Steric effects of polar substituents evaluated in terms of energy by means of isodesmic reactions†

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Received 19th November 2007, Accepted 10th January 2008
First published as an Advance Article on the web 18th February 2008
DOI: 10.1039/b717913h

Steric effects of various polar and some charged groups were estimated on sterically crowded cyclopropane *cis*-1,2-bisderivatives **2** or **3**, in which the variable substituent is in the proximity of a *t*-butyl group or of a methyl group. The steric energy was evaluated with reference to the pertinent mono derivatives, that is as reaction energy of an isodesmic reaction, in which the crowded compound is formally synthesized from simple derivatives. Energies were calculated within the framework of the density functional theory at level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) for 11 dipolar and 5 charged substituents. Interaction of charged substituents is not only steric (destabilizing) but also inductive (stabilizing). The steric effects evaluated in this way differ distinctly from the standard steric constants derived purely from the van der Waals radii of the substituents.

Introduction

The most successful evaluation of steric effects and their separation from inductive effects was achieved by Taft.[1] When the hydrolysis of various substituted esters is kinetically followed both in acidic and alkaline media, the steric effect makes the reaction slower in both media almost in the same extent, while the inductive effect is in the two reaction media just opposite. In this way, a scale of inductive constants σ^* and of steric constants E_s were created;[1–3] a rate constant k or equilibrium constant K could then be approximately expressed by their linear combination, eqn (1), where ρ^* and δ are proportionality constants (regression coefficients).

$$\log k\,[K] = \rho^*\sigma^* + \delta E_s \quad (1)$$

It was recognized early that the constants, both σ^* and E_s, have different physical meaning for alkyl groups and for polar substituents, so that further evaluation can be carried out in four ways as outlined in the following paragraphs, 1. to 4.

1. The constants σ^* of the alkyl groups are small and difficult to estimate,[3–5] so that even their sign is difficult to determine.[6,7] Nevertheless, they have often been discussed, corrected or improved,[4–7] for instance for the possible contribution of hyperconjugation.[8] According to a recent detailed reinvestigation,[7] these substituent effects are better described in terms of polarizability than polarity since they stabilize both cations and anions.[7]

2. The constants σ^* of the polar groups are the most important and have been studied extensively. Most attention has been given[1–3,9] to groups of structure CH_2X, whose constants σ^* were transformed into the inductive constants σ_I of the group X according to the empirical eqn (2).

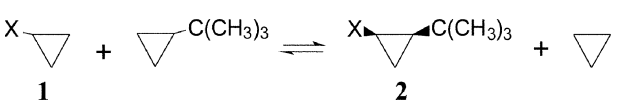
$$\sigma_I(X) = 0.45\sigma^*(CH_2X) \quad (2)$$

The constants σ_I were also determined by alternative independent procedures[6,10,11] and were found to be applicable to diverse reactivities[10–12] and physical quantities.[13] They were the most important achievements of the whole theory and contributed significantly to the popularity of R. W. Taft's work and its 25 000 citations. The inductive effect was evaluated as the most general and most important empirical relationship.[14] Recently, the inductive effect was redefined as an interaction energy of two groups in a saturated system without differentiating the substituent and the reaction centre.[15] A quantum chemical procedure was suggested defining σ_I from the calculated acidity of the corresponding 4-substituted bicyclo[2.2.2]octane-1-carboxylic acid.[16]

3. Steric effects of alkyl groups are considerable but are only very roughly proportional in various systems. The pertinent constants E_s were determined by the outlined procedure and by several others, more specifically.[17] The main progress was achieved by defining[18,19] steric constants υ from the idealized geometry on the basis of van der Waals radii r_V according to eqn (3).

$$\upsilon = r_v - 1.20 \quad (3)$$

Eqn (3) is applicable unambiguously to symmetrical groups. Unsymmetrical groups like CH_2CH_3 can prefer a conformation with minimal steric hindrance; the corresponding minimum value of υ was denoted υ_{mn}. Other values were corrected[19] according to some experimental reaction rates and denoted υ_{ef}; the set of υ values is thus not homogeneous. In our previous communication, we attempted to define new steric constants directly in terms of energy, avoiding geometric considerations.[20] Of several reactions tried, the most suitable was eqn (4), in which a sterically crowded cyclopropane derivative **2** was produced from the pertinent mono derivative **1**; X was an arbitrary alkyl group. The DFT-calculated reaction energies $\Delta_4 E$ were empirically scaled and suggested[20] as a measure of steric effect.



