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Substituent Effects of the Alkyl Groups: Polarity vs. Polarizability

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Substituents effects of the alkyl groups, both straight-chain and branched, were evaluated by means of model reaction series, each comparing the acidities and basicities of the same or very similar compounds. Four such models were examined, one based on known gas-phase experimental data (acidity and basicity of alcohols), the three others on density-functional calculations at the levels B3LYP/6-311++G(2df,2pd)//B3LYP/6-311++G(2df,2pd) or B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p): acidity and basicity of 4-substituted bicyclo[2.2.2]octan-1-ols, stability of borate anions compared to the stability of ammonium cations, and acidity of imines compared to the basicity of ketones. In all cases the alkyl groups stabilize both the anions and cations; with straight-chain alkyls the effect is proportional and can be called polarizability effect. However, simple mathematical expression of the polarizability is not correct because the effect on the cations is always stronger than on the anions. Effects of secondary and tertiary alkyls, in some cases also of branched primary alkyls, are different and deviate from the proportionality. They can be interpreted in some cases as steric effects or hyperconjugation. In any case they are different from the effects of straight-chain alkyls and they are also fundamentally different from the effects of dipolar substituents; both groups should not be correlated together in one reaction series.

Introduction

Substituent effects of alkyl groups on the chemical reactivity are usually much smaller than those of heteroatoms or of the heteroatoms containing groups. On the other hand, they are often found to be quite regular, in many cases simply proportional in different series as expressed by the original Taft equation,[1] Equation (1).

$$Y - Y_o = \rho^* \sigma^* \quad (1)$$

This relationship is not restricted to alkyl groups and the empirical constants σ* may characterize a hydrocarbon residue or a heteroatomic substituent as the case may be. The symbol Y may stand for energy but also for any other physical quantity; $Y°$ relates to the reference compound, the methyl derivative, for which σ* = 0. Equation (1) holds for saturated compounds when direct steric interaction of the substituent with the reaction centre is excluded. It has been used broadly,[1–3] either for all common substituents or particularly for alkyl groups, and was many times analyzed.[2–4] The symbols σ* were later replaced[2,5] by σ_I or σ_F with a different reference value ($\sigma_I = 0$ for hydrogen) but with the same physical meaning. However, the exact physical meaning was doubtful from the very beginning. In particular, it was pointed out several times that the correlations for alkyl groups are principally different from those for dipolar substituents[6–8] but the difference was often not revealed when both groups were correlated jointly since the effects of alkyl groups are much smaller.[9] Opinions were offered that the original values of σ* of alkyls do not express their polarity (that is the permanent dipole moment) but merely their polarizability (dipole induced by interaction with the rest of the molecule);[8] even the less clearly defined property, electronegativity was taken into consideration.[10] Another, quite probable opinion was that they represent the rest of steric effect,[11–13] that has not been removed in deriving the Taft equation.[1] Their right value of σ* should then be zero.[7,13] Alternatively, attempts were made[14] to retain the physical meaning of σ* and Equation (1) was improved by adjoining additional terms[15,16] accounting for polarizability, steric effects or hyperconjugation. Hyperconjugation was both advocated[15] and refused;[16] recently this effect was not revealed in the equilibria of isolated molecules.[17]

Returning to the problem of actual polarity of the alkyl groups, it was later discussed mostly in the terms of parameters σ_I: the only unquestionable result[3] was that the effect is very small compared to the effect of heteroatomic groups. Simple quantum chemical models suggested either weak electron-releasing[18] or weak electron-attracting[19] effect while the effect derived from experiments in solution was merely electron-attracting.[5] All these values were within the uncertainty of the pertinent models and zero values might be considered as standard.[20] In 1991 Charton resu-

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med the problem[21] with the result that there are no proofs of any inductive effect of the alkyl groups and variable reactivity of various alkyls is due to steric effects (in polar media) or also to the polarizability (in other media).

