INTERACTION OF POLAR GROUPS WITH A BULKY HYDROCARBON RESIDUE: POLARIZABILITY AND STERIC EFFECTS

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Energies of two series of branched hydrocarbon monosubstituted derivatives, 2-substituted 2-methylpropanes and 1-substituted bicyclo[2.2.2]octanes with 19 different substituents were calculated at the B3LYP/6-311+G(d,p) level and compared with the energies of straight-chain 1-substituted butanes. The comparison was carried out in terms of isodesmic homodesmotic reactions, in which the substituent is transferred from one hydrocarbon residue to another. The branched derivatives are mostly stabilized, in the extreme case by as much as 30 kJ mol^{-1} confirming that the additive rule used for estimating the enthalpies of formation is not valid for branched derivatives. The stabilization energies ΔE for the individual substituents X are not proportional to any known substituent parameters. In the qualitative respect, they are controlled by the first atom of the substituent – similarly as in the straight-chain isomers – but in the case of sterically demanding substituents they are perturbed by a destabilizing steric effect.

Keywords: Substituent effects; Hydrocarbons; Ab initio calculations; DFT; 2-Methylpropanes; Bicyclo[2.2.2]octanes; Butanes.

Mutual interaction of two groups in one molecule has been investigated mainly with relatively distant groups[1–3]; originally one group was considered as a variable substituent, the other as the functional group (probe)[4]. The substituent effects were classified as inductive, resonance, steric, etc.[2–5], with particular attention to distinguishing pure and composite effects[6]. In a more general approach the interaction of two groups X and Y (polar or charged) has been defined as the reaction energy Δ_1E (or enthalpy $\Delta_1H°$) of the isodesmic reaction, Eq. (*1*), in which a bis derivative is synthesized from two mono derivatives[7,8]; the differentiation of substituent and probe has been removed.

$$\text{X–G–H} + \text{H–G–Y} \rightleftharpoons \text{X–G–Y} + \text{H–G–H} \qquad (1)$$

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The values of $\Delta_1H°$ can be obtained[9] from the experimental enthalpies of formation $\Delta_fH°(298)$ but the accuracy is often not sufficient[10]. In recent work, Δ_1E was calculated theoretically[11] since high-level calculations give good results just for isodesmic equations.

The present paper deals with the extension of the above principle to interaction of two immediately bonded groups. In the attempts made so far[10,12–14], typically one group was polar (X), the other nonpolar and polarizable (a hydrocarbon residue R), as in the isodesmic and homodesmotic[15] reaction, Eq. (*2*).

$$\text{X–R°} + \text{R–H} \rightleftharpoons \text{X–R} + \text{R°–H} \tag{2}$$

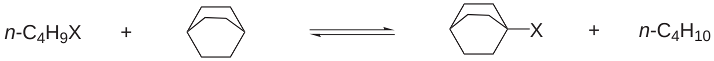
The problem is more difficult than in the case of two polar groups, the main difficulty being in the choice of a reference group R°, which should show ideally no interaction with any substituent X. This is hardly possible. Most work has been devoted to the interaction with R = phenyl[10,12] or vinyl[13] with the intention to evaluate the resonance effect of X but in this case the reaction is no longer homodesmotic[15] and no reference group R° is entirely satisfactory. The commonly used methyl group[10,12] is much smaller than phenyl and of different polarizability, while the *tert*-butyl group[10,13b] brought unknown effects, assumed to be steric in origin. We reinvestigated the problem from the beginning on the simplest case when both R and R° were alkyl groups[14]. In this case Δ_2E should be generally small with respect to the common empirical rules for estimating the enthalpies of formation[16,17]. These rules express $\Delta_fH°$ as a sum of empirical contributions (increments) $h[\text{X}]$ pertinent to individual atoms or groups; the summation extends over the whole molecule:

$$\Delta_fH°(298) = \Sigma h[\text{X}] \; . \tag{3}$$

When Eq. (*3*) holds, Δ_2E of the isodesmic reaction is zero for any given groups R and R°. We confirmed this with good accuracy (less than 1 kJ mol^{-1}) on the calculated energies for the pair *n*-butyl and *n*-pentyl but great deviations were found for methyl and small deviations even for ethyl derivatives[14]. Therefore, *n*-butyl (in the fixed zig-zag conformation, all-*ap*) was recommended as a standard to which the interactions with other groups could be related[14,18]. In this communication we extended this approach to branched hydrocarbon derivatives, viz. *tert*-butyl derivatives **1** and bicyclo[2.2.2]octanyl derivatives **2**. (Some compounds of the latter set were investigated previously[19] from another point of view.) In Eqs (*4*) and (*5*) these compounds are compared with standard *n*-butyl derivatives **3**.

