Steric effects of the alkyl groups: evaluation on isolated molecules by means of isodesmic reactions†

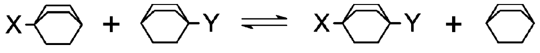
Stanislav Böhm[a] **and Otto Exner***[b]

Received 23rd March 2007, Accepted 4th May 2007
First published as an Advance Article on the web 29th May 2007
DOI: 10.1039/b704459c

Several possible scales of steric effects of the alkyl groups were suggested on the basis of isodesmic model reactions, in which a sterically crowded compound is formally synthesized from simpler derivatives. The reaction energies were calculated within the framework of the density functional theory at the level B3LYP/6-311+G(d.p)//B3LYP/6-311+G(d.p) for 6 model systems and 7 various alkyl groups. The most important systems were *cis*-1,2-dialkylcyclopropanes **1** synthesized from two mono derivatives and sterically crowded derivatives of bicyclo[2.2.2]octane **2** with C_3 symmetry. The scales of steric effects evaluated from the two models were rather different: the first scale depended in effect only on the C atoms in the α and β positions and the effects were almost equal for all primary alkyls. The second scale depended also on the γ position and the effect of the CH_2–*t*-Bu group was much greater than that of the ethyl group. Any relationship between various systems was found rarely, only in the case of very similar reaction series; even in such cases the relationship was sometimes linear, sometimes distinctly curvilinear. It is concluded that any universal scale of steric effects is in principle not possible since these effects depend specifically on the surroundings of the substituent in a particular reaction. Nevertheless, there is a similarity between various scales; a bulky group appears as bulky in any scale. Therefore, very rough correlations of steric effects are possible.

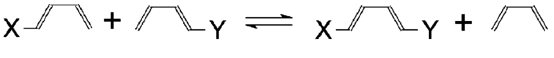
Introduction

The classical definition of substituent effects[1–4] makes use of a model molecule with a variable substituent, a connecting skeleton and a functional group (denoted[4] sometimes as the "probe"), on which a measurable property is monitored. The substituent effect has been defined as the change of this quantity referenced to a standard substituent, usually hydrogen. According to the structure of the model and the character of the measurable quantity the substituent effect was given different names, sometimes very detailed[5] but a separation into inductive, resonance and steric was broadly accepted.[1–3,6,7] We criticized[8] this concept since the "probe" was often an ionized group[1–7,9] and had greater influence on the structure and electron distribution than the variable substituent. A redefinition was suggested,[8] which removes the difference between the substituent and the functional group, and restricts the measurable quantity to reaction energy (or enthalpy or Gibbs energy). In this way the term substituent effect received a more narrow definition but also a clear thermodynamic meaning. For instance the inductive effect was defined[10] by the isodesmic[11,12] and homodesmic[13] reaction, eqn (1), which describes interaction of the groups X and Y without differentiating the substituent and reaction centre.



(1)

Similarly the resonance interaction was defined[14] on the basis of the reaction in eqn (2), although in this case the definition is less straightforward and requires a correction for the simultaneously present inductive effect.



(2)

In both cases the reaction energies were calculated for isolated molecules within the framework of the density functional theory (DFT) and only some particular reactions were anchored on the available experimental data.[10,14] The results of these two studies were somewhat similar: the terms of both inductive effect and resonance effect should be restricted in their validity. The inductive effect is valid in the original simple form only when one of the interacting groups [X and Y in eqn (1)] is charged (COO$^-$, NH$_3^+$) or strongly polar (NO$_2$, CN). Interaction of two less polar groups is more complex.[10,15] The resonance effect in eqn (2) is well defined when X is a donor and Y an acceptor; interaction of two donors or two acceptors cannot be simply described in terms of resonance.[14]

The goal of this paper was to quantify the steric effect in a similar way, that is on the isolated molecules, independently of solvent and of any assumed reaction mechanism. It was clear from the beginning that any broadly applicable scale can hardly be found. There is a general opinion that the steric effects are not linearly dependent in various reactions[16] but rather vary nonlinearly with the substituent, becoming suddenly appreciable at its certain size. We attempted to find at least some similar reaction series in which the steric effects would be proportional or related nonlinearly. In order to deal with effects, which can be classified as purely steric, we restricted the investigation to alkyl substituents.

