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STERIC EFFECTS—III[1]

COMPOSITION OF THE E_S' PARAMETER. VARIATION OF ALKYL STERIC EFFECTS WITH SUBSTITUTION. ROLE OF CONFORMATION IN DETERMINING STERICALLY ACTIVE AND INACTIVE SITES

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Abstract—The steric effect of alkyl groups as parameterized by E_S' covers a range of over seven powers of ten. In this article an attempt is made to portray in mechanism terms the manifold nature of the steric effect as a function of substitution, i.e. the composition of the steric effect. One must consider the contribution of the topological carbon sites as a function of the true coordinates of these atoms. To this end, we evaluate the geometry of these alkyl groups in carboxylic acid indirectly by a search for the probable conformations of these acids. The starting point in this study is the determination of the minimum energy conformations in carboxylic acids using the empirical force field method based on analogous alkylmethyl ketone models.

This approach to the ground state behaviour of these acids leads directly to a division of the complete set of alkyl groups into two subsets within which a *conformational sequence or filiation* is associated with the substitution process which generates the successive alkyl groups of that subset. It is shown that eclipsed conformations are preferred in the case of secondary and tertiary groups bearing Et and Me sub-groups, giving way to preferred bisected conformations when t-Bu and i-Pr sub-groups are present. For further elucidation of steric perturbation terms these two subsets must be considered independently. These important observations lead to an overall coherent interpretation of steric effects.

Three regions of distinct behaviour as a function of substitution have been identified. In Region I (the so-called "*normal*" region, where the contribution of the introduction of successive methyl groups to the overall E_S' increases monotonically), besides excellent topological site correlations, an excellent hybrid correlation is proposed. For a conformationally homogeneous (i.e. eclipsed) set of alkyl groups the overall E_S' of groups is well expressed by a linear combination of the weighted contribution of sub-groups and the Newman six-number. This correlation leads to an interpretation of the composition of the overall steric effect of an alkyl group, as measured by the E_S' parameter, in terms of conformationally defined sites and stresses the steric importance of certain privileged sites. This result is consistent with the molecular mechanics viewpoint of preferred conformations but at variance with previous assumptions.

The *levelling effect* (Region II), in the light of conformational information, is understood in terms of *sterically active* and *inactive sites*, while the *inversion effect* (Region III) is considered to be the result of molecular distortion brought about by relief of local internal steric strain within the alkyl groups. The X-ray structure of $i\text{-}Pr_3CCO_2H$ illustrates this point.

The E_S' scale is based on the $\log(K_R/K_{Me})$ values corresponding to acid catalysed esterification of carboxylic acids in methanol.[1a] This reaction has been subjected to careful scrutiny and it is generally accepted that the variation of $\log(K_R/K_{Me})$ with substituent change is steric in origin.[3] In the preceding paper of this series we have carried out a data analysis on the variation of the steric effects of alkyl groups with substitution using an approach based on the previously developed DARC topological system. In addition to the establishment of correlations having predictive value, this analysis brought out the existence of three distinct regions in which the variation of the steric parameter E_S' follows different trends as a function of the degree of substitution: a normal *augmentation* behaviour region extending over *ca.* 6 log units in which the contribution of the introduction of successive Me groups to the overall steric effect increases monotonically (region I, groups with 1 to 7 carbons); a region in which a *levelling* effect is observed, i.e. the contribution diminishes and becomes nil (region II, groups with 8 and 9 carbons) and a region where this contribution changes sign, an *inversion* effect, (region III, groups with 10 carbons). These differing trends have, we feel, different origins and require, therefore, that the data be organised into subsets to be considered independently, as in the preceding article. Our purpose in the present article is to clarify the mechanisms by which steric effects operate in the reaction used to define the parameter E_S'.

The topological treatment of the preceding article makes it clear that a thorough consideration of E_S' variation in a series requires some knowledge of the topography, i.e. three-dimensional arrangement, of alkyl groups in carboxylic acids. Recent work has shown that the concept of the "cone of preferred approach"[4] or, similarly, the distance between a given atom and the line of perpendicular approach to the CO[5] is a significant factor in determining steric effects. For this reason alone it is imperative to have information concerning the geometry of aliphatic carboxylic acids in low energy conformations. Reliable experimental data are, unfortunately, available only in a few isolated cases.[6] Exact X-ray structures have been obtained for only a small number of hindered carboxylic acids, including our own work on $i\text{-}Pr_3CCO_2H$.[5] Recent developments in molecular mechanics approaches appeared particularly promising in this regard.[7] This study of a set of alkyl groups whose steric parameter E'_S covers a range of more than seven powers of ten begins quite logically then with an examination of the minimum energy conformations of carboxylic acids using the molecular mechanics approach.

Minimum energy conformations

In an effort to rationalise, in conformational terms, the behaviour of the steric effects of alkyl groups with increasing substitution we have undertaken a determination of the priviliged conformations of carboxylic acids. To do this we have used Allinger's version of the empirical force field method:[8] This represents only a part of the in-depth study we are currently carrying out on carbonyl containing compounds (aldehydes, ketones, carboxylic acids).[9]

There is some precedent in molecular mechanics approaches for the replacement of OH by Me.[10] In view of our own interest in ketones we decided to choose as a model for the acids, RCOOH, the corresponding methyl ketones, RCOMe. Calculations were carried out using program BIGSTRN (QCPE No. 348) and the Allinger 1971 force field. Since the beginning of this work Allinger has developed force field parameters for carboxylic acids and esters.[11] Results for simple acids are consistent with those found in this work and justify our choice of model. We are, however, undertaking detailed calculations using this newer force field.