$$n\text{-}C_4H_9X \quad + \quad (CH_3)_3CH \quad \rightleftharpoons \quad (CH_3)_3CX \quad + \quad n\text{-}C_4H_{10} \qquad (4)$$

3 **1**



(*5*)

3 **2**

Compounds with branched chain are known to possess rather different enthalpies of formation than their straight-chain isomers. Deviations from the additive scheme were observed with all additive quantities, not only with the enthalpies of formation; they were particularly great for overcrowded molecules[20]. These deviations were usually unraveled by means of special contributions for atoms respecting even the next neighbors in the given structure[16]. An alternative solution was attempted by Istomin and Palm[21] who replaced the additive relationship, Eq. (*3*), by Eq. (*6*) valid for a mono derivative RX.

$$\Delta_f H°(RX) = h[R] + h[X] + \varphi[R]\,\varphi[X] \qquad (6)$$

The empirical parameters φ[R] and φ[X] express the deviation from additivity. All parameters, *h* and φ, were calculated on the basis of experimental $\Delta_f H°(298)$; only fair fit was achieved[21]. We hoped to obtain more significant results with more systematic and perhaps more dependable data, viz. the energies *E*(DFT) calculated within the framework of the density functional theory[22]. We calculated *E*(DFT) values for 19 common substituents, both polar and charged (compounds **1a**–**1s** and **2a**–**2s**, Table I) and from them the reaction energies $\Delta_4 E$ and $\Delta_5 E$ of the isodesmic reactions, Eqs (*4*) and (*5*), respectively. We wanted to explore whether these energies can be related to the known scales of substituent effects (inductive[3], resonance[3], steric[23,24] and others[21,25–28]) or whether they should be considered as a special effect.

CALCULATIONS

The DFT calculations at the B3LYP/6-311+G(d,p) level were performed exploiting the Gaussian 03 program[29]. Full energy optimization and vibrational analysis were carried out in all cases. The minimum-energy conformation was searched for, starting from two or more initial structures; these can differ only in the conformation around the bonds C(1)–X. The reaction energies Δ_4E and Δ_5E were calculated from these DFT energies and from previous values[14] for the compounds **3**. All energies are listed in Table I.

Calculations of the enthalpies $\Delta H°(298)$ of **1** were carried out with same program[29]. DFT calculations at the level B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p) were carried out at the tight convergence as recommended previously[14].

RESULTS AND DISCUSSION

Comparison with Experiments

Anchoring to some experimental values is important to check the reliability of our theoretical model since some problems were encountered in the previous study of similar compounds[14]. However, the possibilities are limited. The isodesmic reaction, Eq. (*4*), can be examined when the values for two substituents, one charged and one uncharged, are subtracted. We obtained Eqs (*7*) and (*8*) relating to the experimentally investigated compounds.

$$n\text{-}C_4H_9NH_3^+ + (CH_3)_3CNH_2 \rightleftharpoons (CH_3)_3CNH_3^+ + n\text{-}C_4H_9NH_2 \qquad (7)$$

$$\Delta E_{calc} = -13.6 \text{ kJ mol}^{-1}$$
$$\Delta H°(298)_{calc} = -14.7 \text{ kJ mol}^{-1}$$
$$\Delta H°(298)_{exp}{}^{30} = -12.6 \text{ kJ mol}^{-1}$$

$$n\text{-}C_4H_9O^- + (CH_3)_3COH \rightleftharpoons (CH_3)_3CO^- + n\text{-}C_4H_9OH \qquad (8)$$

$$\Delta E_{calc} = -8.1 \text{ kJ mol}^{-1}$$
$$\Delta H°(298)_{calc} = -7.5 \text{ kJ mol}^{-1}$$
$$\Delta H°(298)_{exper}{}^{31} = -3.4 \text{ kJ mol}^{-1}$$

The fit may be viewed as good. The experimental uncertainty 2 kJ mol^{-1} for one compound makes 2.8 kJ mol^{-1} for the isodesmic reaction; with the data from different sources the uncertainty may be still greater. A part of the difference might be caused by the choice of the all-*ap* conformer of butyl derivatives **3** as model; its calculated energy could be somewhat higher than that of the real molecule and calculated Δ_4E too great in the absolute value. Other possible conformations are of no consequence: Conformations on the functional group of **3** were investigated previously and the minimum-energy forms selected[14]. In **1** the conformation on the C–X bond is mostly