In most of the cited papers the interpretation was not unambiguous because of the restricted choice of the compounds investigated: In the most popular series of substituents, Me, Et, $CH(CH_3)_2$ and $C(CH_3)_3$, the polarity and polarizability should change in the same direction (hyperconjugation in the reversed direction), introduction of groups like $CH_2C(CH_3)_3$ would be very important.[8] In many studies, several alkyl groups were included together with dipolar groups in one series, their influence on the resulting correlation was then minute and their proper effect could not be revealed.[9] A significant progress was obtained only from the acid-base reactions in the gas phase since both acids and bases are made stronger by bulky alkyls.[22] The effect of polarizability seemed to be evident and the total substituent effect in an aliphatic series was expressed by the two-parameter equation,[20] Equation (2), where σ_F is a measure of the inductive effect and $\sigma\alpha$ of the polarizability; ΔG_o refers now to hydrogen; σ_F are positive for electron-attracting substituents and $\sigma\alpha$ are negative for all substituents except F.

$$\Delta G - \Delta G_o = \rho_{F\sigma F} + \rho\alpha\sigma\alpha \quad (2)$$

When Equation (2) was applied to polar substituents, the second term was less important, sometimes even statistically insignificant.[20] When it was applied only to alkyl substituents, σ_F of alkyls were taken to be zero.[21] General separation of the two terms of Equation (2) was attempted[23,24] by comparing the gas-phase acidities and basicities of the same series of compounds. For instance for the series of alcohols, the acidobasic equilibria can be written in the form of isodesmic[25] reactions as Equations (3) and (4).

$$ROH + CH_3O^- \rightleftharpoons RO^- + CH_3OH \quad (3)$$

$$ROH + CH_3OH_2^+ \rightleftharpoons ROH_2^+ + CH_3OH \quad (4)$$

In this case polarizability stabilizes both the anions and the cations; it was assumed that its effects are approximately equal in either case. The inductive effects are opposite in sign on the anions and on the cations, and almost equal in the absolute values. These assumptions are expressed in Equations (5) and (6):[23] $\rho\alpha$ is equal in the two equations, ρ_F are given with opposite signs.

$$\Delta_{acid}G - \Delta_{acid}G_o = -\rho_{F\sigma F} + \rho\alpha\sigma\alpha \quad (5)$$

$$\Delta_{base}G - \Delta_{base}G_o = \rho_{F\sigma F} + \rho\alpha\sigma\alpha \quad (6)$$

The parameters σ_F were evaluated by subtracting Equation (5) from Equation (6). For polar groups reasonable estimates were obtained; for alkyls σ_F were small negative[23] (electron-releasing) or zero,[24] like the generally assumed values[21] $\sigma_F = 0$. In a recent quantum chemical approach Catalán[26] used these equations for estimating both polarizability and inductive effect of various groups when he replaced $\Delta G°$ by the reaction energies ΔE(HF) calculated at the HF/6-31G** level. For the alkyl groups, σ_F were negative[26] but agreement of ΔE(HF) with the experimental basicities and acidities was rather bad.

In this work we attempted to improve the above model in two ways. First, the constraint of equal constants $\rho\alpha$ in Equations (5) and (6) was dropped: they are certainly of the same sign but need not be exactly equal;[27] this is expressed by the symbols $\rho\alpha^B$ and $\rho\alpha^A$ in Equations (7) and (8). Similarly $\rho_F{}^B$ and $\rho_F{}^A$ are of opposite signs but not equal in the absolute values. We assumed that under certain conditions, both $\rho\alpha$ and ρ_F could be estimated from the plot of $\Delta_{base}G$ vs. $\Delta_{acid}G$.

$$\Delta_{acid}G - \Delta_{acid}G_o = \rho_F{}^A\sigma_F + \rho\alpha^A\sigma\alpha \quad (7)$$

$$\Delta_{base}G - \Delta_{base}G_o = \rho_F{}^B\sigma_F + \rho\alpha^B\sigma\alpha \quad (8)$$

Second improvement was expected from more effective model compounds. We examined here four model series. The above series of alcohols, Equations (3) and (4), involve apparently the same molecules when measuring both acidity and basicity. However, the reaction energies (or reaction Gibbs energies) are given mainly by the interaction in the anions RO^- and cations ROH_2^+ and these two structures are not identical but differ by two hydrogen atoms. The merit of this model is that several Gibbs energies $\Delta_3G°(298)$ and $\Delta_4G°(298)$ are available from experiments.[28,29]