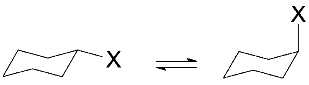
Steric effects of the alkyl groups were quantified either in energy terms based on experiments, or in geometrical terms based on

---

[a] *Department of Organic Chemistry, Institute of Chemical Technology, CZ-16628 Praha 6, Czech Republic*
[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, CZ-16610 Praha 6, Czech Republic*

† Electronic supplementary information (ESI) available: DFT calculated energies of **1** to **6** (Tables S1 and S2) and some calculated geometrical parameters of **2** and **6** (Table S3). See DOI: 10.1039/b704459c

calculations. Several scales of steric constants were thus proposed but there is only very scarce evidence of the extent to which they can be correlated with observed reactivities. Original Taft's separation of inductive and steric effects was based on the kinetics of ester hydrolysis.[7] The inductive constants σ^* were then used broadly whereas the steric constants E_s correlated themselves with the reactivity only in several, rather small reaction series;[7] mostly they have been used[7,17–20] in combination with inductive and resonance effects but their proper contribution was not evident. The values of E_s were revised and improved several times,[21–27] for instance corrected for assumed hyperconjugation[23,26] but the usefulness of this correction has not been sufficiently proven. Several other reactions were claimed[26–29] to depend almost exclusively on steric effects but the generated scales were usually not tested on other reactions. One old attempt seems interesting, that is estimating the steric effect from conformational equilibrium of cyclohexane derivatives,[30] eqn (3). However this equilibrium was estimated only indirectly from kinetic data and few alkyl substituents were investigated. The steric constants determined by various procedures were generally not proportional[16] as could be expected.

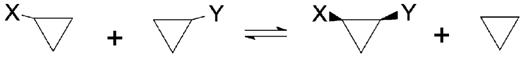


(3)

Apparently better founded are Charton's steric constants υ, defined on a different principle referring only to pure geometry:[31] they represent an idealized radius of a group based on the van der Waals radii r_V of individual atoms. Of various scales of r_V the scale of Bondi[32] was preferred and some values were still corrected. The main problem is with the unsymmetrical groups that can prefer such conformations to escape the steric tension; for instance the groups CH_2CH_3, CH_2Hal and CH_2OH have in the favourable conformations equal values of υ, denoted υ_{mn} (minimum). For the correlations however the effective value υ_{ef} is more important, estimated[31] with respect to some kinetic experiments as previously with the E_s values. There are many objections against the whole theory: the model of rigid spheres is far from reality, the interaction energy is not linearly related to r_V, and there is a great arbitrariness concerning the conformation. Nevertheless, the constants υ were applied many times[33–35] but always together with other parameters (σ_I, σ_R *etc.*). There is a rough correlation of υ with E_s with many unexplained exceptions.[36]

An extension of these ideas are the directional steric constants[37] ("sterimol") B1 to B4, representing either the minimum or maximum dimension of the substituent, measured either in the direction of the connecting bond or perpendicular to it, as when the molecule would be placed into rectangular boxes. These constants could be perhaps of importance for enzymatic reactions but were rarely applicable to kinetics and only exceptionally to equilibria.[38]

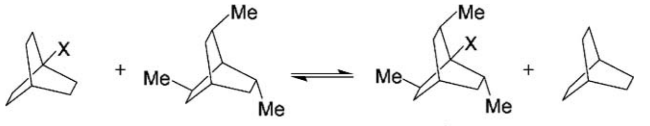
In this work, we describe several new model systems for evaluating the steric effect of alkyl groups. Their merit is that they work in terms of energy of isolated molecules, not only of geometry: two alkyl groups are brought together in the course of an isodesmic reaction. Concerning the exact geometry, we chose molecules in which the alkyls are as near as possible to each other and situated on a very rigid system. These conditions are met with *cis*-1,2-dialkylcyclopropanes **1** and the reaction in eqn (4); this equation also has the merit that it is in principle similar to eqns (1) and (2), which define the inductive effect and resonance effect, respectively. Effects determined on eqn (4) were expected to be somewhat similar to the constants[31] υ_{mn} or sterimol[37] B1, since the two alkyls can take suitable conformations and minimize the steric strain.



1

(4)

The second model we suggested, 1-substituted *trans*,*trans*,*trans*-2,6,7-trimethylbicyclo[2.2.2]octane derivatives **2**, was constructed to reveal the steric effect independent of conformation taking into account also the third atom of the substituent, see eqn (5). Both model systems were then compared with similar models to see whether the steric effects are proportional at least in very similar series.