In an empirical force field method the total energy is determined as the sum of various additive energy contributions (torsional energy, non-bonded interactions, bond stretching, etc.). These terms are expressed as a function of adjustable parameters determined on the basis of experimental data. The conformational results determined by a given method always depend on the basic parameters used; it is well known that the methods sometimes disagree among themselves and with experiment. Thus, for i-PrCOMe, the most stable conformations determined are: a bisected carbonyl conformation for the PCILO method,[12] a conformation with a C–H bond eclipsing the carbonyl group from the Liquori empirical potential method,[13] and a conformation in which a Me group eclipses the CO for the Allinger force field.

In view of the widespread use and success of the Allinger force field it would seem to be the most appropriate choice for our particular problem. It is satisfying to note that this force field incorporates, among other things, a slight attractive term between alkyl groups and the CO which is in agreement with experiment for slightly hindered compounds.[6]

Recognizing the difficulties related to our choice of model and force field we have concentrated our attention on the analysis of *conformational sequences* within a series rather than a minute examination of the results for a single compound. In the simple case of methyl ketones possessing only α-Me groups it is relatively easy to test all possible eclipsed and bisected conformations. When β-substituents are present, however, the total number of conformations to evaluate becomes too great. In this case the choice of structures to be tested is motivated by the results for less hindered compounds than the particular case considered, as well as by a close examination of molecular models.

As already indicated the various calculation methods (quantum mechanical and empirical force field methods) differ on particular points. They all indicate, however, that the bisection of the CO group is more probable as the group becomes more hindered. The precise determination of the point at which eclipsed structures change over in favor of bisected ones is not easy to determine by reason of the small energy changes involved.

It is difficult, therefore, to use the calculated steric energies quantitatively. However, the conformational tendencies within a series of groups may be reliably estimated (Table 1). We may summarise these tendencies as follows:

(a) For primary groups RCH$_2$– the alkyl substituent R eclipses the CO. The stability difference between the eclipsed and bisected conformations decreases with the increasing steric hindrance of R.

(b) For secondary groups, the smaller members are eclipsed but from six carbons on are bisected. The group i-PrEtCH– will be seen below to behave like an eclipsed conformation and constitutes the changeover point between the eclipsed and bisected set.

(c) For the tertiary groups tested, up to seven carbons inclusive, only the group t-BuMe$_2$C–is not eclipsed. It should be pointed out here that the change in priviliged conformation for the groups t-BuMeCH–, t-BuEtCH–, and t-BuMe$_2$C– is reflected in the topological analysis by the large values of the interactions A_2–B_{13} and A_3–B_{13}.

It is logical that tertiary groups with more than 7 carbons have bisected conformations as these groups result from a formal substitution of secondary alkyl groups whose privileged conformations are bisected ones.

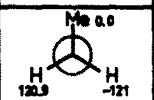
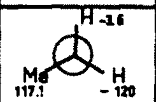
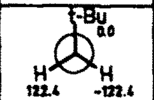
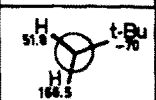
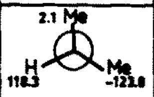
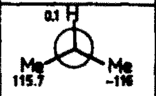
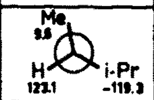
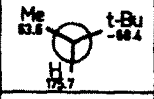
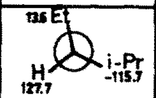
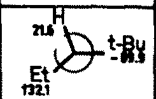
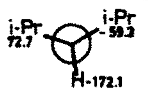
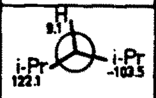
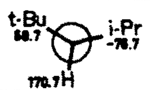
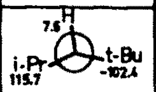
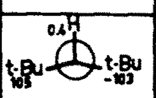
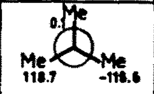
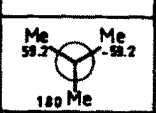
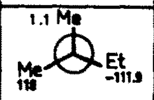
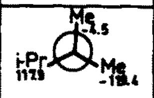
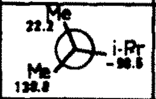
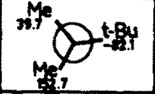
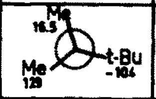
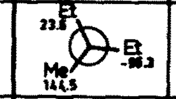
This conformational filiation and its discontinuities are consistent with the spectral data for ketones.[9a] It is also consistent with the X-ray crystal structure of n-Pr$_3$CCO$_2$H which is found to exist in the solid state in an eclipsed conformation.[14] It is evident however that the confidence in the calculations decreases when the molecules are very hindered. A comparison of the molecular dimensions of the acid i-Pr$_3$CCO$_2$H determined by X-ray crystallography[5] shows the bond angles are not correctly estimated and the real bond lengths are much greater than calculated. This cannot result from the fact that a ketone is taken as a model for the acid since the same disagreement is observed in the case of $\alpha,\alpha,\alpha',\alpha'$-tetra-tert-butylacetone.[15]

Augmentation effect

Without considering in detail the contribution of each carbon at each level of substitution (N), it is evident from Fig. 1 that a carbon β to the CO group has a larger contribution to the overall steric effect than a γ carbon. This is true for both bisected and eclipsed conformations. It also holds true in the case of the group, Et$_2$MeC– or $(1^*)(3200)$, whose E'_S value has been calculated using a topological correlation (preceding article). In order to have a more quantitative appreciation of the role of the sub-groups R_1, R_2 and R_3 of the group $R_1R_2R_3C$– we now restrict our attention to a set of conformationally eclipsed groups.

