Steric Interplay between Alkyl Groups Bonded to Planar Frameworks

Ulf Berg,[†] Tommy Liljefors,[†] Christian Roussel,[‡] and Jan Sandström*[†]

*Division of Organic Chemistry 3, Chemical Center, University of Lund, S-221 00 Lund, Sweden, and IPSOI (lab. CNRS 126),
Centre Universitaire St. Jérôme, F-13013 Marseille, France*

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Nonbonded interactions play an important role in determinng the three-dimensional structure and reactivity of organic molecules. The interaction energy, positive or negative, is usually interpreted in terms of repulsion between electron clouds as a result of the Pauli principle (van der Waals repulsion), London dispersion forces, Coulombic interactions, and delocalization of electrons due to through-space or through-bond interactions between atomic orbitals.

Particular interest exists in interactions between alkyl groups, for which van der Waals and London forces probably play the major role. We find that each type of alkyl group (primary, secondary, or tertiary) shows fairly constant conformational behavior, even after some modification, and therefore believe that detailed conformational studies of systems containing mobile alkyl groups are of general interest in providing a basis for predictions of conformations and reactivities in new systems.

This Account focuses on the conformational consequences of interactions between two or more alkyl groups bonded to a planar framework. The alkyl groups may be geminal, as in N,N-dialkylamides and analogues and in 1,1-dialkylethylenes, or vicinal or bonded to more distant atoms. The emphasis is on shapes of molecules in their energy minima, on the heights of barriers separating them, and on the low-energy pathways between the minima. The detailed picture which emerges is the result of a fruitful interaction between experiment and theory.

Variable-temperature NMR spectroscopy (DNMR)[1] is the method of choice for studies of conformational interconversions with free energy barriers in the range of 5–25 kcal/mol. The steric interplay between geminal or vicinal primary or secondary alkyl groups attached to a sp²-hybridized framework frequently gives rise to barriers which fall in the lower half of this range. At low temperatures, two or in some cases three conformers

of the same molecule are detected. This allows their populations to be determined by direct integration or by computer simulation of spectra. In cases where more than two conformers are observed, careful bandshape analysis of spectra at different temperatures provides evidence for preferred conformational interconversion pathways.

Most discussions of energy barriers employ the free energy of activation $(\Delta G^{\ddagger})$, the energy quantity obtainable by DNMR that is least sensitive to systematic errors. $\Delta G^{\ddagger}$ may generally be determined to within 0.1 kcal/mol. The temperature dependence of the rate constants allows the evaluation of the enthalpy and entropy components, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, in principle the most informative parameters. Although accurate determinations of these quantities are possible in favorable cases, the systematic errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are often too large to permit their use in precise discussions. For energy barriers lower than 3 kcal/mol, the J method of Parr and Schaefer[2] may be applicable. It is presently restricted to benzene derivatives with alkyl substituents and requires the accurate determination of long-range coupling constants over six bonds.

Theoretical calculations can also be of considerable value. They have been used to aid the assignment of NMR signals to specific conformers and indicate possible pathways for conformational interconversion. The size of the molecules of interest and the need to extensively explore conformational space and to use full geometry relaxation in the calculations on sterically crowded conformers and transition states preclude the use of the costly quantum chemical methods. Instead molecular mechanics (empirical force field) has proved a valuable tool in these studies. In this method the steric energy is expressed as a sum of energy contributions:

$$E_{\text{steric}} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{vdW}} + E_{\text{dipole}} + \text{cross terms}$$

The energy contributions are calculated with empirically parameterized potential functions, and the total steric energy is found by energy minimization with respect to all internal degrees of freedom. The potential function for nonbonded (van der Waals) interactions includes an attractive part (due to London dispersion forces) as well as a repulsive part. As pointed out below, it is of great importance to take the attractive dispersion forces into account when discussing interactions between large alkyl groups. Two comprehensive reviews

Ulf Berg was born in 1943. After obtaining his doctoral degree in Lund in 1974, he spent a postgraduate year with J. Metzger at Universite Aix-Marseille. Since 1981 he has been Docent of Organic Chemistry at the Chemical Center in Lund. His research focuses on conformational analysis of organic molecules by NMR and by computational methods.

Tommy Liljefors, born in 1941, obtained his doctoral degree in Lund in 1973 and was a postdoctoral student of N. L. Allinger in Athens, Georgia. He was appointed Docent of Organic Chemistry at the Chemical Center in Lund in 1978. His current research involves conformational analysis, structure-activity relationships, and force-field calculations.