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† Electronic supplementary information (ESI) available: DFT calculated energies and some geometric parameters of the cyclopropane derivatives **1** to **3**. See DOI: 10.1039/b717913h

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1 **3** (5)

A similar reaction, eqn (5), with the same group X as in eqn (4), yielded much smaller steric energies $\Delta_5 E$, but roughly proportional to $\Delta_4 E$. Reactions of eqn (4) and (5) are both isodesmic[21,22] and homodesmic.[23] The principle of isodesmic reactions was analyzed in some detail[15,24] and applied broadly for defining substituent effects of various kinds.[16,20,22] Values of $\Delta_4 E$ were suggested as a new measure of steric effects;[20] they should be scaled to be comparable to the common values[19] υ_{ef}. In eqn (6), 0.029 is an empirical constant; the symbol υ_{12} should denote interactions in the neighbouring positions 1,2.

$$\upsilon_{12} = 0.029\ \Delta_4 E\ (\text{kJ mol}^{-1}) \quad (6)$$

4. The steric effects of polar substituents is the subject of the present communication. For polar groups, the steric constants need not be defined unambiguously; there are doubts as to whether they can be called steric. Let as observe eqn (4) as an example. When X is a polar group—or even a charged group—one can imagine that it induces charges in the *t*-butyl group of **2**; in this way, this molecule is stabilized and the apparent steric constant is reduced. We wanted to estimate roughly this effect and to compare quantitatively the steric effect on energy with the common steric constants[19] υ based on the van der Waals radii, that is apparently on a purely geometric dimension. Note, however, that within the Born–Oppenheimer approximation, pure geometry is defined only for the atomic nuclei; the so-called van der Waals radii are defined (in several different ways[19]) through the electron density. Moreover, some constants υ were estimated only from reactivities in solution[19] and their empirical confirmation was based only on multiple regressions, which included further empirical parameters.[25–27] The older constants E_s correlate with υ very roughly, with unexplained exceptions,[28] and are generally still less dependable.

For all these reasons, we believed that a more objective scale of steric effects would be useful, based on the energy of a concrete molecule instead of on uncertain constructions, even when this concrete molecule was only one of many possible models. Such a scale could serve as a reference, unambiguously defined and easy to calculate. Estimating which portion is the purely steric effect is of secondary importance and is more difficult. We returned to eqn (4) and (5) and calculated their reaction energies at the level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p), which was well-tried for various substituent effects[7,15,16] in molecules of similar size; in particular, it was found satisfactory even for steric effects.[20,29] We investigated a group of common polar substituents including also, as the limiting case, several charged groups. These should be compared with isoelectronic groups (for instance CO_2^- with NO_2) to distinguish roughly the steric, van der Waals effect from the polar effects due to induced charged.

Calculations

The DFT energies of substituted cyclopropanes **1–3** were calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) level with the GAUSSIAN 03 program.[30] Possible conformations were always taken into consideration and calculations were started from the appropriate structures; planarity or any symmetry was never anticipated. No correction for the zero-point energy was introduced. All structures were checked by vibrational analysis and behaved as energy minima.

The DFT energies are listed in Table S1 (ESI†). Some important geometric parameters of 2 and 3 are given in Table S2. The reaction energies $\Delta_4 E$ and $\Delta_5 E$ of the reactions, eqn (4) and (5), respectively, are listed in Table 1.

