6.73)	20.65 (±1.05)	−0.10 (±0.23)				
4		0.9585	1.91	196.3	−79.84 (±7.19)	20.58 (±1.08)		−0.18 (±0.42)			
5		0.9899	0.97	520.7	−61.98 (±4.31)	17.40 (±0.71)	1.23 (±0.22)		−1.52 (±0.22)		
6		0.9888	1.02	471.3	−68.90 (±4.19)	18.42 (±0.67)		2.13 (±0.42)	1.47 (±0.22)		
					Reaction (3) $>C{=}O \xrightarrow{+H^+} >COH^+$						
7	22	0.9721	2.22	331.5	282.21 (±6.68)	−18.90 (±0.98)	4.97 (±0.35)				
8		0.9590	2.69	222.4	254.20 (±9.40)	−14.90 (±1.28)		9.13 (±0.80)			
9		0.9931	1.13	866.6	259.45 (±4.59)	−14.58 (±0.77)	2.69 (±0.35)		2.02 (±0.27)		
10		0.9888	1.45	529.9	243.12 (±5.30)	−12.09 (±0.80)		4.34 (±0.81)	2.30 (±0.33)		
11		0.9931	1.17	613.9	259.76 (±9.09)	−14.65 (±1.86)	2.73 (±1.07)			2.00 (±0.51)	1.97 (±1.31)
					Reaction (4) $>CHOH \xrightarrow{-H^-} >COH^+$						
12	17	0.9673	3.11	207.4	118.90 (±12.29)	30.46 (±2.09)	−13.53 (±1.04)				
13		0.9429	4.11	115.5	131.90 (±16.99)	24.84 (±2.88)		−11.95 (±1.26)			
14		0.9920	1.59	538.5	145.16 (±7.54)	22.25 (±1.68)	−6.56 (±1.22)		−2.91 (±0.46)		
15		0.9871	2.02	332.0	155.26 (±9.07)	18.48 (±1.71)		−4.56 (±1.27)	−3.49 (±0.52)		

[a] The following meanings apply to the symbols used: n = number of compounds in the data set; R^2 = square of the multiple correlation coefficient; s = standard deviation; F = Fisher's statistic; c_0 = constant term of the regression; the value recorded in the Table for each parameter is the respective regression coefficient.

greater opportunity for electron transfer from filled π-symmetry orbitals of the alkyl substituents into the empty π-orbital delocalised over the C–O system, *i.e.* 'hyperconjugation', in classical terms. It therefore became necessary to introduce a hyperconjugation parameter to describe this third chemical effect. For this purpose, we modified an original suggestion of Kreevoy and Taft[18] who took the number of hydrogen atoms on the carbon atom α to an electron-deficient site as a measure of hyperconjugation (*HypH*). In our case we assumed that C–C and C–H bonds are equally able to hyperconjugate, and therefore used a composite term (*Hyp*) also including the number of carbon atoms occupying such positions (*HypC*) (see Table 1).

When this parameter was also included in the multilinear regression analyses, appreciably better models were derived, as judged by the statistics of the regressions (Table 4, entries 9 and 10, and Figure 2). It is emphasised that the signs of the coefficients associated with each parameter in the model are wholly consistent with chemical intuition. Thus, they indicate that the hydroxycarbenium ion formed is destabilised by increasingly electronegative substituents, but stabilised by more polarisable substituents, as well as by those which are better able to hyperconjugate with the ionic centre.

In support of our assertion that C–C and C–H bonds contribute equally to hyperconjugation, a regression was also run using *HypH* and *HypC* as two separate parameters (*i.e* a four-parameter regression). Entry 11 of Table 4 shows, first, that there is no statistical improvement over entry 9 in using these separate parameters. Secondly, the coefficients derived for *HypH* and *HypC* are essentially equal, reflecting the similar propensities of C–H and C–C bonds to hyperconjugate.