Conformationally homogeneous set. The reaction system used to define the E'_S parameter (esterification) involves attack on the CO of the carboxylic acid from the less hindered side of a low energy conformation. Table 2 lists 13 groups which have been found above to have low lying eclipsed conformations. Our model deals with the steric requirements of this conformationally homogeneous set. These groups all belong to a structural

Table 1. Minimum energy conformations of alkyl groups in carboxylic acids. For each acid the two conformations of minimum energy are given, along with the dihedral angles relative to the carbonyl group

DEL	conformation	steric energy	conformation	steric energy
(1•)(1000)		-1.58		-0.41
(1•)(1111)		-1.95		-1.50
(1•)(2000)		-1.38		-0.17
(1•)(2110)		-0.44		-0.01
(1•)(2111)		0.48		0.57
(1•)(2210)		0.24		0.60
(1•)(2211)		0.68		3.36
(1•)(2220)		0.68		3.06
(1•)(2221)		3.57		5.39
(1•)(2222)		8.78		8.14
(1•)(3000)		-1.16		-0.07
(1•)(3100)		0.59		1.66
(1•)(3110)		1.13		1.21
(1•)(3111)		3.28		4.38
(1•)(3200)		1.25		1.40
(1•)(3300)		3.27		4.32

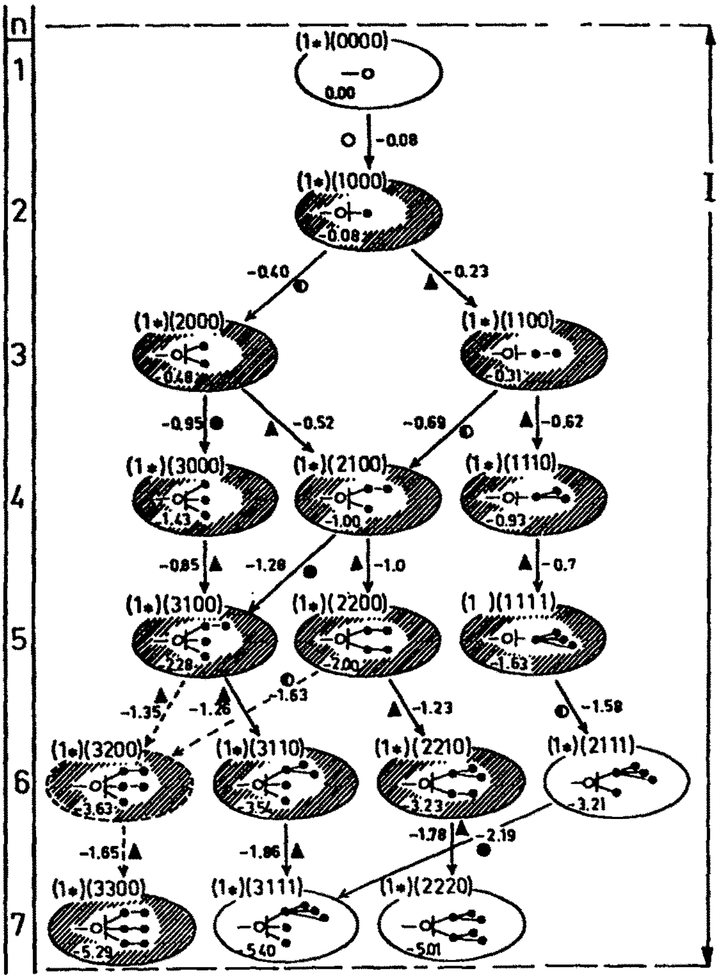


Fig. 1. Eclipsed and bisected conformations of region I (augmentation effect). Shaded figures represent minimum energy eclipsed conformations; non-shaded figures, bisected conformations. In each oval are given (from top to bottom) the topological descriptor of the group, its structure, and the corresponding E'_S value. Along with each arrow, representing the change of level of substitution (n), we have the differences between the E'_S values of the groups involved and a symbol representing the nature of the change: ○ = $-CH_3 \rightarrow -CH_2R$; ◐ = $-CH_2R \rightarrow -CHRR'$; ● = $-CHRR' \rightarrow -CRR'R''$; and ▲ $-C\langle -CH \rightarrow -C\langle -CR$. The E'_S value of the group Et_2 MeC– was estimated in the preceding article using a topological correlation. Note that a carbon β to the carbonyl group has a larger contribution to the overall steric effect than a γ carbon for both eclipsed and bisected conformations.

region in which there is a monotonic increase in the contribution of successive Me groups to the overall steric effect.[1b]

The corresponding E'_S values span a range of more than five powers of ten. Figure 2 represents a 3-dimensional conformational model, where:

$$|E'_S(R_1)| \leq |E'_S(R_2)|$$

The sub-group R_3 is, however, not necessarily the most hindered. This is the case for primary, but not secondary and tertiary groups.

Within the framework of this 3-dimensional model we have attempted to determine the contributions of sub-groups (R) to the overall steric effect E'_S of group $R_1R_2R_3C-$ making use of equations involving linear combinations of the E'_S values of these sub-groups.

Correlation in terms of the steric effect of sub-groups and six-number. In the first model to be tested we have considered the effect of the group $R_1R_2R_3C-$ as the result of the superposition of the three groups R_iCH_2-. This

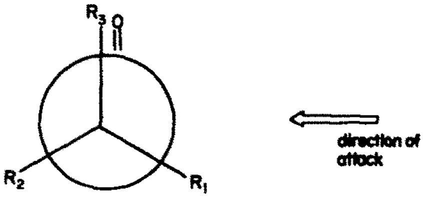


Fig. 2. Eclipsed conformations used in correlations (Tables 1 and 2). For secondary and tertiary groups $|E'_S(R_1)| \leq |E'_S(R_2)| \geq |E'_S(R_3)|$. For primary groups RCH_2-, the group R corresponds to R_3.