Table 1 Calculated reaction energies of the isodesmic reactions, eqn (4) or (5), and derived steric constants of substituents

Substituent	$\Delta_4 E$/kJ mol^{-1}, eqn (4)	υ_{12}	υ_{ef} ref. 19	$\Delta_5 E$/kJ mol^{-1}, eqn (5)
H	0	0	0	0
CH_3	17.66[a]	0.51	0.52	6.21[a]
C_2H_5	18.29[a]	0.53	0.56	5.77[a]
$CH(CH_3)_2$	21.73[a]	0.63	0.76	7.41[a]
$C(CH_3)_3$	42.75[a]	1.24	1.24	17.66
C≡CH	8.06	0.23	0.58	0.59
CF_3	21.47	0.62	0.90	7.02
CN	4.68	0.14	0.40	−1.05
$Si(CH_3)_3$	23.04	0.67	1.40	8.43
NH_2	19.93	0.58	0.35	3.39
NO_2	15.12	0.44	0.35	5.43
OH	−0.95	−0.03	0.32	−6.29
OCH_3	7.88	0.23	0.36	3.97
SO_2CH_3	21.00	0.61	1.13	6.32
F	5.84	0.17	0.27	1.68
Cl	10.72	0.31	0.55	1.91
$C{\equiv}C^-$	−3.20	−0.09		−0.94
CO_2^-	9.06	0.26		4.55
NH_3^+	−7.78	−0.23		−4.50
$N(CH_3)_3^+$	31.91	0.93		12.66
O^-	−11.59	−0.34		−3.28

[a] Ref. 20.

Results and discussion

Steric effects of nonpolar and polar groups

The interaction energies in *t*-butyl cyclopropane derivatives **2** and methyl derivatives **3** are represented by reaction energies in eqn (4) and (5), respectively. They are listed in Table 1, columns 2 and 5. The first question was whether the two scales are proportional, which is in principle not necessary. Proportionality of steric effects was observed only in very similar reactions and even there, the dependence need not be linear.[20] The dependence of $\Delta_4 E$ and $\Delta_5 E$ is shown in Fig. 1. Note that the $\Delta_5 E$ values are rather small; for instance, they could hardly be determined by experiments with an acceptable accuracy. Therefore, most of the attention was given to the greater values of $\Delta_4 E$, which were also used to calculate new steric constants υ_{12} according to eqn (6). These are given in Table 1, column 3, but let us stress that they are purely formal values obtained only by scaling $\Delta_4 E$ to be comparable to the standard values υ. Concerning the dependence of $\Delta_5 E$ on $\Delta_4 E$ (Fig. 1), no exceptional deviations and particular features were detected; the observed scatter may be partly attributed to the small scale of $\Delta_5 E$. The only, perhaps significant, deviation may be that of the substituent OH. We examined whether it could be connected to change of conformation but found the same conformation for **2** and **3** with X = OH (H apart from the *t*-butyl or methyl group).

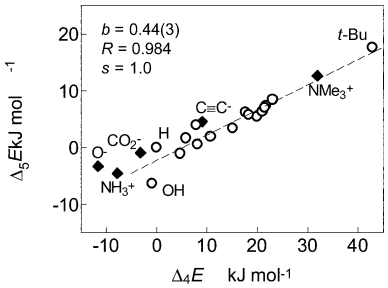
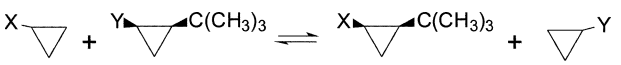


Fig. 1 Comparison of the interaction (steric) energies of substituents in two reactions: *x*-axis, strong effects in eqn (4), *y*-axis, weaker effects in eqn (5); ○ uncharged substituents X, ♦ charged substituents; the statistics relate to the former set; some deviating substituents are marked.