2

(5)

The reaction energies were calculated at the level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) which was well-tried for various substituent effects[10,14,15] in molecules of similar size and was found to be satisfactory even for steric effects.[39] (Recently reported failure[40] of this theoretical model was established only on one example and should be checked on a series of compounds.)

Calculations

The DFT energies of 1,2-disubstituted cyclopropanes **1** and **3**, cyclopentanes **4** and **5**, 1-substituted *trans*,*trans*,*trans*-2,6,7-trimethylbicyclo[2.2.2]octanes **2** and 1-substituted 2,2,6,6,7,7-hexamethylbicyclo[2.2.2]octanes **6** were calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) level with the GAUSSIAN 03 program.[41] Possible conformations were always taken into consideration and calculations were started from the pertinent near 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 energies are listed in Tables S1 and S2 (ESI†). Some important geometric parameters of **1** are given in Table 1, those of **2** and **6** in Table S3.

Results and discussion

Steric effects of two adjoining alkyl groups

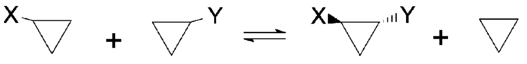
This concept of the steric effect was based on *cis*-1,2-cyclopropane derivatives **1**, which were formally synthesized in the isodesmic reaction, eqn (4). The two alkyl groups X and Y are brought and kept together by the relatively rigid cyclopropane system. The two *cis* alkyl groups are situated in the synperiplanar (*sp*) conformation, which is generally somewhat unnatural and is found only in few molecules. On the other hand, it allows the steric effects to be observed very clearly. The DFT calculated reaction energies of this reaction, Δ_4E, are listed in Table 1, column 2. On

Table 1 Some calculated geometrical parameters of cyclopropane derivatives **1** and energies of the isodesmic reactions, eqn (4), (6), (11) and (12)

	1 (*cis*-1,2-cyclopropanes)					**3**	**4**	**5**
Substituents	$\Delta_4 E$/kJ mol^{-1}	C1–C2/Å	∠C–C1–C2/°	∠C1–C2–C/°	τ^a	$\Delta_6 E$/kJ mol^{-1}	$\Delta_{11} E$/kJ mol^{-1}	$\Delta_{12} E$/kJ mol^{-1}
Me Me	6.21	1.515	123.1	123.1	0.0	0.41	9.71	1.08
Me Et	6.77	1.514	123.1	123.4	0.3	0.40	3.45	−4.89
Me Pr	6.72	1.517	123.4	123.4	0.6	0.46	—	—
Me i-Bu	7.12	1.516	123.5	123.2	0.3	0.43	—	—
Me neo-Pe	7.05	1.518	123.2	122.3	1.3	0.46	10.52	21.97
Me i-Pr	7.41	1.516	123.5	125.8	0.7	0.55	17.56	1.37
Me *t*-Bu	17.66	1.519	126.8	129.8	4.9	0.84	20.67	5.78
Et Et	7.03	1.513	123.6	123.6	0.0	0.47	−0.86	−10.61
Et Pr	7.07	1.514	123.6	123.5	0.0	0.51	—	—
Et i-Bu	7.58	1.515	123.9	123.2	0.2	0.30	—	—
Et neo-Pe	7.43	1.517	123.7	122.4	1.6	0.45	6.03	17.10
Et i-Pr	7.83	1.515	124.0	124.0	1.0	0.62	11.83	−4.15
Et *t*-Bu	18.29	1.518	127.3	130.0	5.1	0.77	17.70	−0.55
Pr Pr	7.14	1.514	123.4	123.4	0.0	0.58	—	—
Pr i-Bu	7.58	1.516	123.8	123.2	0.1	0.51	—	—
Pr neo-Pe	8.92	1.515	124.6	125.1	0.4	0.46	—	—
Pr i-Pr	7.76	1.518	123.9	124.0	0.9	0.62	—	—
Pr *t*-Bu	18.29	1.518	127.2	129.9	5.1	0.82	—	—
i-Bu i-Bu	8.16	1.517	123.7	123.7	0.0	0.54	—	—
i-Bu neo-Pe	7.96	1.515	123.3	122.7	1.3	0.48	—	—
i-Bu i-Pr	8.23	1.517	123.5	124.2	1.0	0.51	—	—
i-Bu *t*-Bu	19.44	1.520	126.9	130.3	5.1	0.66	—	—
neo-Pe neo-Pe	7.93	1.520	122.4	122.4	0.0	0.77	13.99	43.61
neo-Pe i-Pr	8.46	1.519	122.9	124.1	0.3	0.60	18.00	21.83
neo-Pe *t*-Bu	18.89	1.521	126.1	130.0	4.9	0.80	39.14	31.01
i-Pr i-Pr	11.99	1.520	—	—	0.0	0.89	25.12	1.80
i-Pr *t*-Bu	21.73	1.523	128.9	131.6	3.7	1.27	29.74	6.46
t-Bu *t*-Bu	42.75	1.532	134.7	135.4	0.8	1.49	63.94	21.63