Christian Roussel was born in 1946, obtained his doctoral degree in Marseille in 1973, and has been Professor of Applied Organic Chemistry at Universite Aix-Marseille since 1982. He has been visiting scientist at the Chemical Center in Lund on numerous occasions. His research interests include conformational analysis, synthesis of heterocyclic compounds, and industrial synthesis.

Jan Sandström was born in 1925, obtained his doctoral degree in Lund in 1956, and since 1971 has been Professor of Organic Chemistry at the Chemical Center in Lund. His primary research interest is conformational analysis of organic compounds.

[†] University of Lund.
[‡] Centre Universitaire St. Jérôme.
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of molecular mechanics are available.[3]

An important feature of the method is that it is possible to locate all stable conformers by variation of the input structure. Molecular mechanics calculations are particularly valuable in studies of conformational interconversion pathways, their energy barriers, and transition-state geometries. Although methods are available for "direct" calculation of transition states, the most common starts at an energy minimum and moves the molecule along the minimum energy pathway across the saddle point by "driving" or stepwise incrementing one or more torsional angles. This method has some serious pitfalls, and a safer but more expensive procedure calculates a complete conformational map, i.e., forms a grid of fixed values for the relevant torsional angles and calculates the corresponding energies.

In terms of general shape, substituents can be divided into three main classes: (i) substituents with local C_∞ axes, such as halogens, cyano groups, etc.; (ii) planar substituents, such as aromatic rings, the formyl group, and others, and (iii) polyhedral substituents such as alkyl groups. When two or more alkyl groups approach each other, their polyhedral shapes lead to more varied interactions than with cylindrical or planar groups. They are sterically anisotropic, and, depending on their preferred orientations, they may transmit conformational information from alkyl group to alkyl group along the periphery of a π system and cause induced transformations far from the inducing center. This may lead to long-range conformational control of reactivity and selectivity and is a manifestation of what we have defined as *the gear effect*.[4] With this term we defined "a conformational transmission caused by interaction between polyhedral substituents, and dependent upon their polyhedral shape". Mislow et al.[5] have proposed a narrower definition and one which is in closer agreement with a mechanical analogue. These authors propose the term *static gear effect* for the meshing of alkyl groups in the ground state, and *dynamic gear effect* for special effects on the rate or mechanism of a process, attributable to intermeshing of a chemical rotor with a neighboring group. It is unfortunate that two different definitions of the gear effect have been proposed. Although our definition has the advantage of being applicable to the majority of alkyl group interactions, a disadvantage is that the name leads the reader to expect true intermeshing states or processes.

In several studies, where methyl groups appear "smaller" than expected, the authors invoke "cogwheeling" or "gearing", but in a thorough study Mislow et al.[5] interpret the observed discrepancies in other terms. In a similar way, simultaneous conformational changes of neighboring alkyl groups have been interpreted as coupled disrotatory processes,[6] but as will be shown in this Account, the cogwheel analogy is misleading and the experimental results are explained by stepwise rotations. On the other hand, bona fide
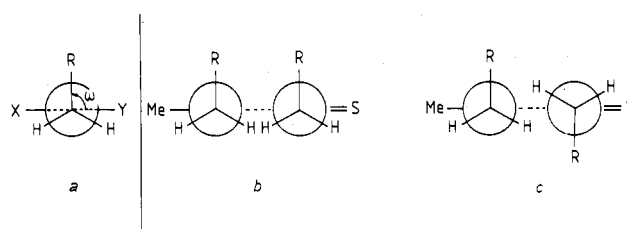
Scheme I

cases of coupled rotations are encountered in interactions between aromatic rings.[7,8] Particularly beautiful and striking examples are found in di-9-triptycylmethane derivatives.[9,10]

Interactions between Primary Alkyl Groups

A single primary alkyl group attached to a planar framework can be expected to have a twofold rotational barrier, V_2, with energy minima of the "perpendicular" type a, where the angle ω depends on the relative sizes of the flanking groups X and Y (Scheme I). [This picture does not apply to carbonyl compounds, e.g., propanal, where the eclipsing tendency of the C=O and C—CH$_3$ bonds forces the ethyl group into the plane.[11]]