In contrast to proton addition to the carbonyl group, attack by hydride anion occurs at the carbon atom of the carbonyl group [reaction (2), Scheme] leading to the same alkoxide anion as generated by acid ionisation of the corresponding alcohol. As already noted, data for hydride addition are not currently experimentally measurable, and so heats of reaction must be derived from thermochemical cycles dependent on knowledge of heats of formation [equation (viii)]. Such data, the first 18 entries under reaction (2) compiled in Table 3, have been submitted for regression analyses as outlined above.

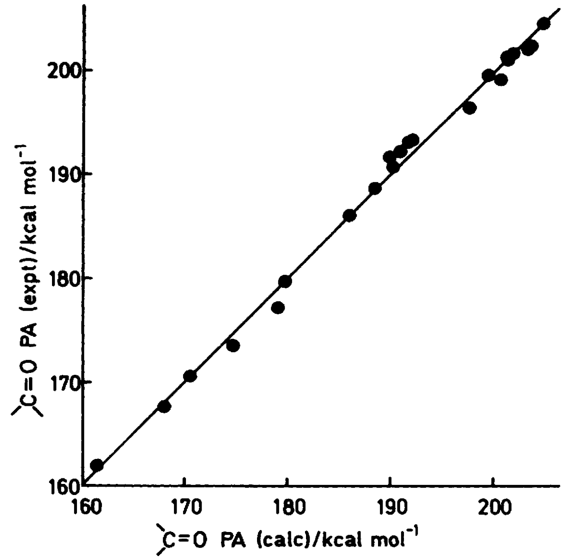


Figure 2. Experimental proton affinity values of $R^1R^2C=O$ plotted against those calculated by entry 9, Table 4 (*n* 22; R^2 0.9931; *s* 1.13 kcal mol^{-1})

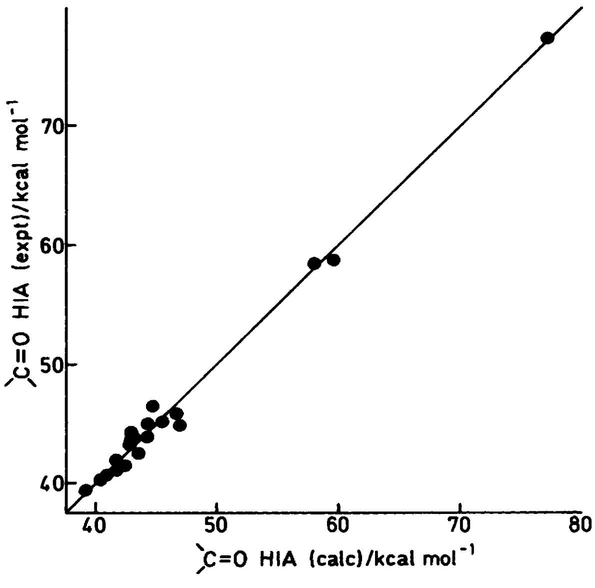


Figure 3. Experimental hydride ion affinities of $R^1R^2C=O$ plotted against those calculated by entry 5, Table 4 (*n* 20; R^2 0.9899; *s* 0.97 kcal mol^{-1})

However, Cook's D statistic[17] revealed that the few molecules containing electronegative substituents influence the magnitudes of the regression coefficients to an unacceptably high degree. This data set was therefore supplemented by additional data for CF_3COCH_3 and $(CF_3)_2CO$. For these molecules only, we used gas-phase acidity values in equation (viii) which had been derived by extrapolation from entry 1 of Table 4, and the calculated $\bar{\chi}_{12}$ and N_c values. For the full data set of 20 points, multilinear regression now led to stable models (entries 5 and 6 in Table 4, and Figure 3) which again necessitated a three-parameter treatment. Thus, a hyperconjugation term is again significant. We interpret this as reflecting the destablisation introduced on hydride addition, due to removal of any hyperconjugation present in the neutral carbonyl precursor prior to reaction.[19] The coefficients of the other two parameters are also chemically sensible, in reflecting the higher stabilisation of the anion with both increasingly electronegative, as well as increasingly more polarisable, substituents.