Table 2. Steric parameters of alkyl groups having eclipsed conformations

Group	Overall Steric Parameters of Groups E'_s	Ordering of Sub-Groups [a]			E'_s Parameter of Sub-Groups R_iCH_2-			E'_s Parameter of Sub-Groups R_i			Six-number Parameter of Sub-Group R_i		
		R_1	R_2	R_3	$E'_s(1)$	$E'_s(2)$	$E'_s(3)$	$E'_s(1)$	$E'_s(2)$	$E'_s(3)$	$\Delta 6_1$	$\Delta 6_2$	$\Delta 6_3$
CH_3-	0.0	H	H	H	0.00	0.00	0.00	1.12	1.12	1.12	0	0	0
$MeCH_2$-	−0.08	H	H	Me	0.00	0.00	−0.08	1.12	1.12	0.00	0	0	0
$EtCH_2$-	−0.31	H	H	Et	0.00	0.00	−0.31	1.12	1.12	−0.08	0	0	0
i-$PrCH_2$-	−0.93	H	H	i-Pr	0.00	0.00	−0.93	1.12	1.12	−0.48	0	0	6
t-$BuCH_2$-	−1.63	H	H	t-Bu	0.00	0.00	−1.63	1.12	1.12	−1.43	0	0	9
Me_2CH-	−0.48	H	Me	Me	0.00	−0.08	−0.08	1.12	0.00	0.00	0	0	0
EtMeCH-	−1.00	H	Et	Me	0.00	−0.31	−0.08	1.12	−0.08	0.00	0	3	0
Et_2CH-	−2.00	H	Et	Et	0.00	−0.31	−0.31	1.12	−0.08	−0.08	0	3	3
i-PrEtCH-	−3.23	H	i-Pr	Et	0.00	−0.93	−0.31	1.12	−0.48	−0.08	0	6	3
Me_3C-	−1.43	Me	Me	Me	−0.08	−0.08	−0.08	0.00	0.00	0.00	0	0	0
$EtMe_2C$-	−2.28	Me	Et	Me	−0.08	−0.31	−0.08	0.00	−0.08	0.00	0	3	0
i-$PrMe_2C$-	−3.54	Me	i-Pr	Me	−0.08	−0.93	−0.08	0.00	−0.48	0.00	0	6	0
Et_3C-	−5.29	Et	Et	Et	−0.31	−0.31	−0.31	−0.08	−0.08	−0.08	3	3	3

[a] The Sub-Groups R_1, R_2 and R_3 correspond to the minimum energy conformations determined above (Fig.2).

model, expressed by eqn (1), leads to a satisfactory correlation (Table 3).

$$E'_s(R_1R_2R_3C-) = \sum_i a_i E'_s(R_iCH_2-) + a_0 \qquad (1)$$

The values of the coefficients a_i are related to the spatial orientation of the sub-groups (Fig. 2). In this approach the atoms of the sub-groups R_iCH_2- are in the same topological situation as the atoms of the overall group $R_1R_2R_3C$-.

The steric importance of the number of atoms in position 6 relative to the CO oxygen taken as 1, i.e. the six-number, has been pointed out qualitatively by Newman.[16] The quantitative importance of the "change in six-number" as a significant parameter in the correlation of the rates of alkaline hydrolysis of alkyl acetates has been shown by Hancock.[17] In this study it is particularly interesting to determine the importance of the six-number effect by correlation since the molecular mechanics method does not provide us with a means of separating such an effect from others which may be operating. A correlation of the E'_s values of primary groups RCH_2- where R = Me, Et, i-Pr, and t-Bu as a function of E'_s of R and the six-number (eqn 2), furnishes an indication of the reality of the six-number effect.

$$E'_s(RCH_2-) = aE'_s(R) + b\Delta 6 + a_0. \qquad (2)$$

This result is confirmed by the excellent correlation

Table 3. Correlation of overall steric effects by additive contributions of sub-groups. Eclipsed set (Table 2)

Corr. Eq.	Parameters	a_0	a_1	b_1	a_2	b_2	a_3	b_3	r	ψ
1	$E'_s(RCH_2)$	−0.134	12.59	-	2.89	-	0.96	-	0.988	0.187
2	$E'_s(R)$ & $\Delta 6$	−0.053	0.51	−0.095	-	-	-	-	0.997	0.160
3	$E'_s(R)$ & $\Delta 6$	−1.39	0.91	−0.75	0.46	−0.31	−0.10	−0.21	0.996	0.139
4	$E'_s(R)$	−2.96	1.24	-	1.10	-	0.786	-	0.800	0.723
5	$E'^c_s(R)$	−2.25	6.88	-	2.37	-	0.707	-	0.991	0.159
6	$E'_s(R)$ & Δn	−1.40	6.74	−2.23	2.15	−0.612	0.653	−0.278	0.995	0.149
7	$E'^c_s(R)$ & Δn	−2.32	7.10	−2.27	2.34	−0.578	0.779	−0.221	0.995	0.143

Correlations 6 and 7 compare $E'_s(R_1R_2R_3C)$ and $E'^c_s(R_1R_2R_3C)$ in the same way, i.e. in terms of the same 6 parameters, $E'_s(R_i)$ and Δn_i. It is seen that the derived parameter E'^c_s offers no advantage over the simpler E'_s, in this context.

obtained from eqn (3) for the complete set of groups in Table 2.

$$E'_S(R_1R_2R_3C-) = \sum_i (a_iE'_S(R_i) + b_i\Delta 6_i) + a_0. \qquad (3)$$

While the correlations based on eqns (1) and (3) are excellent, eqn (3) provides a more detailed analysis of the contributions of sub-groups and privileged topological sites (the six-number) to the overall steric effect. Equation (1) contains the six-number contribution *implicitly* within the E'_S values of the group R_iCH_2–. In eqn (3), which makes use of a different model, these contributions are absent from the $E'_S(R_i)$ terms and are included *explicitly* as Δ terms, with a concomitant increase in precision.