Using the J method,[2] Parr and Schaefer have found that the ethyl group in ethylbenzene takes up conformation a with $\omega = 90°$ and $V_2 = 1.15$ kcal/mol. With increasing size of R and/or X or Y [the smaller size of X and Y has the largest effect on the barrier], the barrier increases and becomes accessible to NMR bandshape analysis (>4 kcal/mol). If X $\neq$ Y, the RCH$_2$ protons in a are diastereotopic[12] and exchange places when RCH$_2$ rotates by 180°. Then the barrier follows from bandshape analysis of the AB NMR spectrum. Systematic studies of torsional barriers for RCH$_2$ groups as functions of different flanking groups X and Y exist for 3-RCH$_2$-4-R′-Δ^4-thiazoline-2-thiones,[13,14] for substituted benzyl halides,[15] and for 2-RCH$_2$-1,3,5-trineopentylbenzenes.[16] These studies confirm a as the stable rotamer, in which the repulsion between R and the framework is minimized.

As a first example of interplay between two primary alkyl groups, consider *N,N*-dineopentylthioacetamide.[17] The ^{1}H NMR spectrum at −50 °C shows large geminal nonequivalence in both methylene groups. Such a pattern is in agreement with perpendicular conformations for both neopentyl groups, arising from the strong deshielding effect of the thiocarbonyl group in the plane.

The neopentyl groups may be syn or anti periplanar (parallel or antiparallel, b and c), and according to molecular mechanics calculations both arrangements correspond to energy minima, but with the parallel one

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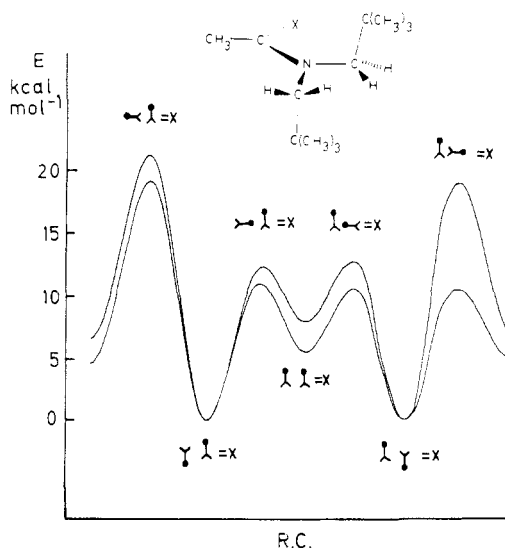
Figure 1. Energy profile for the rearrangements of N,N-dineopentylacetamide (lower trace) and -thioacetamide (upper trace) calculated by the molecular mechanics method.[17] The reaction coordinate (RC) involves rotation of both neopentyl groups to varying degrees.

disfavored by 7.9 kcal/mol. The calculated energy surface (for a section, see Figure 1) shows that the low-energy path from one anti-periplanar form to its enantiomer involves *stepwise* rotations of each neopentyl group inward toward the other RCH_2 group and not toward the flanking group (= S or CH_3) and thus that the parallel arrangement is a high-energy intermediate. The energy barrier calculated for this route (13.1 kcal/mol) is in good agreement with experiment ($\Delta H^{\ddagger}$ = 14.1 kcal/mol). When R = i-Pr (b and c), the barrier is still high enough to be measured by DNMR ($\Delta G^{\ddagger}_{169}$ = 8.2 kcal/mol; ΔE_{calcd} = 7.9 kcal/mol), whereas for smaller R (Me, Et, and Ph), the barriers fall below the DNMR limit. However, molecular mechanics calculations predict similar energy surfaces for all these systems. Only when very bulky flanking groups are introduced, as in N,N-dibenzylthiopivalamide[17] and N-tert-butyl-N-benzylcarbamoyl chloride,[18] does the benzyl barrier become accessible ($\Delta G^{\ddagger}$ = 6.4 and 11.4 kcal/mol).

Tetraneopentylethylene presents a more complex system. The ^1H NMR spectrum shows one AB system for the methylene protons at slow exchange[19] and yields $\Delta H^{\ddagger}$ = 20.2 kcal/mol for the site exchange of these nuclei.[20] Molecular mechanics indicate alternating anti-periplanar neopentyl groups in the lowest energy minimum, and the site exchange is found to proceed by a stepwise rotation mechanism.

A barrier (E_a) of 11.5 kcal/mol was found for exchange between the enantiomeric *anti*-periplanar conformations in 1,2,3,4-tetramethyl-5,6-dineopentyl-benzene.[21] A concerted rotation was proposed, but in the light of later findings on analogous systems,[17] a stepwise mechanism seems more reasonable.