TABLE I
Calculated energies of 2-substituted 2-methylpropanes **1** and 1-substituted bicyclo[2.2.2]octanes **2**, and energies of the isodesmic reactions Δ_4E and Δ_5E

Compound	Substituent X	**1** E(DFT), a.u.	**1** $\Delta H°(298)$, a.u.	**2** E(DFT), a.u.	Δ_4E kJ mol^{-1}	$\Delta_4H°(298)$ kJ mol^{-1}	Δ_5E kJ mol^{-1}
a	H	–158.5064326	–158.368875	–313.3717029[a]	0.00	0.00	0.00
b	CH_3	–197.8313933	–197.664942	–352.6984378[a]	–1.66	–3.77	–6.32
c	t-C_4H_9	–315.7910470	–315.537073	–470.6583232	28.51[c]	25.92[c]	23.25[c]
d	CH_2Cl	–657.4541810	–657.295011	–812.3212816[a]	1.44	–0.85	–3.37
e	CF_3	–495.6595560	–495.513804	–650.5264681[a]	3.10	1.11	–1.21
f	CHO	–271.8567892	–271.708543	–426.7236166	0.00	–1.24	–4.09
g	COOH	–347.1368410[b]	–346.981473	–502.0040490[a]	3.40	1.76	–1.68
h	$COOCH_3$	–386.4465450	–386.262065	–541.3136251[a]	6.12[c]	7.08[c]	1.37[c]
i	CN	–250.7702387	–250.632336	–405.6383402[a]	1.27	–0.46	–6.17
j	NH_2	–213.8753558	–213.719802	–368.7426325[a]	–11.80	–14.57	–17.06
k	$N(CH_3)_2$	–292.4961190	–292.282231	–447.3625734	14.94[c]	13.00[c]	11.83[c]
l	NO_2	–363.0738862	–362.931238	–517.9406034[a]	–10.63	–13.48	–14.43
m	OH	–233.7529303	–233.609836	–388.6191210[a]	–22.44	–24.28	–24.86
n	OCH_3	–273.0581820	–272.886170	–427.9244130[a]	–5.40	–8.16	–7.92
o	F	–257.7841274	–257.654041	–412.6494679[a]	–30.24	–33.77	–30.43
p	Cl	–618.1356117	–618.006275	–773.0023372[a]	–13.94	–16.57	–17.77
q	COO^-	–346.5785090	–346.437723	–501.4461049[a]	–0.97	–2.94	–7.07
r	O^-	–233.1437580	–233.016923	–388.0129694[a]	–30.56	–31.79	–40.91
s	NH_3^+	–214.2443760	–214.073958	–369.1160143[a]	–25.40	–29.25	–42.12

[a] Lit.[19] [b] The more stable *sp*-conformation (the carbonyl oxygen synperiplanar with one C atom); the less stable *sc*-conformation (the ether oxygen synperiplanar with one C atom) has E(DFT) –347.1357840 a.u. [c] Obtained with the new calculated DFT energies for the compounds $C_4H_9C(CH_3)_3$ –315.8009561, $C_4H_9COOCH_3$ –386.4479255, $C_4H_9N(CH_3)_2$ –292.5008580 a.u.

unambiguous: the groups NH_2 and $N(CH_3)_2$ are pyramidal, in CHO, $COOCH_3$, NO_2 and CO_2^- the oxygen atom is flanked with one carbon atom. Two conformations were found only with the group COOH (Table I, footnote *b*); population of 25% of the minor conformer is insignificant. The bicyclooctane derivatives **2** possess similar conformations; some of them were mentioned already previously[19].

The difference between the calculated values $\Delta_4 E$ and $\Delta_4 H°(298)$ are negligible. We examined several times the necessity of calculating the zero-point energies and enthalpies with the intention to reach better agreement with experiments[,14]. With aromatic and other rigid molecules, the difference was negligible[11b]; in some cases[32] even ΔE seemed to be more closely related to the experimental values than $\Delta H°(298)$. However, a difference between $\Delta_4 E$ and $\Delta_4 H°(298)$ was observable with aliphatic derivatives[14], although one could not decide which calculated quantity fitted the experiments better.