Correlations 1 and 3 then furnish a rather plausible account of the composition of the revised Taft steric parameter, E'_S, namely: (a) a conformational effect determined by the relative positions of the sub-groups with respect to the CO group; (b) non-identical contributions from the three groups R_1, R_2 and R_3; and (c) a six-number effect, proportional to the number of atoms in position 6 relative to the CO oxygen.[18]

For our set of conformationally similar (i.e. eclipsed) groups we have obtained a straightforward interpretation of the Taft E'_S scale in terms of known steric effects. Even the well-known "telescopic effect"[19] of the steric constants of the groups Me, Et, i-Pr and t-Bu is explained by a simple conformational effect. The three-dimensional model proposed in this note leads to very satisfying results concerning the contribution of sub-groups and the six-number to steric effects because it involves a conformationally homogeneous set of groups. The choice of this set was made possible by the molecular mechanics method. It is the complementary nature of the two approaches which allows a detailed picture of the nature of steric effects.

Previous attempts, by Fujita *et al.*,[20] at the correlation of overall steric effects of alkyl groups as the weighted sum of individual contributions are of interest here, particularly since the conformational assumptions used and the conclusions reached are different from the present work. In the absence of information to the contrary, the groups in Fig. 2 were taken in order of increasing steric hindrance, i.e. $|E_S(R_1)| \le |E_S(R_2)| \le |E_S(R_3)|$. Finding this assumption insufficient to account for the available data they proposed an additional assumption in which interactions between R_2 and R_3 have for effect the orientation of R_3 towards the incoming reactant, necessitating an "exalted" steric contribution of the group R_3 in certain cases. The present work, in which the empirical force field method permits a more rational choice of conformation, suggests that the exaltation effect is an artifact.

The non-viability of "Hyperconjugation-Corrected" steric parameters. Another conclusion reached by Fujita *et al.*, with which we are at odds, concerns the status of the "hyperconjugation-corrected" parameters.[21] They suggest that the corrected Hancock parameters are superior to the original Taft constants as a scale of steric effects basing their conclusion on the fact that the correlation (eqn 4) in terms of E'_S is less significant than the correlation (eqn 5) in terms of E'^c_S.

$$E'_S(R_1R_2R_3C-) = \sum a_iE'_S(R_i) + a_0 \qquad (4)$$

$$E'^c_S(R_1R_2R_3C-) = \sum a_iE'^c_S(R_i) + a_0. \qquad (5)$$

Statistically specking, however, it is not valid to compare the correlations in terms of E'^c_S and E'_S since the former contains three additional parameters "hidden" within the E'^c_S values, i.e. the $0.306\ (n_H - 3)$ terms. The correct way to compare E'_S and E'^c_S is to consider correlations with 6 rather than 3 parameters, as follows:

$$E'_S(R_1R_2R_3C-) = \sum (a_iE'_S(R_i) + b_i\Delta n_i) + a_0 \qquad (6)$$

and

$$E'^c_S(R_1R_2R_3C-) = \sum (a_iE'_S(R_i) + b_i\Delta n_i) + a_0 \qquad (7)$$

where:

$$\Delta n_i = n_{i,H} - 3$$

The correlations based on eqns (6) and (7) are excellent and entirely equivalent, indicating that, from this point of view, there is no reason to suppose that the derived E'^c_S scale is superior to the simpler E'_S. Equations (6) and (3) are seen to be similar since the Δn terms in (6) are proportional to the $\Delta 6$ terms in (3) for alkyl sub-groups. In our opinion the Δn term in eqn (6) is not associated with hyperconjugation; it represents rather the contribution from the six-number.

Hancock's observation[17] concerning the contribution of the six-number to E_S supports our analysis of the E'_S values of 13 selected alkyl groups. This finding, as well as the detailed dependence on conformation, argues against the generalized use of the van der Waals radius relative to hydrogen ($\nu = r_X - r_H$) as a steric parameter.[22] Moreover, for groups which have a non-zero six-number (i.e. the term Δn of eqn (2) is non-zero) ν cannot really correspond to an actual distance and represents an oversimplified view of steric effects.

The levelling effect

Sterically active and inactive sites. We have seen above how the progression of steric effects for groups having stable eclipsed conformations (region I) may be predicted on the basis of molecular mechanics calculations. A simple explanation of the levelling effect (region II) may be obtained from the same source. In this context we distinguish between those sites which contribute to the overall steric effect and those which do not, termed sterically "active" and "inactive" sites respectively. In region I the contribution to the introduction of successive Me groups increases monotonically. All of the sites contained within region I are therefore considered to be sterically "active". In contrast to this, region II (the levelling effect) contains sites which contribute significantly to the overall steric effect and others whose contribution is small or nil, i.e. the sites in region II are either sterically active or inactive (Fig. 3).