Table 2 Short-range polar effects of charged substituents by comparison with isoelectronic groups (kJ mol^{-1})

Substituent	Reference group	Δ_7E, eqn (7)	Δ_8E, eqn (8)
$C{\equiv}C^-$	$C{\equiv}N$	−7.9	0.1
CO_2^-	NO_2	−10.9	−0.9
NH_3^+	CH_3	−25.4	−10.8
$N(CH_3)_3^+$	$C(CH_3)_3$	−10.6	−5.0
O^-	F	−17.4	−5.0

We gave most attention to groups bearing a charge and wanted to explore whether this charge influences significantly the substituent effects, which then could not be denoted as purely steric. One can imagine that the charge produces induced charges in the near *t*-butyl group of **2** (or in the methyl group of **3**); the molecule would be stabilized and the apparent "steric" constant (always destabilizing) would be reduced. In agreement with this, the values of Δ_4E and Δ_5E for charged groups are small and may become even negative, that is stabilizing (Table 1). We attempted to obtain a semiquantitative description of this effect by comparing the charged groups with similar isosteric and isoelectronic groups without charge (Table 2). The energy difference may serve as an estimate of the short-range polar effect. The values given in Table 2 were obtained by simple subtracting Δ_4E or Δ_5E of the two groups but they can also be given a physical meaning in terms of the isodesmic reactions eqn (7) or (8), where an uncharged group Y is exchanged for the isosteric charged group X.



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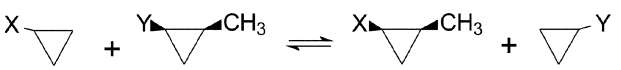

(8)

The values of Δ_7E and Δ_8E are stabilizing and their relative values confirm the expectation. They are smaller (in absolute values) when the charge is further apart or sheltered by further atoms. Nevertheless, they are not more than rough estimates. We have not attempted any electrostatic calculations since the interaction with the induced dipole depends on the fourth power of the distance (r^{-4}), and a reasonable estimation of r is the main problem in such calculations. Our conclusion is that the estimated steric effects of charged groups are biased since they include electrostatic induction; this may apply also, to a smaller extent, to some strongly dipolar groups (CN, NO_2) but would be difficult to prove and to estimate quantitatively.

Relation to the standard steric constants

Scaled reaction energies Δ_4E - υ_{12} of the isodesmic reaction, eqn (4), have been plotted in Fig. 2 *vs.* the standard steric constants[19] υ_{ef}. One could expect some parallelism but not an exact linear dependence since Δ_4E are values of energy and υ_{ef} should be based merely on the geometry.[19] Note, however, that any purely geometric volume of an atom does not exist; the van der Waals radius depends on an assumed electron distribution and on a deliberate limit; it can be defined differently. Moreover, some values of υ_{ef} (for unsymmetrical groups) were estimated from the experimental values of reactivity.[19]

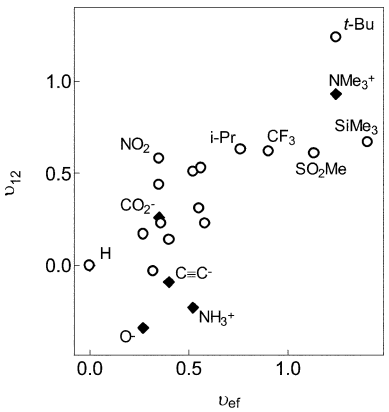

Fig. 2 Plot of the scaled steric energies determined in this work υ_{12} *vs.* the standard steric constants υ_{ef}: ○ uncharged substituents, ♦ charged substituents; some important substituents are marked.

The most conspicuous features of Fig. 2 are the big deviations downward of the charged substituents, particularly O^-, NH_3^+ and $C{\equiv}C^-$. This is in agreement with the explanation given in the preceding section: the charged substituents exert a stabilizing effect due to induction in the crowded molecule **2**. The deviations are only in qualitative agreement with the effects estimated in Table 2; a more quantitative approach cannot be attempted, in our opinion. The forced conclusion is that charged substituents must not be included in the scale of steric constants. Note that they are not present in Charton's tables;[19] their values of υ_{ef} were calculated here from the van der Waals radii according to eqn (3). Another consequence, perhaps less evident but important, is that the same effect, although weaker, must be observed also with polar uncharged groups. We examined in detail the pertinent substituents in Fig. 2 but found no general proof. While the deviations of groups SO_2CH_3 and CF_3 could be attributed to such induction, this is certainly not observable with the substituent NO_2. We also attempted to account for the substituent polarity by multiple regression of Δ_4E with υ_{ef} and with the inductive constants σ_I but no dependence on the latter was observed, similarly as on further substituent constants. Evidently there is another effect, which we can call deformability. The van der Waals radius relates to the isolated molecule and gives no idea how the electron distribution and energy are charged in the proximity of another atom. A striking example is the substituent $Si(CH_3)_3$. In comparison with $C(CH_3)_3$, it has an almost equal van der Waals radius but it is apparently "softer", that is, it can be deformed with less energy. In our opinion, this principal discrepancy cannot be improved and is the reason why the steric