Three further models were also based on a similar comparison: acidities and basicities of 4-substituted bicyclo-[2.2.2]octan-1-ols, stability of alkylborate anions compared to the stability of ammonium cations, and acidity of methyl alkyl ketimines compared to the basicity of methyl alkyl ketones. The reaction energies were calculated within the framework of the density functional theory (DFT).[30] This enabled us to investigate more variable structures of the alkyl substituents than in the experimental studies. Detailed description of the models with the isodesmic (and homodesmotic[31]) reactions will be postponed into the next section, where these models will be treated separately.

With all the improvements, the main drawback of our models remains that they are dealing with rather small effects and also the possibilities of the DFT calculations are limited.[32,33] Therefore, it would not be helpful to discuss the behaviour and deviations of the individual alkyl groups in the individual models; we must focus attention on the overall trend, that is mainly to the slopes $\rho\alpha^A$ and $\rho\alpha^A$ in Equations (7) and (8).

Results and Discussion

Acidities and Basicities of Alcohols

Experimental gas-phase Gibbs energies[28,29] of the reactions of Equations (3) and (4) were plotted against each other in Figure 1. In spite of the small number of points, the following conclusions are evident. The four *n*-alkyl groups and isobutyl are situated near a straight line with a

positive slope: the greater alkyl makes the acid more acidic and the base more basic. The effect can be understood in terms of polarizability but the simple electrostatic model would fail in the quantitative sense: ρa^A and ρa^B in Equations (7) and (8) are not equal; the effect on the basicity is stronger roughly by a factor of 1.5. In our opinion the failure of electrostatic models is mainly in the assumed fixed position of the charges.[32,34] In Equations (3) and (4) one must assume that the positive charge is more localized and situated nearer to the polarizable medium but in any case the electrostatic calculation is a very rough approximation.[32]

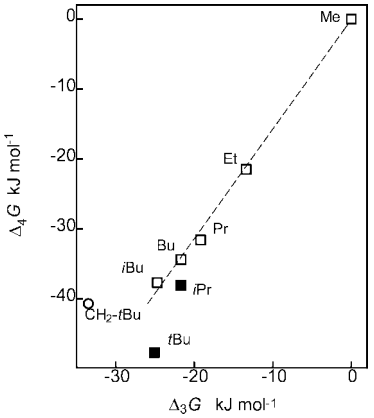


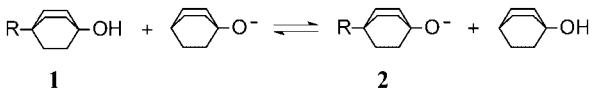
Figure 1. Comparison of the experimental gas-phase acidities (x axis) and basicities (y axis) of aliphatic alcohols R-OH; □ and ○ primary alcohols, ■ secondary and tertiary alcohols; the straight line relates to the points □ without the deviating point ○.

The secondary and tertiary alkyl substituents, i.e. the groups isopropyl and *tert*-butyl, deviate distinctly in Figure 1, influencing more the basicity. This could be interpreted either as a small electron-releasing inductive effect or steric effect affecting more the bulkier cation OH_2^+ than the smaller anion O^-. For the deviation of the substituent CH_2-*t*Bu there is no simple explanation.

Note that the aliphatic alcohols represent our only model based on experimental quantities and its qualitative agreement with the other models is very important. On the other hand, it would not be safe enough to calculate effectively the values of Δ_3E and Δ_4E within the framework of our DFT approach, which was recently questioned both for quite small molecules[32] and longer aliphatic hydrocarbons.[33]

Substituted Bicyclo[2.2.2]octan-1-ols

This is just an extension of the first model. While in Equations (3) and (4) the alkyl groups were bonded directly to the oxygen atom, in Equations (9), (10) they are separated by the bicyclic skeleton.