In region II the contribution of a β carbon is greater than that of a γ carbon, as has been observed above for region I. An important feature which distinguishes region II from I is the predominance of bisected conformations in the former. For example, all the groups derived from the group i-Pr_2CH– by successive substitutions have bisected conformations. The rationale behind the exis-

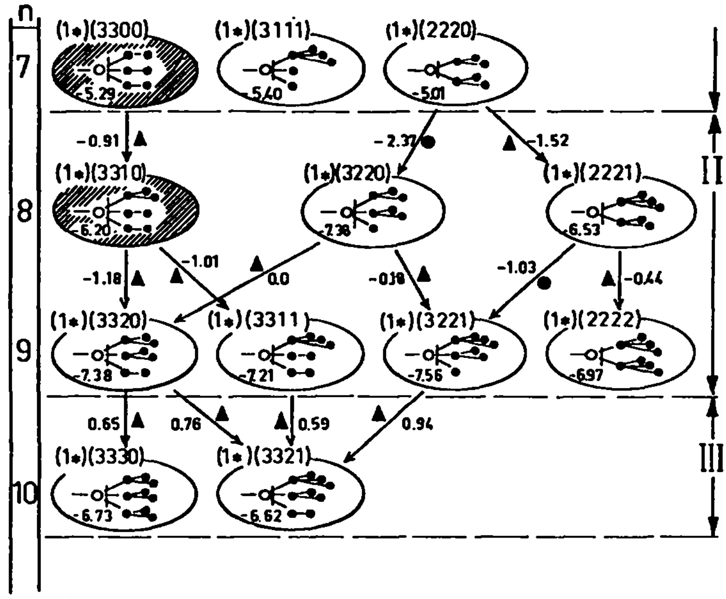


Fig. 3. Eclipsed and bisected conformations of regions II (levelling effect) and III (inversion effect). The symbols have the same meaning as for Fig. 1.

tence of active and inactive sites may be obtained from conformational data derived using the molecular mechanics method. It is found quite simply that active sites are directed towards the CO group and inactive sites are directed away. The fact that certain sites are sterically inactive is surely related to restricted internal rotations of sub-groups with increasing substitution, otherwise averaging of contributions would result. One clear example of the levelling effect is the progression i-Pr$_2$CH- (1*)(2220), t-BuPr^{i}CH- (1*)(2221), t-Bu$_2$CH- (1*)(2222), for which the more stable conformations are given in Fig. 4(a). In the case of the group i-Pr$_2$CH- one of the sides is substantially more open than the other due to the occupation of an active site by hydrogen. The formal transformation of i-Pr$_2$CH- to t-BuPr^{i}CH- results in replacement of this H by a Me group and, hence, a large increase in the steric effect ($\Delta = -1.52$). The formal transformation of t-BuPr^{i}CH- to t-Bu$_2$CH- involves, however, the replacement of an "inactive" H by a Me group, and the increase in steric effect is slight ($\Delta = -0.44$).

Another series in which there is an even more marked levelling effect is the following: (Fig. 4b) i-Pr$_2$CH- (1*)(2220), i-Pr$_2$MeC- (1*)(3220), i-Pr$_2$EtC- (1*)(3320). Here

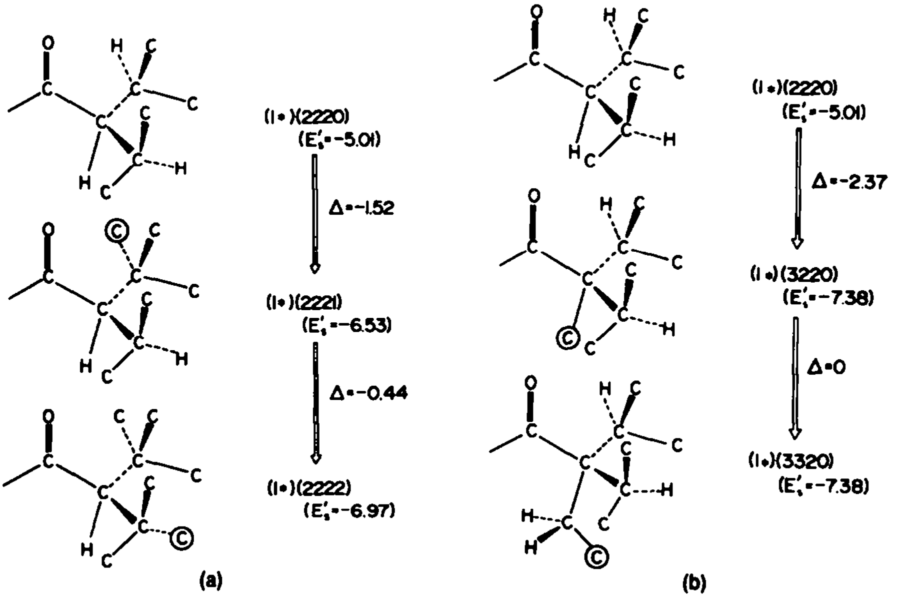


Fig. 4. Sterically "active" and "inactive" sites. In each series:

a. i-Pr$_2$CH-→t-BuPr^{i}CH-→t-Bu$_2$CH-
b. i-Pr$_2$CH→i-Pr$_2$MeC-→i-Pr$_2$EtC-

the first replacement of H by C corresponds to the occupation of an active site (large effect) while the second corresponds to the occupation of a sterically inactive site (small or negligible effect).

we see that the transformation i-Pr_2CH– to i-Pr_2MeC– involves a substitution at the α-carbon which, in general, involves a large increase in the steric effect; here $\Delta = -2.37$. The transformation i-Pr_2MeC– to i-Pr_2EtC– brings about the formal substitution of an inactive H by Me and produces no change whatsoever.