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effects are not proportional in different reaction series, unless these series are very similar. Such an example is shown in Fig. 1 but great deviations were observed in series only slightly less similar.[20] Correlations with steric constants described in the literature[19,25,26] are only multiple regressions, in which υ was only one of several explanatory variables; the relative importance of these variables would require a more detailed statistical analysis, also with respect to the recently observed difference in resonance effects of donor and acceptor substituents.[31] With multiple regression, it may be that a substituent effect is attributed to another explanatory variable; this is evident, for instance, from a correlation, in which no inductive effect was found,[19] although it cannot be absent.

Steric effects on geometric parameters

Substituent effects on energy and on geometry are not always parallel and their comparison has sometimes revealed different mechanisms of interactions of the subgroups of substituents.[20,31] Such comparisons are of merit, as they do not depend on any constants σ or on similar constructions, but use only directly observable quantities. In compounds **2** and **3**, the steric strain can be relieved in several ways: extended bond length C1–C2, widened bond angles $\vartheta_1 = \angle$ X–C1–C2 and $\vartheta_2 = \angle$ C1–C2–C, or non-zero dihedral angle $\tau = \angle$ X–C1–C2–C. Previous experience of alkyl substituents[20] revealed that changes in the bond length C1–C2 are negligible and the values of τ are mostly small, but always quite irregular: attention was focused on the average values of bond angles, $(\vartheta_1 + \vartheta_2)/2$. A plot of $(\vartheta_1 + \vartheta_2)/2$ against Δ_4E for compound **2** is shown in Fig. 3. Deviations of charged substituents were expected. For the other groups, an approximate linearity is observed but it is strongly dependent on the substituent t-C_4H_9. The deciding effect of the extreme points can also be observed in Fig. 1 and in many other empirical relationships.[32]

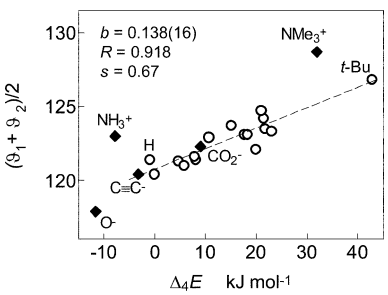

Fig. 3 Dependence of the bond angles ϑ_1 and ϑ_2 in the cyclopropane derivatives **2** on the relative energy Δ_4E of the same compounds, eqn (4): ○ uncharged substituents X, ♦ charged substituents; the statistics relate to the former set; some important substituents are marked.

The conclusions from Fig. 3 may be summarized thus: the energy values, Δ_4E, are prevailingly of steric origin when they are roughly proportional to changes of geometry.

Conclusions

The principle of steric hindrance is certainly not to be doubted, but the problem is whether the steric effects of individual groups can be arranged into a unified scale of constants, which would be valid for various molecules in various reactions. In this work, we have defined one scale based on energy, strictly thermodynamically defined, free of artificial constructions and independent of solvent effects. However, this scale is not generally applicable, in particular for charged and strongly polar groups, it does not describe pure steric effects. As far as we know, exact parallelism of steric effects was observed only in very similar model reactions (Fig. 1 of this work or ref. 20); in slightly less similar reactions, the proportionality is violated.[20] When we summarize these results together with earlier results of multiple regression,[19,25,26] we are of the opinion that a universal scale of steric effects is not possible.

Acknowledgements

This work was carried out within the framework of the research project Z4 055 0506 of the Academy of Sciences of the Czech Republic.

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