1 2 (9)

3 (10)

The interposed bicyclooctane residue should make the substituent effects perhaps more regular but certainly much smaller. The DFT calculations should be in this case rather reliable since similar derivatives as the alcohols **1** and the ions **2** and **3** were investigated many times theoretically[35–38] and good agreement with experiments[20] was reached. Nevertheless the calculated reaction energies are very small and the results would not be dependable as themselves, that is if they were not in essential agreement with the first model based on experiments. We calculated the reaction energies Δ_9E and $\Delta_{10}E$ at the level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) well tried in previous work.[36] Energies of the individual compounds are listed in Table S1 (Supporting Information), the relative acidities Δ_9E and basicities $\Delta_{10}E$ in Table 1. The plot of Δ_9E vs. $\Delta_{10}E$ is shown in Figure 2. It resembles Figure 1 as far as the slope is concerned, but the scaling is several times smaller; hence also the scatter is apparently greater. The basicities are again affected more than acidities (factor of 1.3). Deviations of the points *i*-Pr and *t*-Bu cannot be attributed to steric effect but rather to an electron release. We have no simple explanation for the deviations of the points Me and *i*Bu, the main problem is that the effects are too small.

Table 1. DFT calculated reaction energies of the isodesmic reactions, Equations (9)–(12) (in kJ mol^{-1}).

Substituent R	Δ_9E	$\Delta_{10}E$	$\Delta_{11}E$	$\Delta_{12}E$	$\Delta_{13}E$	$\Delta_{14}E$
Me	–2.96	–1.26			0.00	0.00
Et	–2.88	–3.59	0.00	0.00	–2.15	–9.67
Pr	–3.57	–4.67	–4.16	–5.50	–3.50	–14.25
*i*Pr	–3.30	–5.28			–6–30	–20.59
Bu	–4.01	–5.18	–5.67	–8.62	–3.82	–16.82
*i*Bu	–2.24	–4.69	–8.58	–12.63	–11.25	–19.44
*t*Bu	–3.55	–6.35			–8.94	–25.63
Pent			–6.42	–10.49		
*i*Pent			–8.47	–11.11		
CH_2-*t*Bu	–4.74	–6.58	–11.51	–19.15	–18.56	–28.74
$(CH_2)_2$-*t*Bu	–5.69	–7.14	–11.08	–13.63	–10.65	–30.18

In contradistinction to Figure 1, we encounter in Figure 2 the problem of variable conformation. The actual energies of **1**, **2**, **3** are given by the Boltzmann distribution of all conformers but the minimum-energy conformation need not be the same in the ionic forms **2** and **3** as in the parent molecules **1**: changes of conformation (configuration) with ionization[39,40] or with solvation[41] may affect markedly the acidobasic properties. For evaluating just the substituent effects we kept the same conformation in the corresponding

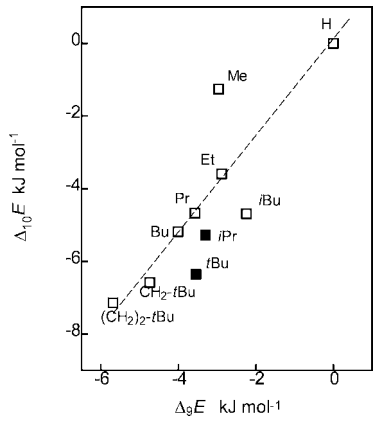


Figure 2. Comparison of the calculated experimental gas-phase acidities (*x* axis) and basicities (y axis) of 4-alkyl-bicyclo[2.2.2]-octan-1-ols 1; □ primary alkyls, ■ secondary and tertiary alkyls; the straight line is valid for the points □ without the deviating points for Me and *i*Bu.

species **1**, **2** and **3**, even when another conformation could coexist. For *n*-alkyl groups we chose the *all-ap* ("*all-trans*") conformation, in the case of more complex groups this conformation was kept at least in a part of the molecule. Even so, the conformation in the ionic species was not equal in all details, for instance in the exact dihedral angles. The scatter in Figure 2 might be attributed partly also to this fact.