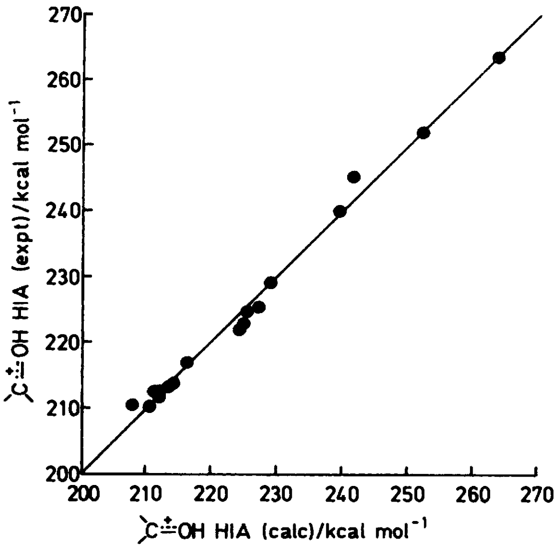


Figure 4. Experimental hydride ion affinities of $R^1R^2COH^+$ plotted against those calculated by entry 14, Table 4 (*n* 17; R^2 0.9920; *s* 1.59 kcal mol^{-1})

The reaction which completes the thermochemical cycle is the loss of hydride anion by alcohol [reaction (4) of the Scheme], equivalent to the reverse of hydroxycarbenium ion hydride anion affinity. The charged product is here identical to that given by carbonyl protonation. Results of regression analyses for this system are consistent with those of the preceding reactions, in that models dependent on just electronegativity and substituent polarisability are inadequate. Addition of the hyperconjugation parameter leads to statistically and chemically sensible models (Table 4, entries 14 and 15, and Figure 4).

Discussion

The models can conveniently be summarised with reference to Figure 5, where the regression results are shown diagrammatically alongside a semiquantitative representation of the relative enthalpies of formation of the molecules and ions involved in the four reactions of the Scheme. More detailed, quantitative, comparison of these models is best made by considering how the addition of appropriate substituents to formaldehyde or methanol influences the corresponding heats of reactions. In order to develop the discussion, we chose as representative molecules the series CH_3CHO, $(CH_3)_2CO$, CF_3CHO, and $(CF_3)_2CO$, as well as the respective alcohols. A breakdown is given in Table 5 of the various contributions of residual electronegativity, substituent polarisability, and hyperconjugation to the systems studied. These are given by the relevant product terms of regression coefficient (Table 4 and Figure 5) and the value of the parameter (Table 1). We begin the discussion by comparing the two reactions which lead to the same anion product [reactions (1) and (2)].

The methyl and trifluoromethyl group effects are close to additive, both for residual electronegativity and polarisability. Furthermore, the contribution to the respective heat of reaction by each substituent acting by a particular effect is essentially the same in both of these reactions, within the limits of the statistical technique and the methods used for calculating the HIA

Table 5. Contributions of various effects to the heats of reaction for the proton and hydride addition reactions studied