Hexaethylbenzene and its carbonyl transition-metal complexes provide interesting systems with several in-
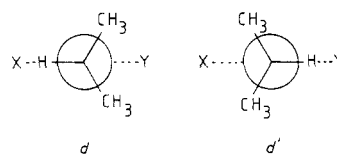
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Scheme II

teracting primary alkyl groups. According to an X-ray crystallographic study and molecular mechanics calculations, the hydrocarbon has the alkyl groups projecting alternantly above and below the ring plane in the energy minimum, and the same is found for the tricarbonyl-chromium and -molybdenum complexes.[22a] The barrier to site exchange of the ethyl groups was found by ^{13}C DNMR to be ca. 11.5 kcal/mol in these complexes, and nearly the same value was found for the hydrocarbon by molecular mechanics, which indicates a stepwise, uncorrelated exchange process. When one of the carbonyl ligands is replaced by the bulky triphenyl-phosphine ligand, the steric constraints force all ethyl groups to project toward the uncomplexed side of the benzene ring. In more recent work[22b,c] using other ligands, the alternation of the ethyl groups is shown to be broken in a less regular way.

Conformations determined by *attractive* nonbonding interactions are found in 1,3,5-trineopentylbenzenes,[23-25] where the rotamer with all three neopentyl groups projecting toward the same side of the benzene ring is favored over the 2-proximal, 1-distal rotamer. [Another important case is the equilibrium between 1,4- and 1,6-di-*tert*-butylcyclooctatetraene,[26] which, however, falls outside the scope of this work.] Molecular mechanics predicts that attractive effects make the syn-periplanar conformations the most stable ones for *trans*-1,2-dineopentyl- and *trans*-1,2-diisobutyl-ethylene,[20] but experimental evidence is lacking.

In summary, two primary alkyl groups in geminal or vicinal positions take up antiparallel conformations. This seems to hold from ethyl and benzyl to neopentyl groups. The enantiomerization of these structures in all likelihood takes place in steps, since molecular mechanics calculations for correlated motions lead to rotational barriers far in excess of the experimental ones, while calculations for stepwise processes agree with experiment.

Interactions between Secondary Alkyl Groups

An isopropyl group attached to a planar framework assumes one of the "bisected" conformations d or d′ [2] [d and d′ may in some cases be better represented as enantiomeric pairs of slightly twisted structures, separated by a low barrier], Scheme II (with the exception of carbonyl compounds like 2-methylpropanal[11]). The equilibrium between these conformations depends on the sizes and shapes of groups X and Y.[2,4b,27] Cyclopropyl[28] and cyclohexyl[4b,29] groups behave similarly, and

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Table I.
Rotamer Populations[a] and Experimental and Theoretical Barriers for N,N-Diisopropylamides and Analogues (1)

R	X=Y	solv	p_e	p_h	p_g	$\Delta G^{\ddagger,b}$ kcal/mol	ΔE_{calcd} kcal/mol	ref
H	C=O	(CD₃)₂O	0.69	0.31		7.8 (e → h)	5.6 (e → f → h)	31
							8.8 (e → g → h)	39
H	C=S	CHCl₃	0.01	0.99				36
CH₃	C=O	CHCl₂F	0.96	0.04		12.2 (e → h)		31
CH₃	C=S	CHCl₂F	0.24	0.76		13.8 (e → h)		31
		CHCl₃	0.21	0.78	0.01			36
CH₃O	C=O	CHCl₂F	0.31	0.69		9.5 (e → h)	6.8 (e → f → h)	35a
							9.7 (e → g → h)	39
CH₃O	C=S	CHCl₂F	0	1.00				35a
CH₃S	C=O	CHCl₂F	>0.99	0.001–0.002		13.1 (e → h)[c]	9.4 (e → f - h)	35a
							12.5 (e → g → h)	39
CH₃S	C=S	CHCl₂F	0.59	0.37	0.04	13.6 (e → h)	11.4 (e → f - h)	35a
						12.0 (g → h)	12.3 (e → g → h)	39
CH₃Se	C=Se	CHCl₂F	0.41	0.46	0.13	13.6 (e → h)	11.7 (e → f → h)	35a
						12.8 (g → h)	12.3 (e → g → h)	39
Ph	CO	(CD₃)₂O	1.0					35c
Ph	CS	(CD₃)₂O	0.95	0.035	0.015	13.2 (e → h)		35c
						9.3 (g → h)		
Ph	CSe	(CD₃)₂O	0.87	0.104	0.026	13.7 (e → h)		35c
						8.9 (g → h)		
CH₃S	C=S⁺CH₃	CHCl₂F	0.5	0.5		12.3		31
	N=S=O	CHClF₂	unobsd	ca. 1.0		9.3 (h → e)[c]		37
	N=O	CHClF₂	0.08	0.92		8.7 (h → e)	9.6 (h → f)	38
							4.0 (f → e)	