In Figure 3 we compared the substituent effect of alkyl groups and of some dipolar groups, that is the basicities and acidities expressed by the Equations (9) and (10), when R is an alkyl group on the hand, or a dipolar group on the other. Figure 3 confirms in a very apparent way what has been already claimed[9] that the effects of the two groups are fundamentally different both in the qualitative and quantitative sense. The dipolar groups are electron-attracting and make the acids stronger and the bases weaker. The alkyl groups are polarizable and make both the acids and bases stronger; their effect is almost ten times weaker than that of typical polar groups. Correlation of the two groups together in one series has no physical meaning.

Borate and Ammonium Ions

This model might be the best we have found; its only shortcoming is that these compounds are less common. The stability of the borate anions **4** and ammonium cations **5** was examined not in acidobasic reactions but directly related to the isosteric hydrocarbon **6** in the isodesmic reactions, Equations (11) and (12), respectively. Then it is easy to keep the same conformation for all the species, **4**, **5** and **6**.

$$\underset{\mathbf{6}}{RCH_3} + CH_3CH_2BH_3^- \rightleftharpoons \underset{\mathbf{4}}{RBH_3^-} + CH_3CH_2CH_3 \quad (11)$$

$$\underset{\mathbf{6}}{RCH_3} + CH_3CH_2NH_3^- \rightleftharpoons \underset{\mathbf{5}}{RNH_3^+} + CH_3CH_2CH_3 \quad (12)$$

For small groups R, the species **4**, **5**, **6** are very small and the calculations could become less reliable.[32] We omitted the smallest compounds and started the series with ethyl as reference as expressed in the Equations (11) and (12). The relation is then restricted only to primary alkyls R. The DFT calculations were modified by extending the basis set to the level B3LYP/6-311++G(2df,2pd)//B3LYP/6-311++G(2df,2pd). The calculated energies are listed in Table S2, the reaction energies $\Delta_{11}E$ and $\Delta_{12}E$ in Table 1. The scattergram is shown in Figure 4. Since it includes only primary alkyl groups, it is apparently nearer to linearity than the preceding plots. It confirms that both cations and anions are stabilized by larger alkyls and stabilization is greater in the case of cations; the slope was estimated to 1.6. We have searched no explanation for the small deviations of more branched substituents.

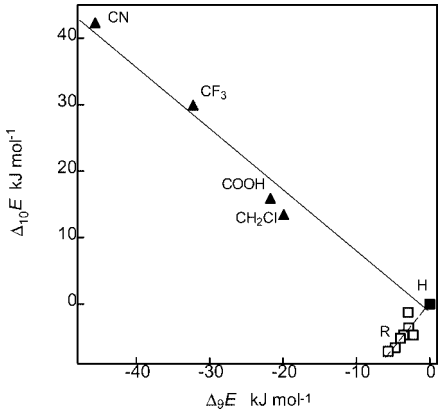


Figure 3. Comparison of the calculated experimental gas-phase acidities (*x* axis) and basicities (*y* axis) of 4-substituted bicyclo[2.2.2]octan-1-ols 1; □ alkyl substituents, ▲ dipolar substituents; the straight lines are estimated.

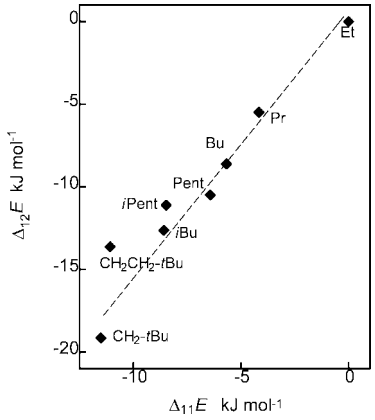
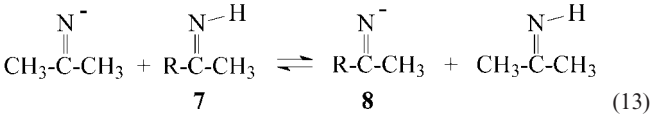


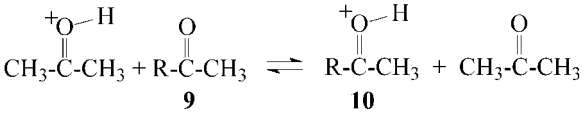
Figure 4. Comparison of the calculated stability of alkylborate anions 3, Equation (11), (*x* axis) and alkylammonium cations 4, Equation (12) (*y* axis); the straight line is estimated and does not respect the two deviating points.