		Reaction (1)[a] $R^1R^2CHOH \longrightarrow R^1R^2CHO^- + H^+$		Reaction (2)[b] $R^1R^2CO + H^- \longrightarrow R^1R^2CHO^-$			Reaction (3)[c] $R^1R^2CO + H^+ \longrightarrow R^1R^2COH^+$			Reaction (4)[d] $R^1R^2CHOH \longrightarrow R^1R^2COH^+ + H^-$			PA of alcohols–ethers[e] $R^1R^2CHOH + H^+ \longrightarrow R^1R^2CHOH_2^+$	
R^1	R^2	$\bar{\chi}_{12}$	N_c	$\bar{\chi}_{12}$	N_c	*Hyp*	$\bar{\chi}_{12}$	N_c	*Hyp*	$\bar{\chi}_{12}$	N_c	*Hyp*	χ_{12}	N_c
H	H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CH_3	H	−0.8	−1.5	1.0	1.8	−4.6	−0.8	4.0	6.1	1.0	−4.9	−8.7	−0.7	3.8
CH_3	CH_3	−1.6	−2.9	2.0	3.7	−9.1	−1.7	8.1	12.1	2.0	−9.8	−17.5	1.2	7.6
CF_3	H	−12.8	−1.5	15.1	1.9	0.0	−12.6	4.0	0.0	15.6	−4.9	0.0	−10.3	3.8
CF_3	CF_3	−26.1	−2.9	30.5	3.7	0.0	−25.6	8.1	0.0	31.9	−9.8	0.0	−20.9	7.6

[a] Calculated from Table 4, entry 1. The values recorded under the parameters are the $\Delta\Delta H_r$ values for the contributions to the respective reaction enthalpies. [b] Entry 5. [c] Entry 9. [d] Entry 14. [e] Proton affinity data from ref. 8, equation (7).

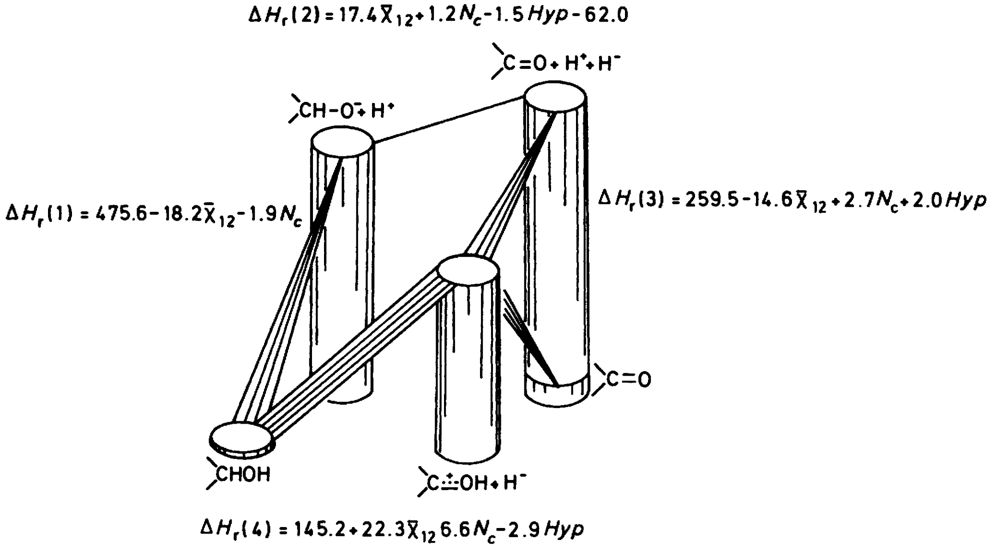


Figure 5. Qualitative pictorial representation of heats of formation and corresponding heats of reaction for H^+ and H^- addition reactions of alcohols and carbonyl compounds

[reaction (2)]. This result is all the more gratifying, seeing as each of these reactions starts from a different substrate (alcohol or ketone), and proceeds *via* fundamentally different bond-fission or -forming types. A methyl group only stabilises alkoxide anion formation by *ca.* 1 kcal mol^{-1} *via* its electronegativity influence when it replaces hydrogen. The electronegativity effect of CF_3 is *ca.* 15 times as great, in both systems. The polarisability effects of both CH_3 and CF_3 are *ca.* 1.5 kcal mol^{-1}, again in both the reaction types. The *loss* of stabilisation due to removing methyl's hyperconjugation effect in the ground state of the ketone is *ca.* 4.5 kcal mol^{-1} for each methyl group.