[a] Fractional population, in most cases determined by band simulation in the region of slow exchange. [b] Should be corrected by a $\Delta S^{\ddagger}$ value of ca. –5 eu before comparison with ΔE_{calcd}. [c] Determined by bandshape analysis of the major signal only.[1]

Scheme III
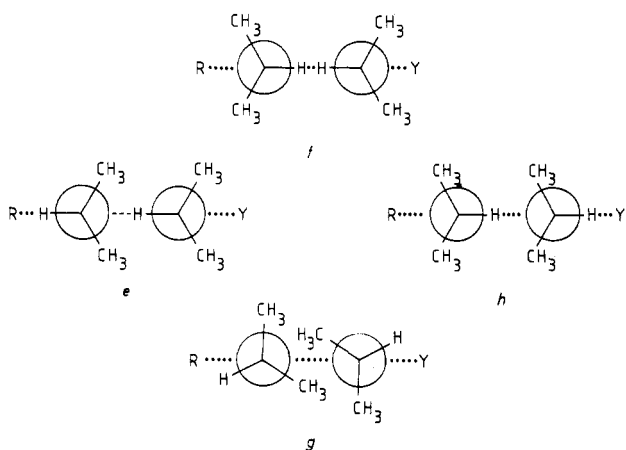
the replacement of an isopropyl methyl group by a carbomethoxy or carboxy group leads to similar conformations.[30]

Calculations on two geminal or vicinal isopropyl groups bonded to a planar framework imply four general types of energy minima (Scheme III).[4b,31] Their relative energies depend on the structure of the framework and on the sizes of the flanking groups, but generally the conformations e and h [gear-meshed according to ref 5] are favored. Nicely interlocking extended cycles based on these conformations are found in tetraisopropylethylene[32,33] and hexaisopropylbenzene.[34] The rotamers of type g always appear as a pair of enantiomers separated by a low-energy barrier, and this may be true for the other rotamers as well,

depending on the shapes of R and X.

N,N-Diisopropylamides, -thioamides,[31,35,36] and -selenoamides[35] and N,N-diisopropylsulfinylhydrazine[37] and -nitrosamine[38] (1) conform to Scheme III, in that
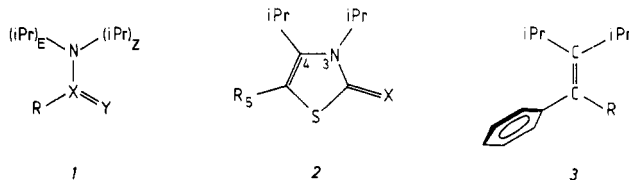
rotamers e and h are observed in most cases. The populations of e and h and the barriers separating them are determined by the sizes of R and Y. Each isopropyl group tends to turn its bulky side toward the smaller of its neighbors. Therefore a large R and a small Y (e.g., 1, R = CH₃S, XY = CO) favor rotamer e, whereas for R = H and XY = CS, rotamer h dominates strongly. When both R and Y are large, then both isopropyl groups tend to present their methine proton toward the flanking groups; i.e., rotamer g appears. The largest population of this rotamer, 13%, is observed when R = CH₃Se and XY = CSe[35a,b] (Table I).

In none of these cases is rotamer f observed. It should be favored by small flanking groups, and calculations[31] predict that e and f should have rather similar weights when R = H and XY = CO.[31] Most likely the barrier between e and f (to rotation of the (E)-isopropyl group) is too low to permit the observation of the individual rotamers even at –150 °C.

In the thiazolinethiones 2, rotamers of types e and h also dominate, but when R₅ = CH₃, a third rotamer

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of type f appears, and its population increases with decreasing size of X in the series $X = S > {}^+SCH_3 > 0$. When $R_5 = H$, only two rotamers are observed, yet it is likely that in this case f is even more populated but that the e → f barrier is too low to permit the observation of the individual rotamers.

In alkenes of type 3, the aromatic ring is for steric reasons almost orthogonal to the plane of the double bond, and the conformations of the isopropyl groups are therefore determined by the steric requirements of R and of the face of the benzene ring.[40] The gear-meshed rotamers e and h are observed except when R = H (no e) and R = *t*-Bu (no h but 20% of g), but the equilibria are in most cases so biased toward h that less than 10% of e is observed.