Another possibility of improving the calculations was searched in the model B3LYP/AUG-cc-pVTZ//B3LYP/6-311+G(d,p). As found previously[14], this model requires calculations at the tight convergence but the results obtained were little different from the simpler model and they did not work better in any correlation.

A weak point of the above experimental test is that it is based on charged substituents that will be almost unexploited in the following correlations. A more general but less accurate test is possible with the enthalpies of formation based mainly on the experimental enthalpies of combustion[16b,17]. It can be carried out only for Eq. (*4*); for Eq. (*5*) there are no data. Even the results with Eq. (*4*) were not convincing. When we compared the calculated reaction energies $\Delta_4 E$ with the pertinent experimental enthalpies[17] $\Delta_4 H°(298)$, the deviation of the substituent t-C_4H_9 was decisive but it was not evident whether it is due to failure of the calculations or to experimental uncertainty. We still examined the enthalpies of formation of some similar sterically crowded hydrocarbons but the data were relatively uncertain, based on very old measurements or even on estimates[33]. A reason for this deviation could be the conformation of compounds **3** that was assumed to be all-*ap* in the model calculations[14] but could differ, particularly in the case of hydrocarbons such as **3c**. Therefore, we proceeded to a better system using as reference the methyl derivatives whose conformation is unambiguous. In our opinion, Eq. (*9*) is the best isodesmic reaction for comparison with the experimental enthalpies of formation and was used only for this purpose. Its merits are that it avoids problems with the conformations and that the pertinent experimental enthalpies are most reliable.

$$CH_3X + t\text{-}C_4H_{10} \rightleftharpoons t\text{-}C_4H_9X + CH_4 \qquad (9)$$

The reaction energies Δ_9E were calculated from the DFT energies of Table I, the pertinent experimental enthalpies were taken from lit.[17]. Test presented in Fig. 1 reveals good correlation with two evident outliers. Note that the experimental errors may be rather great and unpredictable. According to a suggested classification[17], most of the relevant data belong into the category with the average uncertainty ≤10 kJ mol^{-1}. In the light of this classification the fit in Fig. 1 is surprisingly good and the deviation of the substituent OCH_3 could be attributed to a random experimental error. On the other hand, deviation of the point for hydrogen may be systematic since the experimental data for this particular substituent belong into a better category[17] with the uncertainty ≤2 kJ mol^{-1}. Choice of hydrogen as reference substituent agrees with the common view but was several times doubted and discussed[14] due to its exceptional small volume and low polarizability; this effect was sometimes of importance[34], sometimes not[14]. In order to avoid any complications, we excluded hydrogen from the following correlations. This resulted, in most cases, in significant improvement of the fit.

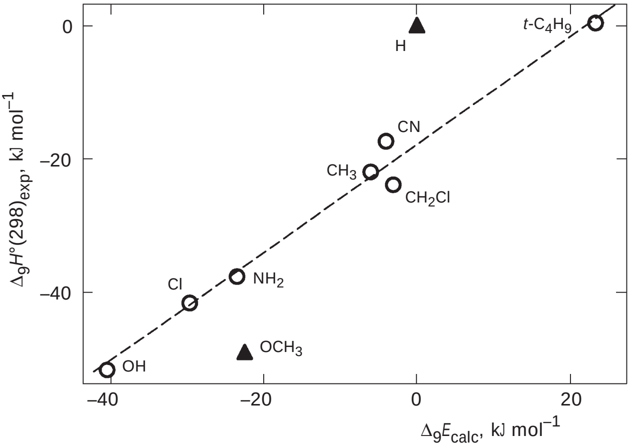


FIG. 1

Comparison of calculations and experiments on the basis of the isodesmic reaction Eq. (*9*): experimental $\Delta_9H°(298)$ plotted vs the calculated Δ_9E(DFT); the regression line and the statistics have been calculated after excluding the deviating points denoted ▲. $b = 0.80(5)$, $R = 0.992$, $s = 2.4$ kJ mol^{-1}

The main defect of Fig. 1 is of course the slope that is significantly different from unity. The substituent effects are systematically overestimated as it was already observed with DFT calculations at the same level[35]. We conclude that our theoretical model is adequate to our main goal, i.e. quantification of substituent effects, but calibration would be necessary to get exact enthalpies of formation.