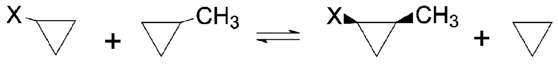
[a] Dihedral angle C–C1–C2–C.

the first sight these values are sufficiently large compared to the possible uncertainty of the method. This is evident when they are compared to the *trans* isomers **3**, eqn (6), in which the steric effects are negligible and exceed 1 kJ mol^{-1} only in two cases (Table 1, column 7). These effects will not be discussed; rather they will serve as boundary values showing the limits of both the quantum-chemical model and of the concept of the steric effect.



3 (6)

On the first sight, the values of $\Delta_4 E$ can be divided into three groups: for all primary alkyls they are almost equal, for the secondary alkyl group i-C_3H_7 slightly greater and for the tertiary alkyl *t*-C_4H_9 much greater. In the correlation analysis the fundamental question is whether the effects are proportional when one of the alkyl groups is held constant. To this purpose we chose the methyl group as the standard constant group, that is the reaction energies $\Delta_7 E$, eqn (7), as the reference series.



(7)

Reaction energies of further series with different constant groups were plotted *vs.* $\Delta_7 E$ in Fig. 1. Linear dependences were obtained but the points were distributed irregularly along the regression lines and this makes any statistical treatment unreliable. As expected, primary alkyl groups behave almost as one substituent and the pertinent straight lines have slopes insignificantly greater than unity; isopropyl derivatives have a slope of 1.24 and *tert*-butyl derivatives a slope of 2.59. There is only one deviating point of the i-Pr derivative but the deviation has little significance. In any case it has been proven that in very similar reactions (differing here only by the constant group Y in **1**) the steric effects can be proportional. For defining the

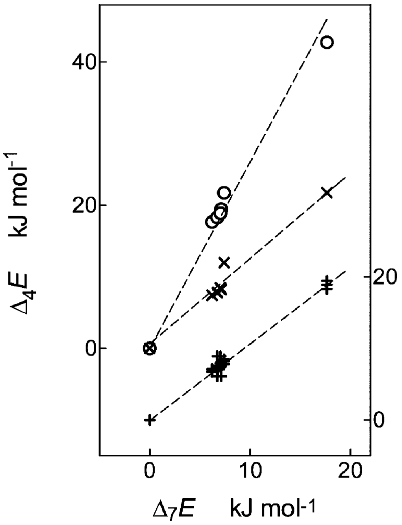
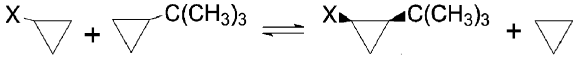


Fig. 1 Plot of the interaction energies of two alkyl groups in *cis*-1,2-dialkylcyclopropanes **1**, eqn (4), with different constant groups Y. *x*-Axis: Y = CH_3; *y*-axis: symbol +, Y = C_2H_5 or C_3H_7 or i-C_4H_9 or CH_2–*t*-C_4H_9; symbol ×, Y = i-C_3H_7; symbol ○, Y = *t*-C_4H_9.

steric parameters ("constants") and perhaps for calculating new values for further groups we recommend using *t*-butyl derivatives according to eqn (8). The steric constant υ_{12} is then defined by eqn (9); the proportionality constant 0.029 is purely arbitrary and should only bring the values of υ_{12} to a scale comparable to the standard values υ.