Thus we see that the molecular mechanics method is a valuable tool for rationalizing the progression of steric effects. The technique must be used with caution, however, as the steric limits of the method are relatively unknown. The fact that there is consistency between the E'_S values and the molecular mechanics method would appear to justify its use in this qualitative fashion.

Inversion effect—molecular distortion

The two cases of "inversion" involved in this work (region III), i-Pr_3C– (1*)(3330) and t-BuPr^{i}EtC– (1*) (3321), involve extremely congested groups to which the generalities discussed above are probably not applicable. This effect is illustrated in Fig. 3. The inversion effect constitutes a rather intriguing problem since it represents a rather substantial and unexpected rate enhancement with increasing substitution. In view of this and some recent interest[23] in the biological properties of tri-isopropyl-acetic acid (TIPA) we decided to investigate the molecular structure of this compound.[5]

Figure 5 illustrates the structure obtained for TIPA by X-ray crystallography. The acid is, of course, a dimer in the solid state. It is immediately evident that the molecule has a highly distorted structure: the angle $C_1C_2C_3$ (104.0°) is considerably compressed and the bonds C_2C_3, C_2C_4 and C_2C_5 elongated. Mutual repulsions among the three i-Pr groups produce an umbrella-like opening of the molecule. The disposition of these i-Pr groups is not symmetrical with respect to the OCO plane. One group lies above the plane with its Me's directed away from the back-side of the molecule; the two others are directed below the OCO plane each with its pair of Me groups towards the back-side of the molecule. The angle between these groups is 115.2° and may be compared to the value of 118° between the geminal t-Bu groups in *α,α,α′*, *α′*-tetra-tert-butylacetone.[15,24]

In spite of the opening of the $C_4C_2C_5$ angle the molecule is seen to be highly strained when one considers that the pairs of Me groups 9 and 11, and 8 and 10 possess pairs of hydrogens whose non-bonded distances are 2.21 and 2.12 Å, shorter than twice the van der Waals radius for hydrogen (2.4 Å).

The fact that molecular distortion does occur with increasing substitution is, of course, not unexpected. What is surprising is that the steric effect is diminished, i.e. there is a definite increase in reactivity. The question that comes to mind at once is whether or not one can specify the relationship between this distortion and the diminution of the steric effect.

Comparison of two X-ray structures. This question can be answered by comparing the structures of TIPA and tri-n-propylacetic acid (TNPA).[14] The latter structure has bond distances and angles that are not unusual and may be used as a reference point. The group n-Pr_3C– has, moreover, a steric effect similar to that of the group Et_3C– which has been shown to be highly predictable.[16] The atoms which play a predominant role in the determination of the steric effect are those in the γ position.[18] In the case of acid TIPA there are six Me groups in this position.

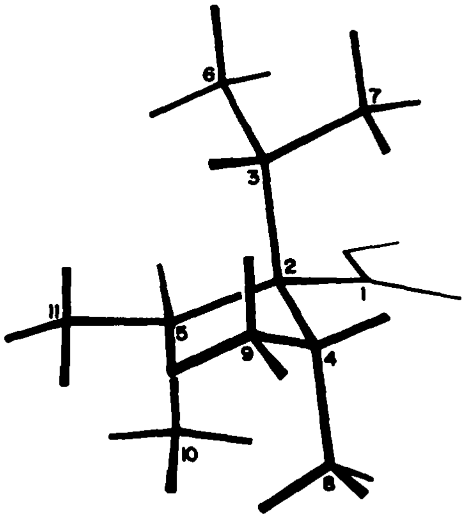


Fig. 5. X-ray structure of *tri-iso*-propylacetic acid (TIPA). Bond angles: $<1,2,3 = 104.0°$; $<1,2,4 = 108.2°$; $<1,2,5 = 108.2°$; $<3,2,4 = 110.4°$; $<3,2,5 = 110.2°$; $<4,2,5 = 115.2°$. Bond lengths: 1,2 = 1.537 Å; 2,3 = 1.630 Å; 2,4 = 1.596 Å; 2,5 = 1.586 Å. It is seen that the methyls (6 and 7) attached to carbon 3 are directed towards the carbonyl group while those attached to carbons 4 (8 and 9) and 5 (10 and 11) are directed away. Interactions between the i-Pr group above the OCO plane and those below the plane are minimised by a gear effect.[6] The two i-Pr groups below the plane are seen to interact strongly with one another (carbon 9 and 11, and 8 and 10) resulting in a highly strained molecule. (The diagram was obtained using the Evans and Sutherland "Picture System").

The acid TNPA has three methylene groups in the γ position. One of these must have but slight influence on the steric effect since it lies in the plane defined by the atoms OCO. Two others, whose effect we will see to be important, lie above and below the OCO plane. The terminal methyls are folded away from the CO, so their contribution to the overall steric effect is negligible.

Wipke has shown that the steric congestion about a CO group can be described by an empirical function related to the "cone of preferred approach" defined about a line perpendicular to the CO group.[4] His analysis deals with rigid cyclic ketones whose structures are calculated by the molecular mechanics method. In the present case, the carboxylic acid structures at our disposal correspond to the solid phase. If the assumption that there is some similarity between the structure in the solid and liquid phase is made, we may use this information to gain some insight into the steric environments of the CO groups in the two cases of interest. Indeed it seems probable that this compound exists in a locked conformation in the liquid phase in view of the gear[25] or cogwheel effects exhibited in Fig. 5.