Substituent Effects

For evaluation of the substituent effect we shall use the butyl derivatives **3** as standard and consider the two series of interaction energies, $\Delta_4 E$ and $\Delta_5 E$ (Eqs (*4*) and (*5*)), as the scales of substituent effects representing interaction with bulky branched alkyls. When investigating the interactions between two polar groups[19], different behavior was observed according to whether the groups were uncharged or at least one charged. Therefore, all our correlations were carried out twice: with all substituents and only with uncharged substituents. The effect of charged groups was merely disturbing: they behaved differently and/or affected the results too much by the effect of distant points. The statistics that follow relate to correlations with uncharged groups excluding hydrogen as explained in the preceding section.

The first result is that $\Delta_4 E$ and $\Delta_5 E$ are closely correlated: regression of $\Delta_5 E$ upon $\Delta_4 E$ yielded $b = 0.93 \pm 0.03$, $R = 0.995$, $s = 1.4$ kJ mol^{-1}. The substituent effects in the larger molecule of **2** are not greater (probably even smaller) than in **1** and only the atoms adjacent to the substituent are responsible for the interaction. On the other hand, the effects in both series seem to be rather complex at first sight. They are stabilizing particularly for strong donors (OH, NH_2, F, Cl) and slightly destabilizing for acceptors (CF_3, COOR but not NO_2); some destabilizing steric effect seems to occur with $N(CH_3)_2$ and t-C_4H_9. We carried out correlations with the well-tried scales of substituent effects: inductive constants[3] σ_I, resonance constants[3] σ_R, σ_R^+ or σ_R^- (or the same constants determined in the gas phase[5]), steric constants[23] υ or directional steric constants[24] B1 to B4, polarizability[25] σ_α, electronegativities[26] $\chi^{(1)}$ of the first atom of the group or electronegativity parameters[25] σ_χ , group electronegativities[27] ι and electronegativity parameters derived from NMR data, either from ^{13}C NMR shifts or from $^3J_{1H,1H}$ coupling constants[28]. This set of possible explanatory variables was still extended by the geometry parameters that could not be previously correlated with any common property: the bond angles[36] $\tau = \angle$C–C–C in **1** and $\alpha = \angle$C6–C1–C2 in benzene derivatives[37]. We have not revealed any significant relation of Δ_4E to any of these parameters (simple linear regression) or to their combination (multiple linear regression using both the descending and ascending method). Particular attention was given – without success – to various steric parameters[23,24] and to the electronegativity of the first atom that was found[14] to be operative in the interaction with the methyl group, Eq. (*10*).

$$CH_3X + n\text{-}C_4H_{10} \rightleftharpoons n\text{-}C_4H_9X + CH_4 \qquad (10)$$

Therefore, we tried a semiquantitative rationalization based on comparison of the two reactions, Eqs (4) and (*10*). In both the substituent is transferred from a smaller alkyl group to a longer or wider group, and the substituent effect is mostly stabilizing. The reaction energies Δ_4E and $\Delta_{10}E$ are compared in Fig. 2. With $\Delta_{10}E$ the interaction is stabilizing for all substituents and depends essentially on the first atom of the substituent; with Δ_4E this picture is preserved for the majority of substituents (denoted by ○ in Fig. 2). The dependence on the first atom is striking when one observes the adjacent position of very different substituents like NH_2 and NO_2 or CH_3 and CN (within the cluster of points in the middle of Fig. 2). We expressed[14] this regularity by the electronegativity[26] of the first atom but the exact definition and physical meaning of electronegativity remains some-

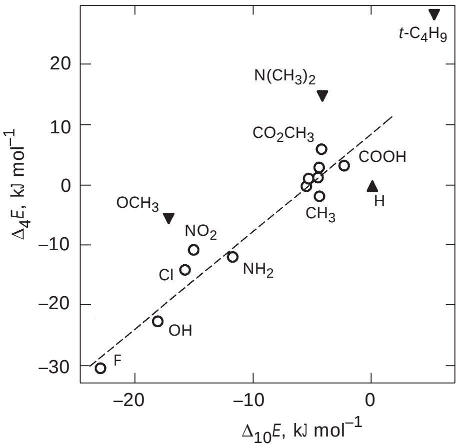


FIG. 2

Comparison of the interaction energies Δ_4E in *t*-butyl derivatives, Eq. (*4*), and $\Delta_{10}E$ in methyl derivative, Eq. (*10*), with reference to *n*-butyl derivatives as standard; ▼ deviating sterically demanding derivatives, ▲ hydrogen substituent; the regression line and the statistics relate to the remaining points denoted ○. $b = 1.63(12)$, $R = 0.974$, $s = 2.7$ kJ mol^{-1}