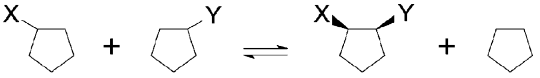
(8)

$$\upsilon_{12} = 0.029\Delta_8 E \text{ (kJ mol}^{-1}\text{)} \tag{9}$$

The symbol υ_{12} should show that the values express the interaction in the adjoining positions 1,2. We do not claim that this scale of steric constants would be perhaps better than the scales in use, since it will be shown that the steric effects are variable. Our scale should serve merely as a reference and has the main merit that it is thermodynamically defined on isolated molecules. The values of υ_{12} are given in Table 2, column 2. When these constants are defined, one can express the interaction energy in the reaction of eqn (4) as a function of the two substituents, eqn (10). Statistics for eqn (10) are: $R = 0.9944$ $s = 0.61$ kJ mol^{-1} $N = 29$

$$\Delta_4 E = (28.6 \pm 0.4)\upsilon_{12}(\text{X})\upsilon_{12}(\text{Y}) - 0.8 \pm 0.2 \tag{10}$$

The correlation is very good but the equation is of little importance due to the restricted range of validity. The fit could be still improved if the constants υ_{12} were optimized with respect to all data instead of defined on a particular series. However, such statistical values have a disadvantage in that they should always be recalculated when new data are obtained,[42] while the values defined as above can simply be added; the new data can be added to the old ones. In any case eqn (10) proves that proportional steric effects are possible in a restricted series of extremely similar reactions. On the other hand, the proportionality is violated even in reaction series that are apparently still very similar. We observed this already in the analogous reactions of 1,2-disubstituted cyclopentanes, *cis* **4** and *trans* **5**, eqns (11) and (12), respectively.



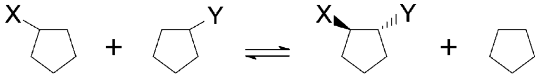
4

(11)

Table 2 New calculated steric constants and energies of the isodesmic reactions eqns (5) and (14)

	Steric constants		Reaction energies/kJ mol^{-1}	
Substituent	υ_{12}[a]	υ_{C3}[b]	$\Delta_5 E$	$\Delta_{14} E$
H	0	0	0.00	0.00
Me	0.51	0.33	18.73	26.02
Et	0.53	0.62	35.57	50.58
Pr	0.53	0.63	35.61	50.80
i-Bu	0.56	0.78	44.26	63.20
neo-Pe	0.55	1.03	58.82	95.06
i-Pr	0.63	0.92	52.57	88.85
t-Bu	1.24	1.24	70.57	134.82

[a] Determined from substituted *t*-butylcyclopropanes, eqn (8).
[b] Determined from bicyclo[2.2.2]octane derivatives **2**, eqn (5).



5

(12)

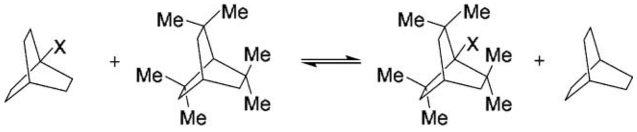
In these reactions, the groups X and Y also prefer the conformations as mutually remote as possible but the steric strain is also partly balanced by the changes of conformation of the cyclopentane ring. This effect is quite irregular and the calculated reaction energies $\Delta_{11}E$ and $\Delta_{12}E$ sometimes do not follow the size of the substituents X and Y. Some values of $\Delta_{11}E$ and $\Delta_{12}E$ are given in Table S1 (ESI†) and will not be discussed in detail.

Steric effects independent of conformation

The constants υ_{12} are evidently almost independent of the branching of the alkyl substituent in the β position: their values for all primary groups are practically equal. We searched for model compounds, in which even the steric effect of further apart atoms would be observed, and found as most suitable the relatively sophisticated compounds **2**, eqn (5). With symmetrical substituents the molecules **2** possess C_3 symmetry; with unsymmetrical substituents they exist in three degenerate conformations. The steric effect of the remote parts of the substituent can be foreseen. The reaction energies $\Delta_5 E$ are given in Table 2, column 4. As expected they are large and differ deeply from $\Delta_7 E$ or $\Delta_8 E$. For better comparison with υ_{12} they were rescaled to a comparable scale and denoted υ_{C3}, eqn (13).

$$\upsilon_{C3} = 0.0176\Delta_5 E \text{ (kJ mol}^{-1}\text{)} \tag{13}$$

The constants υ_{C3} (Table 2, column 3) differ from υ_{12} fundamentally: the effect of the third atom is appreciable, for instance the value for CH_2–*t*-Bu is greater than that for i-C_3H_7 and much greater than that for i-C_4H_9. The constants υ_{C3} may thus describe well the steric requirement of any group but it is not known to what extent they can correlate reactions more or less similar to the reaction of eqn (5). We carried out a comparison with the reaction of eqn (14), in our opinion possibly the most similar to eqn (5): the compounds **6** differ only by the number of methyl groups from **2**.