Methyl Ketimines and Methyl Ketones

This only model, Equations (13) and (14), contains double bonds adjoining to the alkyl groups and was included to investigate the hyperconjugation or a similar effect.



7 **8** (13)



9 **10** (14)

Both series were investigated at possibly most similar configuration and conformation: ketimines at the configuration *E* as shown in the formula **7**, ketones were protonated at the position near to the methyl group to yield the *E* configuration **10**. Protonation of the carbonyl group at the two sterically different positions was observed in acetophenone derivatives[40] but not in other ketones.[42] We calculated energies of both possible configurations of **10**, differing by the position of the proton. In all cases the stereoisomer E, shown in **10**, was more stable (with R = Et by 4.4, with *t*Bu by 5.9 kJ mol^{-1}) and the second stereoisomer can be neglected. The DFT energies given in Table S3 and reaction energies $\Delta_{14}E$ in Table 1 refer the isomer E.

The plot of the basicities of **9** vs. the acidities of **7** is shown in Figure 5. Apparent is the greater effect on the basicity (slope 4.6), incomparable with the previous models, and strong deviations of the groups *i*Pr and *t*Bu. According to the classical concept of hyperconjugation,[43] structure of **7** is expressed by the resonance **7A** ↔ **7B** or **9A** ↔ **9B**, which should be perceptible, in **10A** ↔ **10B** it should be strong and in **8** practically absent. The result should be that basicity of **8** is strengthened and acidity of **7** weakened.

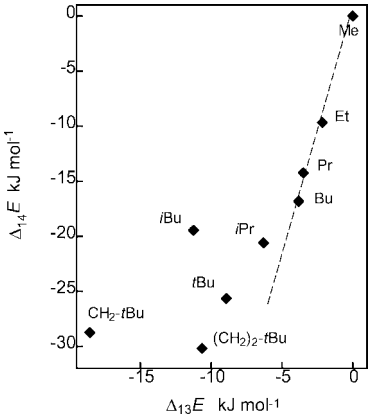
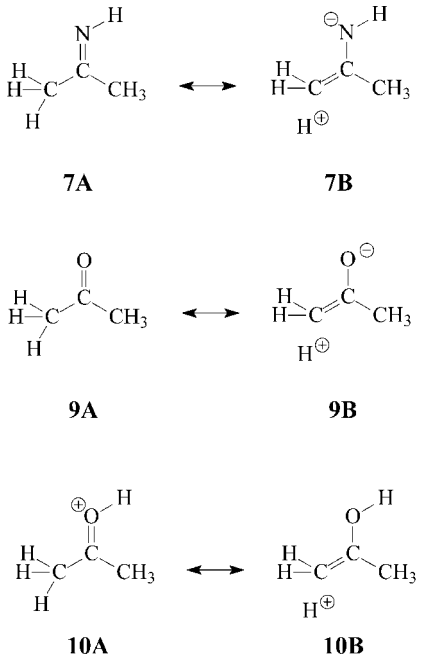


Figure 5. Comparison of the calculated acidity of alkyl methyl ketimines 7 (*x* axis) and basicity of alkyl methyl ketones 8 (*y* axis); the straight line was drawn only through the points for *n*-alkyl substituents.



7A **7B**

9A **9B**

10A **10B**

These predictions were fulfilled in the slope of the correlation; also the deviations of the points *i*Pr and *t*Bu are in agreement. However, this slope and generally the interaction energy of alkyl groups with a double bond must have still another ground since the sequence of points is different. Hyperconjugation should give the sequence of alkyl reactivity Me > Et > *i*Pr > *t*Bu, the so-called Baker–Nathan order.[17,43] This was not observed: the effect of the methyl group remained to be the weakest. We searched further confirmation of the hyperconjugation in the calculated bond lengths (Table 2). Good evidence was obtained from the bond length C(1)–C(=X) which should acquires double-bond character in **7B**, **9B** and **10B**, and is actually shortened; the shortening is greatest in methyl derivatives. Lengthening of the C–H bonds is less conclusive: in the fixed conformation only the C–H bond antiperiplanar to the double bond C=X is lengthened. In summary, hyperconjugation can explain qualitatively some observed quantities but not all, better the geometrical parameters than the energies. Similar results were obtained[17] on aromatic derivatives at a different level of computation. The Baker–Nathan effect is evidently due to the steric hindrance to solvation.[17,43]