A parallel analysis can be effected on the data for reactions (3) and (4) each of which leads to a hydroxycarbenium ion (protonated carbonyl) (*cf.* Figure 5). An equivalent picture emerges from this comparison. Thus, the respective electronegativity effects of CH_3 and CF_3 are essentially the same for the two fundamentally different reactions (CH_3 *ca.* 1 kcal mol^{-1}; CF_3 *ca.* 15 kcal mol^{-1}). The polarisability effects of a methyl or CF_3 group are also roughly equal for the two reactions (*ca.* 4.5 kcal mol^{-1}), at least, within the limits of the standard errors associated with the regression coefficients. The differences in the hyperconjugation contributions in the two reactions are considered to be real, and not a result of inherent error. The larger effect is shown by CH_3 in the generation of hydroxycarbenium from alcohol. On the other hand, the 2.5 kcal mol^{-1} smaller effect in the case of carbonyl protonation is, we believe, due to the fact that hyperconjugation is already present to an extent in the ground state of the substituted ketone or aldehyde. This cannot therefore be taken into account in the ion. If this latter interpretation is correct, the difference just calculated should match the value calculated for reaction (2) given as 4.5 kcal mol^{-1}. Although agreement is not good in this set of results (calculated throughout by taking N_c values for polarisability), closer agreement is obtained when α_d is used as the effective polarisability parameter {*i.e.* for entries 15, 10, and 6 in Table 4, $\Delta\Delta H_r(Hyp)$ [reaction (4)] − $\Delta\Delta H_r(Hyp)$ [reaction (3)] = $\Delta\Delta H_r(Hyp)$ [reaction (2)]}.

This cross-comparison of the various effects for the anion- and cation-generating reactions can be taken further. It is intuitive that a substituent's electronegativity will stabilise negative charge formation to the same extent that it will destabilise positive charge formation. This is indeed observed to be the case. In contrast, the polarisability effect of a substituent is about three times more important in the case of cation stabilisation, as in the case of anions, although here again they might be naïvely anticipated to be equal. In fact, we have observed the increased polarisability-derived stabilisation in cations before in comparison of alcohol–ether proton affinity with alcohol acidity.[8] Essentially identical results were obtained then, as in the current study. We can only repeat our previous opinion that the exact nature of *intra*molecular ion stabilisation by polarisability is not well understood, because of the complicating effects of structural variations, particularly conformational effects which can influence local dielectric constant, uncertainty of exact charge distribution, and undefined mechanisms of charge-induced dipole interaction, especially in view of the large field strengths in the presence of a charged centre. Identical effects for both cation and anion should not necessarily be anticipated.

Much closer agreement for the polarisability contributions is observed between reactions 3 and 4, and the proton affinity of alcohols–ethers (Table 5, last reaction), in all of which a formal positive charge is introduced into the molecule. Although the electronic structure of the cations generated differs fundamentally (electron deficient as opposed to electron saturated), the CH_3 polarisability effects are gratifyingly close (Table 5).

There appear to be no special stereochemical effects, even in the more bulky systems. We had anticipated, for example, that the reaction $Bu^t_2CO \rightarrow Bu^t_2CHO^-$ might deviate from the general trend since a hindered sp^2 centre is leading to a presumably even more hindered sp^3 centre. Within the accuracy of the method and the data, this is not observed.

The nearest precedent for the treatment described in this paper is that of Koppel and Mölder.[20] They used a multiparameter treatment involving up to five independent variables to derive linear models for various gas-phase proton affinity series. Amongst their parameters, they included the *mean* polarisability of substituents, and σ^* to reflect electronegativity. We have already shown in earlier papers,[6,8] and have reconfirmed in the present study, that mean polarisability is inappropriate for the description of intramolecular charge-induced dipole interactions in ions. It is therefore not surprising that Koppel and Mölder's correlations only approached the accuracy of those reported in this paper when several more structural parameters were included.

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