6

(14)

The comparison is carried out in Fig. 2. As expected the steric effects in eqn (14) are larger and reveal a very strong steric hindrance. Importantly, the dependence is with certainty not linear; the steric effects are not additive but they reinforce each other. This is in fact in agreement with the general opinion about these effects that they may become suddenly stronger with the increasing steric hindrance.

Comparison of the old and our scales of steric constants is not simple, also because of different reference substituents and different scaling. We attempted to compare at least the most important constants in Table 3 after they had been rescaled (for this purpose only) to two fixed points: zero for methyl and 10 for *t*-butyl. Differences between the individual sets are striking,

Table 3 Steric constants of the alkyl groups rescaled to a common scale[a]

	$E_s{}^b$	$E_s{}^{\circ c}$	$E_s{}^{\circ d}$	$E_s{}^e$	$\upsilon_{ef}{}^f$	$\upsilon_{mn}{}^f$	B1[g]	B4[g]	υ_{12}	υ_{C3}
H	−8.1	—	—	—	−7.2	−7.2	−4.9	−11.2	−7.0	−3.6
CH_3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
C_2H_5	0.5	1.5	1.3	0.2	0.6	0.0	0.0	10.0	0.3	3.2
i-C_3H_7	3.1	4.4	4.1	1.6	3.3	—	4.9	12.0	1.6	6.5
t-C_4H_9	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
C_3H_7	2.3	2.7	2.6	1.3	2.2	0.0	0.0	15.6	0.3	3.3
i-C_4H_9	6.0	5.0	5.3	2.5	6.4	0.0	0.0	23.3	0.7	4.9
CH_2–*t*-C_4H_9	11.3	—	—	—	11.4	—	—	—	0.5	7.7

[a] All scales were linearly transformed to reach the fixed values: zero for CH_3 and 10 for *t*-C_4H_9. [b] Determined from experimental data from kinetics, ref. 7. [c] Corrected for assumed hyperconjugation, ref. 23. [d] Values reported in ref. 44, corrected for hyperconjugation according to ref. 26. [e] From the hydroboration reaction, ref. 28. [f] Derived from the van der Waals radii, ref. 31. [g] The sterimol constants, ref. 37.

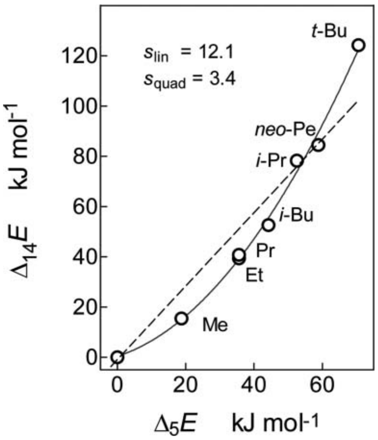


Fig. 2 Plot of the interaction energies of the alkyl groups with a constant environment in two similar, sterically crowded bicyclo[2.2.2]octane derivatives **2** [eqn (5)] and **6** [eqn (14)]; standard deviations from the linear and quadratic interpolation are given.

even when some important items are lacking. Nevertheless some regularities emerge and our two kinds of constants, υ_{12} and υ_{C3}, may be seen as two prototypes. The constants υ_{12} have some similarity with υ_{mn} or B1 and can measure interaction of two groups in adjoining positions. The constants υ_{C3}also take into account the more distant part of the substituent, similarly to the constant υ_{ef} or E_s. The correction for hyperconjugation, $E_s{}^\circ$, seems to be unimportant in this connection and the constants sterimol[37] B4 have probably no significance. Our parameters have the merit of a definite physical meaning and can be easily and unambiguously calculated for any required alkyl group. In our opinion they can serve as standards but direct correlation with various sets of data cannot be expected.

Steric effects on geometrical parameters

The steric strain in crowded compounds like **1**, **2** or **6** is relieved in all degrees of freedom but more apparently in the parameters near to the variable substituent. The question was whether there is any proportionality among individual parameters on the one hand and with the interaction energies on the other. In **1** one can expect that with the increasing strain the intraannular bond C1–C2 is elongated, the bond angles $\vartheta_1 = \angle$C–C1–C2 and $\vartheta_2 = \angle$C1–C2–C are widened and the dihedral angle τ = C–C1–C2–C differs from zero. The values are given in Table 1 and compared with the interaction energies in Fig. 3. There is an evident, perhaps not exactly linear, dependence of the average angles $(\vartheta_1 + \vartheta_2)/2$, while the bond lengths C1–C2 depend on the energy only roughly—they are more sensitive to the structural changes in the β position. The dihedral angles τ are appreciable only in few derivatives and are changed slightly and irregularly.