The steric anisotropy created by two gear-meshed isopropyl groups is clearly demonstrated by 1,3-dibenzyl-4,5-diisopropylimidazoline-2-thione,[41] 4. In this
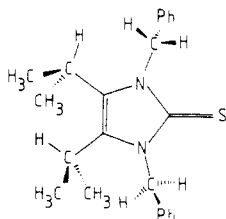
4 anti

apparently symmetrical (C_{2v}) molecule, three rate processes are observed. The high-energy process ($\Delta G^{\ddagger}_{229}$ = 11.5 kcal/mol) is identified as the exchange of the isopropyl groups between two gear-meshed conformations of types e and h (Scheme III). The two other processes are the rotations of the N-benzyl groups between perpendicular energy minima of type a (Scheme I). The barriers are quite different ($\Delta G^{\ddagger}_{205}$ = 10.6 and 8.5 kcal/mol) because one benzyl group rotates past the thiocarbonyl group and the other past the less bulky face of the isopropyl groups ("Janus-like" substituents).

Consider the mechanism for the exchange between the most prevalent, gear-meshed forms e and h. An uncritical application of the cogwheel analogy implies that the rotation of the two isopropyl groups is concerted and disrotatory. However, the barrier to rotation of the isopropyl group in the 3-isopropyl-4-methyl analogue of 2 ($\Delta G^{\ddagger}_{298}$ = 15.1 kcal/mol)[4b] and of the 4-isopropyl group in 2, $R_5 = CH_3$ (11.9 kcal/mol),[42] indicates a different conclusion. As the total barrier in a concerted rotation must be close to the sum of the barriers for the individual groups and as an isopropyl group, whatever its rotational state, cannot be a neighbor smaller than a methyl group to another rotating isopropyl group, the total barrier in 2, $R_5 = CH_3$, should not be much less than 15.1 + 11.9 = 27.0 kcal/mol; the experiment yields 16.5 kcal/mol. This indicates that a stepwise rotation, via either f or g, is the preferred mechanism, a conclusion which is supported by molecular mechanics calculations employing only rigid rotations.[4b]

In another study,[35a] use was made of the observation that 1, R = CH_3Se and XY = CSe, at −63 °C (slow
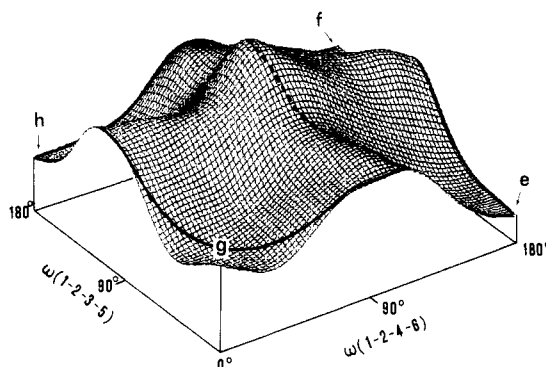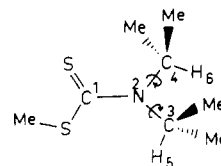
Figure 2. Potential energy surface (MM2[3a]) for the rotation of the two isopropyl groups in methyl *N,N*-diisopropyldithio-carbamate. The full lines indicate stepwise pathways, and the dotted line indicates the concerted disrotatory pathway.

exchange) contains rotamers e, g, and h in the proportions 41:13:46. The comparatively large population of g permits a detailed analysis of the exchange-broadened spectrum, showing that the e ⇌ h exchange proceeds with g as an intermediate. Therefore the isopropyl groups rotate one at a time, in the present case with very similar barriers (Table I).

Evidence for a stepwise rotation is also found by highfield NMR in the series 1, R = Me, Et, and Pr and XY = CS[36] and R = Ph and XY = CS and CSe.[35c] Solutions of these compounds at ca. −100 °C contain only 1–3% of rotamer g, and when the temperature of a sample is raised from the slow-exchange limit, the h resonances broaden first while the e resonances stay sharp to higher temperatures. This indicates that the h ⇌ g exchange (rotation of the isopropyl group next to R) has a lower barrier than the g ⇌ e exchange (rotation of the other isopropyl group), i.e., that the isopropyl groups rotate one at a time.