Table 2. Some calculated bond lengths in alkyl methyl ketimines **7**, alkyl methyl ketones **9** and their ions (in Å).

Substituent R	Bond	7	8	9	10
Me	C(1)–H	1.087	1.088	1.086	1.086
		1.093	1.100	1.092	1.090
		1.093	1.100	1.092	1.099
	C(1)–C(=X)	1.505	1.565	1.515	1.467
Et	C(1)–H	1.096	1.100	1.097	1.099
		1.096	1.100	1.098	1.106
	C(1)–C(=X)	1.512	1.569	1.523	1.472
*i*Pr	C(1)–H	1.095	1.098	1.097	1.092
	C(1)–C(=X)	1.523	1.588	1.529	1.472
*t*Bu	C(1)–C(=X)	1.535	1.607	1.542	1.482

Substituent Effects of the Alkyl Groups

In the previous sections somewhat differing results were obtained from different model systems. The graphs in Figs. 1 to 5 are merely scattergrams than linear dependences; deviations of individual points cannot be explained. We are also aware of the shortcoming that all the models were not investigated exactly on the same set of substituents. Nevertheless, some common features are evident and can be summarized as follows. The alkyl groups behave as weaker substituents than dipolar groups and their effect is also quite different in character (Figure 3). Greater alkyls make generally both the acids and bases stronger. This effect can be called polarizability but contrary to the previous opinions it is always stronger on the basicity than on the acidity; this would be compatible with the simple electrostatic concept only if one assumed that the positive charge in the cations is located differently than in quite similar anions (in **3** differently than in **2**, in **5** than in **4**). Good proportionality is observed only in the effects of *n*-alkyl groups, deviations occur mainly with strongly branched alkyls and can be attributed to different conformations of the differently charged compounds. On the whole, the alkyl groups do not provide suitable systems for studying the substituent effects since these effects are rather small.

Conclusions

Several well-known empirical correlations were reinvestigated recently using quantum-chemical calculations with the result that their range of validity should be restricted: This concerned the inductive effect,[36] resonance of substituents[44] and even the Hammett equation.[45] The main shortcoming of the traditional treatment was that different phenomena were treated under one heading. The results of this paper belong into this category. We recommend the constants σ* to be removed from the literature and in the correlation with σ_I or σ_F the alkyl groups to be always separated from the dipolar groups. While the polar effects of the alkyl group should be better understood as polarizability, their steric effects[1] and their application are still unclear.

Computational Methods

The DFT calculations were carried out according to the original proposal,[30] using the Gaussian 03 program.[46] The computational level used was B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) for the compounds **1** to **3**, and B3LYP/6-311++G(2df,2pd)//B3LYP/6-311++G(2df,2pd) for the compounds **4** to **10**. Full geometry optimization was carried out separately for each configuration and conformation; planarity or any symmetry precondition was never anticipated. Vibrational analysis was carried out in all cases: all structures belonged to the energy minima. No correction was applied for the zero-point energy and no attempt was made to estimate $\Delta H°(T)$. According to our previous experience[35,47,48] the above theoretical models do not give better fit with experiments when applied to isodesmic reactions, that is to relative values. The problem was discussed previously.[48]

The DFT energies are listed in the Supporting Information; of the geometrical parameters only selected relevant bond lengths are given in Table 2.

Supporting Information (see also the footnote on the first page of this article): Tables S1 to S3 contain the DFT calculated energies of bicyclo[2.2.2]octanols **1** and their ionized forms, alkylborate anions **4** and alkylammonium cations **6**, ketimines **7**, ketones **9** and the pertinent ions, respectively.

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