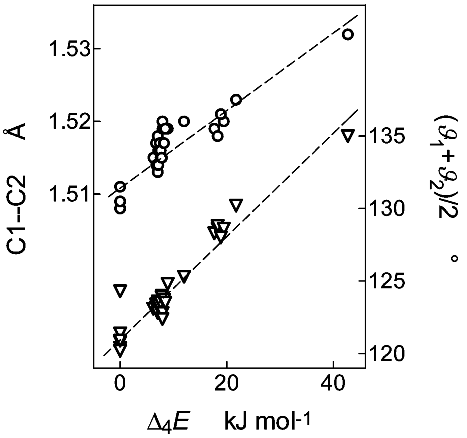


Fig. 3 Comparison of the steric effects in *cis*-1,2-dialkylcyclopropanes **1** on the energy (*x*-axis) and on the geometry (*y*-axis): the extended bond C1–C2 and widened angles $\vartheta_1 = \angle$C–C1–C2 and $\vartheta_2 = \angle$C1–C2–C.

On one example we attempted to calculate the relaxation energies from fixed structures. *cis*-1-Methyl-2-*t*-butylcyclopropane (**1**, X = CH_3, Y = *t*-C_4H_9), with the fixed bond length C1–C2 and angles ϑ_1, ϑ_2 as they are in the mono derivatives, has energy of 31.2 kJ mol^{-1} higher than calculated for these mono derivatives according to eqn (4) ('pure' van der Waals compression). When only the C1–C2 bond length is relaxed, energy drops only by 0.8 kJ mol^{-1}; when ϑ_1 and ϑ_2 are relaxed, it drops by 12.44 kJ mol^{-1}. With relaxation of all parameters, it drops by 12.5 kJ mol^{-1} to reach the value 18.7 kJ mol^{-1} (as given in Table 2) expressing the steric hindrance in real molecules according to eqn (4). Even with some doubts about calculations of fixed structures, one can conclude that relaxation proceeds by deformation of the angles; the C1–C2 bond is also deformed but does not contribute to the energy.

In the molecules of **2** and **6** we observed elongated bond lengths C1–C2, C1–C6 and C1–C7 (generally of different length, Table S3, ESI†); their average length was approximately proportional to the interaction energy (graph not shown). Some calculated bond lengths may seem to be too long, up to 1.657 Å, but this is possible in crowded molecules.[43] All bond angles C(X)–C1–C2 (three different values) and C1–C2–C(H_3) (three values in **2**, six values in **6**) were widened but dependence on the interaction energy was only qualitative. It has been thus confirmed that energy and geometrical parameters can be controlled by substitution in a different way.

Conclusions

Our scales of steric effects of alkyl groups, obtained by means of isodesmic reactions, have the merit that they are thermodynamically well defined and can be simply extended to further substituents, alkyls or even polar groups, by simple DFT calculation. On the other hand, interpretation of our quantitative results confirmed only what had been claimed several times in a qualitative sense. Firstly the steric effects can be very strong even when it is not anticipated from the space-filling models; the strong effects much exceed the possible uncertainty of our DFT approach. Secondly we found several convincing examples that the steric effects are different in different reactions and that even in very similar reactions they need not be linearly related. In our opinion the universal scales of steric effects have no physical meaning (problematic van der Waals radii, kinetics of specific reactions in solution) and little practical applicability (only in combination with other parameters). In this respect the steric effect differs from the inductive and also from the resonance effects.

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.