The rotational process has also been studied by complete molecular mechanics calculations in several *N,N*-diisopropylamides and -thioamides (1, XY = CO or CS), driving the rotation of the isopropyl groups one at a time or simultaneously.[39] The barrier for concerted, disrotatory e ⇌ h exchange is about twice as high as that for the stepwise process. For the latter, the calculated barriers agree reasonably well with experiment (Table I). The energy map for 1, R = CH_3S and XY = CS (Figure 2), clearly shows that the preferred pathway from e to h requires rotation of one isopropyl group at a time with rather little simultaneous movement of the other group. Similar results have been obtained for *N,N*-diisopropylnitrosamine.[38]

The prevalence of the stepwise mechanism in exchange processes in gear-meshed systems is emphasized by recent calculations on tetraisopropylethylene by Ermer.[43] The calculations reproduce the all-gear-meshed C_{2h} ground-state conformation found crystal-

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lographically,[44] and they predict a stepwise rotation via three higher lying energy minima. The highest transition state is found at 17.59 kcal/mol above the ground state, in good agreement with experiment ($\Delta G^{\ddagger}$ = 17 kcal/mol[33]). Gear-meshed conformations of type e or h also appear in similar systems, like 1,4-dichloro-2,3-bis(dichloromethyl)benzene and analogues,[45] where $\Delta G^{\ddagger}$ to e ⇌ h exchange is about 17.5 kcal/mol.

The structures of numerous N,N-diisopropylamido derivatives and analogues are known from X-ray crystallographic studies. In most cases, gear-meshed isopropyl conformations of types e or h are found,[37,46-48] and one case of five gear-meshed isopropyl groups has been observed.[49] However, as mentioned previously, rotamer f with clashing methines may appear in five-membered cyclic systems, and it is favored by small flanking groups, a situation existing in a zinc complex of tris(4,5-diisopropylimidazol-2-yl)phosphine.[50]

tert-Alkyl–*tert*-Alkyl Interactions

Hindered rotation of *tert*-butyl groups has been observed by ^{1}H and ^{13}C NMR spectroscopy, mostly in saturated systems. In tri-*tert*-butylmethane[51] and tri-*tert*-butylsilanes,[52-54] molecular mechanics calculations reproduce the experimental barriers and indicate correlated rotations.[52,54]

In 1,8-di-*tert*-butylnaphthalenes,[55] the *tert*-butyl groups display hindered rotation with low barriers, but according to molecular mechanics[56] the rotations are uncorrelated. An X-ray crystallographic study and molecular mechanics[57] agree that the 1,8 carbons are deflected by 21–22° and the *tert*-butyl groups by 31–32° in opposite directions from the mean plane. Mislow et al. find the same general behavior for 1,8-bis(trimethylgermyl)naphthalene and its tin analogue.[58,59]

The Methyl Group. Interactions with Other Alkyl Groups

The methyl group poses a special challenge, because it is the smallest alkyl group which, in principle, can be involved in gearing. Its conformational behavior is of special importance since it is often chosen as a reference
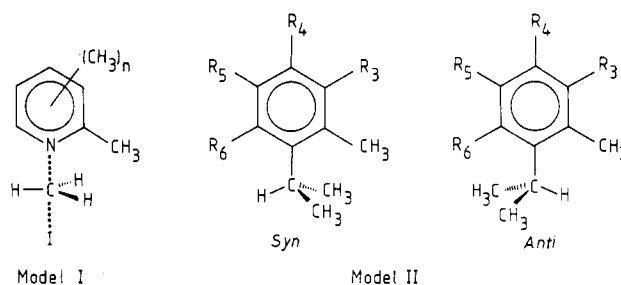
for the steric requirements of other alkyl groups and compared to, e.g., chlorine and bromine.[60]

Hindered rotations of methyl groups with substantial barriers have been observed in very congested environments.[61,62] It should be possible to observe conformational effects due to interactions between methyl and neighboring alkyl groups also under less forced conditions. However, intergroup interactions may be obscured by the anisotropy of the interactions between the methyl group and the framework. One example is found in *cis*-2-butene, in which both methyl groups prefer the orientation found in propene, i.e., with one CH bond eclipsing the double bond. This orientation entails maximal repulsion between the methyls and leads to opening of the CH_3—C=C angles.[63] Similarly, the preferred orientation in propane (5) is governed by

5   6
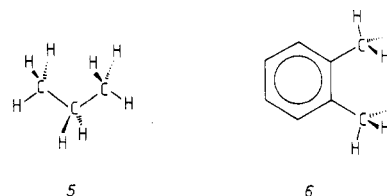
the staggering of the methylene and methyls groups and not by interaction between the methyl groups.[64] Such an "anisotropy of the framework" is probably partly responsible for apparent variations in the size of methyl groups in different environments. On the other hand, the gear-clashed conformation found in *o*-xylene (6)[65] should reflect the true interaction between the methyl groups, since the effect of the framework is minimized by symmetry.