The relevant datum in the context is the distance d between an atom and the line passing through the CO carbon, perpendicular to the OCO plane (Fig. 6). It is this distance which has a direct influence on the steric effect, since it reflects the ability of an atom to hinder the approach of reactant along the most favourable direction of attack. It is directly related to the "cone of preferred approach".[4]

In the structure of TNPA two methylene groups in the γ position are sterically "interesting". The distance d for these two methylenes, located above and below the OCO plane are 1.47 and 1.80 Å respectively. When one con-

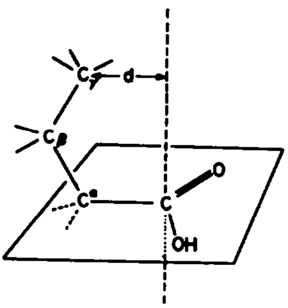


Fig. 6. Important factor determining overall steric effect: distance d between an atom and the line of perpendicular approach to the carbonyl.

siders the value of 2.2 Å for the van der Waals radius along the C–H bond, it is evident that these methylene groups have an important contribution to the steric effect. In the case of TIPA there are six Me groups in the γ position. Two of these (6 and 7) are located above the OCO plane with distances 2.24 and 1.47 Å respectively, from the perpendicular (Table 4). Two others (9 and 11) lie very close to the OCO plane and are relatively distant from the perpendicular (3.86 and 3.94). Below the OCO plane, the two remaining Me's (8 and 10) have distances 2.04 and 2.62 Å. This comparison of the molecular structures of TNPA and TIPA reveals that while the former has both directions of approach to the CO hindered, the latter has one direction very hindered, the other being more accessible than anticipated.

Comparison of an X-ray and a model structure. Another way of explaining the unusual reactivity of TIPA in esterification is to compare the real X-ray structure with an idealized one using standard bond lengths and angles. To do this we have fixed all C_{sp3}–C_{sp3} bond lengths at 1.54 Å, with appropriate angles at 109°28′. The dimensions of the CO group are taken from the TNPA structure. The dihedral angles are those determined by the TIPA structure. A comparison of the distance d between the carbons 6, 7, 8, 9, 10 and 11 and the perpendicular in the real and idealized structure (Table 4) may now be made.

Let us first consider the model structure from which the effects of molecular distortion have been eliminated. Here one of the i-Pr groups is located above the OCO plane. This group has two carbons in the γ position (6 and 7) whose distances from the perpendicular are 2.32 and 1.61 Å respectively.

This side of the molecule is thus rather hindered and we may enquire what geometrical modifications occur on passing to the real X-ray structure: it is seen that these carbons are even closer to the perpendicular line so that this side of the molecule is even more congested than in the model structure. The two remaining i-Pr groups are directed below the OCO plane. In the model structure we see that this side of the molecule is significantly less congested than the upper side. On passing from the model to the real structure the relevant distances from the perpendicular are, in contrast to the upper side of the molecule, increased by significant amounts. It is therefore apparent that the direct result of molecular distortion, in the present case, is a net increase in congestion on one side of the molecule concominant with a net decrease on the other side. The anomalous steric effect of the group $i\text{-}Pr_3C$– is thereby elucidated.

The above observations bring out a rather interesting point: the fact that the more highly substituted side of the molecule is the least congested. This is contrary to expectation and the result of the conformation imposed by steric constraints.

Ultimately, the factor which determines the overall steric effect (E_S') is the free energy difference between the transition and initial states. Among the elements that make a significant contribution to this free energy is the accessibility of the reaction site as defined by molecular geometry.[4] Here, conformation and distortion (or the lack of it) are often crucial.

Overview

In this article we have seen how the molecular mechanics method may be used to gain *qualitative* information about minimum energy conformations of alkyl groups in carboxylic acids. This information is put to use in quantitative correlations which allow some interesting conclusions concerning the composition of the overall steric effect of groups, as measured by the E_S' parameter.

One noteworthy observation on the complete set of E_S' values for alkyl groups is that the intuitive association of increasing degree of substitution with increasing steric effect is not always valid. This is evident in the region

Table 4. Comparison of the X-ray structure of *tri-iso*-propylacetic acid (TIPA) with a model structure

		X-Ray (Å)	Standard Model (Å)
Upper side of carboxyl group	d_6	2.24	2.32
	d_7	1.47	1.61
Lower side of carboxyl group	d_8	2.62	2.40
	d_9	3.94†	3.83†
	d_{10}	2.03	1.82
	d_{11}	3.86†	3.78†

Here d_n is defined as the distance between a given carbon atom and a line perpendicular to the OCO plane passing through the carbonyl carbon (Fig.2). (The relevant data for TNPA are 1.47 and 1.80 Å).

† These atoms contribute but slightly to the steric effect as they lie in the OCO plane.

where the levelling effect holds and is even more strikingly portrayed by the inversion effect. In the case of the acid i-Pr_3CCO_2H extensive molecular distortion, produced by the high degree of substitution, results in the group i-Pr_3C– having a more positive E'_s value than the group i-Pr_2EtC–.

The preceding article uses a topological approach directed principally towards the *prediction* of steric effects. The present one uses a variety of complementary approaches whose aim is the *interpretation* of steric effects. None of the approaches used is sufficiently powerful to give, by itself, a comprehensive picture of steric effects. It is concordance of results which gives a coherent general picture. The quantitative use of the molecular mechanics method for moderate to extremely hindered groups, both in terms of ground states and appropriately chosen transition state models, must wait until suitably parametrized force fields become available. These force fields must be adapted to the particular problem of carboxylic acids and congested environments, necessitating structural determinations by X-ray crystallography. The various approaches delineated in the previous article, as well as the present one, constitute a valuable predictable and interpretative probe for steric effects.

It is hoped that our results and views on highly substituted and congested compounds will stimulate further progress towards the comprehension of steric effects, an old and intuitive concept about which the last word has yet to be said.

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