References

1 V. A. Palm, *Grundlagen der quantitativen Theorie der organischen Reaktionen*, Akademie Verlag, Berlin, 1971.
2 Yu. A. Zhdanov and V. I. Minkin, *Korrelyatsionnyi Analiz v Organicheskoi Khimii*, Rostov State University, Rostov-on-Don, 1966.
3 O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, New York, 1988, ch. 5.
4 R. D. Topsom, *Prog. Phys. Org. Chem.*, 1976, **12**, 1–201.
5 R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 1–83.
6 F. H. Westheimer, in *Steric Effects in Organic Chemistry*, ed. M. S. Newman, Wiley, New York, 1956, pp. 523–555.
7 R. W. Taft, in *Steric Effects in Organic Chemistry*, ed. M. S. Newman, Wiley, New York, 1956, pp. 556–675.
8 O. Exner, *J. Phys. Org. Chem.*, 1999, **12**, 265–274.
9 H. C. Brown, D. H. McDaniel and O. Häfliger, in *Determination of Organic Structures by Physical Methods*, ed. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, pp. 567–662.
10 O. Exner and S. Böhm, *J. Phys. Org. Chem.*, 2004, **17**, 124–130.
11 A. Pross, L. Radom and R. W. Taft, *J. Org. Chem.*, 1980, **45**, 818–826.
12 O. Exner, *Org. Reactivity (Tartu)*, 1995, **29**, 1–6.
13 P. George, M. Trachtman, C. W. Bock and A. M. Brett, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1222–1227.
14 O. Exner and S. Böhm, *J. Phys. Org. Chem.*, 2006, **19**, 1–9.
15 O. Exner and S. Böhm, *J. Phys. Org. Chem.*, 2006, **19**, 393–401.
16 Ref. 3, ch. 5.3.
17 W. A. Pavelich and R. W. Taft, *J. Am. Chem. Soc.*, 1957, **79**, 4935–4940.
18 R. Fellous, L. Lizzani-Cuvelier, R. Luft, J. P. Rabine and M. Rouillard, *Bull. Soc. Chim. Fr.*, 1974, 2482–2488.
19 G. Ananchenko, E. Beaudoin, D. Bertin, D. Gigmes, P. Lagarde, S. R. A. Marque, E. Revalor and P. Tordo, *J. Phys. Org. Chem.*, 2006, **19**, 269–275.
20 V. Nummert, M. Piirsalu, V. Mäemets and I. Koppel, *Collect. Czech. Chem. Commun.*, 2006, **71**, 1557–1570.
21 A. Babadjamian, M. Channon, R. Gallo and J. Metzger, *J. Am. Chem. Soc.*, 1973, **95**, 3807–3808.
22 I. A. Koppel, *Reakts. Sposobn. Org. Soedin.*, 1966, **2, No. 2**, 26–30.
23 C. K. Hancock, E. A. Meyers and B. J. Yager, *J. Am. Chem. Soc.*, 1961, **83**, 4211–4213.
24 J. P. Idoux, P. T. R. Hwang and C. K. Hancock, *J. Org. Chem.*, 1973, **38**, 4239–4243.
25 I. V. Talvik and V. A. Palm, *Reakts. Sposobn Org. Soedin.*, 1971, **8**, 445–462.
26 Ref. 1, ch. X.
27 S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, 1976, **12**, 91–118.
28 R. Fellous and R. Luft, *J. Am. Chem. Soc.*, 1973, **95**, 5593–5595.
29 R. T. M. Fraser, *Nature*, 1965, **205**, 1207.
30 E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, ch. 8.6.
31 M. Charton, in *Similarity Models in Organic Chemistry, Biochemistry and Related Fields*, ed. R. I. Zalewski, T. M. Krygowski and J. Shorter, Elsevier, Amsterdam, 1991, pp. 629–687.
32 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451.
33 M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 3691–3693.
34 M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 3694–3697.
35 M. Charton and B. I. Charton, *J. Org. Chem.*, 1982, **47**, 8–13.
36 C. Hansch and A. J. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979, ch. II-3.
37 A. Verloop, W. Hoogenstraaten and J. Tipker, in *Drug Design*, ed. E. J. Ariens, Academic Press, New York, 1976, vol. VII, pp. 165–207.
38 O. Exner and S. Böhm, *Collect. Czech. Chem. Commun.*, 2006, **71**, 1239–1255.
39 S. Böhm and O. Exner, *J. Comput. Chem.*, 2006, **27**, 571–577.
40 S. Grimme, *Angew. Chem., Int. Ed.*, 2006, **43**, 4460–4464.
41 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision B.03*, Gaussian Inc., Pittsburgh, PA, 2003.
42 O. Exner, in *Correlation Analysis in Chemistry*, ed. N. B. Chapman and J. Shorter, Plenum Press, New York, 1978, pp. 439–540.
43 According to the Cambridge Structural Database, the central bond in a fragment $(C–)_3C–C(–C)_3$ is longer than 1.6 Å in 157 of 1356 molecules.
44 J. Shorter, in *Advances in Linear Free Energy Relationships*, ed. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, pp. 71–118.