It is desirable to find a model in which a methyl group interacts with another alkyl group in such a way that it cannot be considered spherical and described by one van der Waals radius; in the cogwheel analogy, to show that the "cogs" of a methyl group are not too small to transmit conformational information to neighboring alkyl groups. We have devised two models for this purpose.

Model I   Model II

In model I, a 3-methyl group reduces the rate of the reaction of the pyridine with methyl iodide by a mechanism shown to be conformation dependent by comparison with rigid analogues mimicking the steric requirements of the 2-methyl group in its key confor-

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mations.[66] In model II, we make use of the observation that the low-energy conformation of an isopropyl group is the bisected one with the methyl groups oriented toward the larger of the flanking groups. When R_6 = CH_3 and R_3 = R_4 = R_5 = H, the two forms have equal weights. Introduction of a methyl group in position 3 increases the population of the syn form to 69%; i.e., negative buttressing occurs. A similar effect is found when R_3 = Br. On the other hand, when R_6 = Br, methyl or bromine in position 5 has a normal positive buttressing effect, and the population of the syn form increases from 55% to 65 and 61%, respectively.

A reasonable explanation for this observation, supported by molecular mechanics calculations, is that in the 2,3-dimethyl derivatives the preferred conformation for the ring methyl groups is that of **6**, which however is unfavorable in the anti form **7**. A similar conformation of the 2-methyl group is enforced by a bromine atom in position 3. When position 3 is free, the 2-methyl adopts less strained conformations which are gear-meshed with either the methyls (**8**) or the methine (**9**) of the isopropyl group.

7   8   9
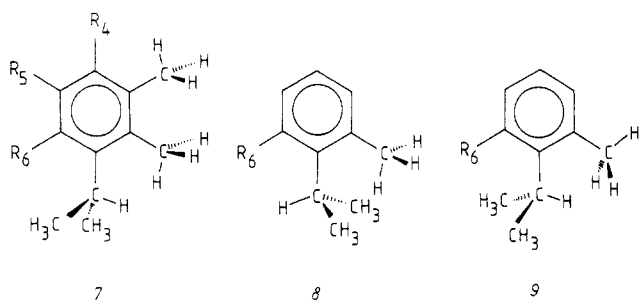
Thus, while a bromine substituent reacts on a buttressing neighbor by bond bending, a methyl group reacts by rotation (and probably also by some bending), i.e., by transferring information by means of its polyhedral shape.

Concluding Remarks

Early conformational analysis of alkyl groups in general involved changes of only one geometric variable, usually a dihedral angle, as exemplified by the important studies of ethane and *n*-butane. The development

of new techniques, in particular dynamic NMR spectroscopy and molecular mechanics calculations, has permitted a much more detailed analysis of all important geometric variables, stressing the multidimensional character of each conformational problem.

This Account concentrates on interactions between two alkyl groups undergoing conformational changes. In such cases, two dihedral angles are involved, and a clear picture of both static and dynamic aspects can be obtained by calculating a map that represents the energy of the system as a function of the two dihedral angles. Mechanical models of such systems lead to the assumption that the processes are synchronous, i.e., that rotation of one alkyl group forces the other to rotate simultaneously. However, rigorous treatments have shown that this picture is often false and that stepwise rotations are the rule with simple alkyl groups attached to planar frameworks. The energy map permits a ready distinction between the two cases.

The interaction between neighboring alkyl groups can serve to relay information about the size and shape of a substituent in one part of a molecule to a distant reaction site, thereby affecting reaction rates. A kinetic study of the formation of (methylthio)thiazolium salts from thiazoline-2-thiones and methyl iodide[4b,67] illustrates this point.

The development of conformational analysis during the last decade, employing spectroscopic and computational methods, has permitted unprecedented insight into the detailed behavior of organic molecules. Further development of molecular mechanics, including improved treatment of polar molecules and large assemblies of molecules in solution and in crystals, may well lead to important advances in the analysis of conformational effects on reaction kinetics, spectroscopic properties, and substrate-receptor interactions in important biological systems. Even if each system is unique and must be treated as such, it is evident that generalizations about interactions between alkyl groups and analogues will always be useful in predicting the gross features of systems of interacting groups.

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