what obscure[14]. On the other hand, certain substituents evidently deviate from the relationships of Δ_4E and $\Delta_{10}E$ and have a destabilizing effect on Δ_9E. It is natural to ascribe this effect to steric interaction of these groups with *t*-butyl group. Striking is particularly the difference between the sterically demanding substituents $N(CH_3)_2$ or OCH_3 on the one hand and the smaller groups NH_2 or OH on the other. Also the position of the point for hydrogen on the opposite side of the straight line would confirm the idea about steric effects. However, we did not obtain quite satisfactory fit by multiple linear regression with Δ_4E using $\Delta_{10}E$ and any steric constant as the two explanatory variables. The relatively best fit ($R = 0.942$, $s = 5.2$ kJ mol^{-1}) was obtained with the directional steric parameters B4 that represent the largest possible width of the substituent in the direction perpendicular to the X–C bond[24]. We conclude that the interaction of polar groups with a branched hydrocarbon residue is more complex than with a straight chain: In addition to the effect of the first atom of the substituent (stabilizing) it contains still some kind of steric effect (destabilizing); this steric effect is not quite exactly described by known steric constants.

We also tested the relationship of Istomin and Palm[21], Eq. (*6*). When it is applied to the reaction of Eq. (*4*), it yields for $\Delta_4H°$:

$$\Delta_4H°(298) = (\varphi[t\text{-}C_4H_9] - \varphi[n\text{-}C_4H_9])\,\varphi[X] = -0.78\,\varphi[X] \quad (\text{kJ mol}^{-1})\,. \qquad (11)$$

Regression was carried out only with 12 items since the values of φ were not available[38] for all substituents (just the most significant were lacking). No fit was obtained ($R = 0.828$, $s = 8.8$ kJ mol^{-1}); the dependence on φ was evidently curvilinear, exclusion of hydrogen was important. In our opinion, the authors[21] were right only in that point that they discovered a new substituent effect, not related to any known scale. However, Eq. (*6*) in its simple form seems to be invalid.

Enthalpies of Formation of Branched Derivatives

The branched derivatives were always included into the additive scheme for estimating the enthalpies of formation but special contributions for the individual atoms were necessary and/or additional correction terms were added[16]. In this way the additive character was formally retained at the expense of an increasing number of parameters; unfortunately even the number of available data is insufficient and the precision attained was lower than for straight-chain compounds[20]. In our opinion this procedure is not satisfactory mainly due to the small number of degrees of freedom. Special contributions for branched derivatives were often derived from a small number of data and it is not sure whether they would be applicable to other compounds. Out of our set **1a**–**1p**, eight compounds were treated within the framework of the best-elaborated system and comparison with experimental $\Delta_f H°(298)$ was carried out[16b]. For instance the molecule of $(CH_3)_3CCl$ (**1p**) requires a special contribution, denoted $C–(C)_3(Cl)$ for a carbon atom bonded to three C and one Cl, while in the molecule of n-C_4H_9Cl there is a carbon atom $C–(H)_2(C)(Cl)$ bonded to one C, one Cl and two H. In addition, with **1p** three special contributions must be added that are applied whenever a methyl group is bonded to a quaternary carbon atom. While these contributions are applicable more widely, the contribution $C–(C)_3(Cl)$ has bee used only to one additional compound. With *t*-butyl fluoride (**1o**) a special contribution $C–(C)_3(F)$ was introduced only for this single compound; hence the agreement with experiment has no meaning. The same applies to 2-methyl-2-nitropropane (**1l**). Additive calculations made in this way cannot help in elucidating the structural dependence of $\Delta_f H°(298)$ of the branched derivatives. Due to the deficient degrees of freedom we could not actually compare the efficiency of the extended additive scheme with direct quantum chemical calculations but it is sure that at the present state the additive scheme is inferior.

CONCLUSIONS

In our opinion, it is hardly possible to treat the interaction of immediately bonded groups in the same way as the interaction of distant groups has been processed, i.e. in terms of several effects characterized by a scale of constants (e.g. σ). Quantum chemical calculations can yield even in this case valuable data, not accessible by experiments, but interpretation in simple terms may be sometimes only semiquantitative. Interaction of polar groups with a branched hydrocarbon residue is best described like in Fig. 2 as a blend of the stabilizing effect (induction) of the first atom and a destabilizing steric effect operative only with bulky substituents.

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