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Influence of C−H···O Interactions on the Conformation of Methyl Groups Quantified from Neutron Diffraction Data

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The effect of C−H···O interactions on the torsional conformation of methyl groups bonded to C(sp^3) is analyzed in a crystal correlation study based on neutron diffraction data. It is found that methyl groups involved in intermolecular C−H···O contacts are systematically rotated out of the perfectly staggered conformation so as to improve the C−H···O geometry. The effect, however, is small with rotation angles of only a few degrees. For C−H···O interactions with H···O distances < 2.8 Å, the torsion angles X−C−C···O and X−C−C−H are well correlated, with the linear regression line having a slope of 0.23(3). The related effect for hydrogen bonds of hydroxy groups bonded to C(sp^3) is described for comparison, and the opposite effect of repulsive C−H···H−C contacts is also shown.

I. Introduction

In recent years, C−H···O hydrogen bonds have been extensively studied, and today, many of their fundamental properties are well understood.[1,2] One of the less investigated features of these interactions is the influence on molecular conformation.[2] In particular for methyl C−H groups, which are almost unpolar, it might be questioned if C−H···O interactions are strong enough to have a noticeable influence on molecular conformation at all. For the C−H···O bonded gas phase dimer methane−water in optimal geometry, quantum chemical calculations obtain dissociation energies of only about 0.6 kcal/mol.[3] With more activated methyl groups R−CH_3, C−H···O energies are somewhat larger, but still of the same magnitude. As a matter of fact, this energetic limitation also limits any possible influence on molecular conformation.

The most direct influence of methyl C−H···X interactions on molecular conformation is on the torsion of the methyl group itself. Such an effect has been positively reported in a handful of crystal structures,[4−6] but a systematic investigation is still lacking. For methyl groups bonded to C(sp^3), the staggered is preferred over the eclipsed conformation by several kcal/mol. The energy difference between the two conformations depends on the residues at C, but the experimental data of 2.9 kcal/mol for ethane and 3.3 kcal/mol for propane may serve as guiding values.[7] To estimate the ability of a single C−H···O interaction to rotate a C(sp^3)−CH_3 group out of the minimum energy conformation, the simple model potential $V = (V_{max}/2)(1 + \cos 3\varphi)$ with a depth of 3 kcal/mol can be conveniently used. For interaction energies of 0.5 and 0.75 kcal/mol, upper limits for the rotation angle of about 16° and 20°, respectively, are obtained. An effect of this magnitute should be clearly discernible from neutron diffraction data, where torsion angles involving H-atoms are determined with precisions around or better than 1°. In the present study, this effect is shown by analysis of neutron diffraction studies. The method used is the crystal correlation technique.[8] For comparison, the opposite effect anticipated for repulsive short H···H contacts is also analyzed.

II. Database Analysis

The hydrogen bond donor strengths and torsion potentials of methyl groups R−CH_3 depend on the nature of R. Therefore, different cases such as C(sp^3)−CH_3, C(sp^2)−CH_3, O−CH_3, N−CH_3, N^+−CH_3, etc., must be treated separately. Unfortunately, the number of accurate neutron diffraction studies is small, allowing statistical analysis only for the most abundant of the methyl groups, that is, C(sp^3)−CH_3. In principle, one should subdivide C(sp^3)−CH_3 further by considering different groups X bonded to C(sp^3), but this is not reasonably possible with the limited quantity of neutron diffraction data.

The analysis is based on the neutron diffraction subset of the Cambridge Structural Database[9] (CSD), release 5.16, with 190 307 entries (October 1998). Ordered and error-free crystal structures with $R < 0.08$ were retrieved. The small number of neutron diffraction crystal structures did not allow making a distinction between different types of O-atom acceptors, although they can have significantly different acceptor strengths.[10] Organic and organometallic crystal structures and room and low temperature data were analyzed in common. Because of thermal vibration effects, methyl C−H bonds are measured about 0.03 Å too short in room temperature neutron diffraction crystal structures,[11] leading to apparent lengthening of corresponding interatomic distances. Since this effect is small compared to the variation of H···O distances, it was not corrected for. Only *inter*molecular contacts were analyzed.

III. Results

Methyl Torsion Angles. For the C(sp^3)−CH_3 groups in the neutron crystal structures used, the distribution of X−C−C−H torsion angles is shown in Figure 1. About 95% of the groups deviate by less than 10° from the ideally staggered conformation with X−C−C−H = 180°, corresponding to energy penalties less than about 0.2 kcal/mol. The other 5% show deviations in the range 10−20°. No C(sp^3)−CH_3 group is observed eclipsed or close to eclipsed. The relatively narrow distribution in Figure 1 shows that the effects of intermolecular interactions on the conformation of C(sp^3)−CH_3 groups can only be small.

O−H···O Interactions. Before the effect of C−H···O interactions on methyl conformations is analyzed, the related

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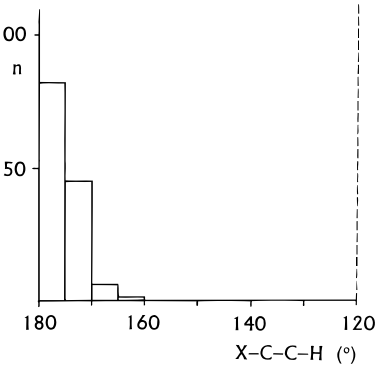
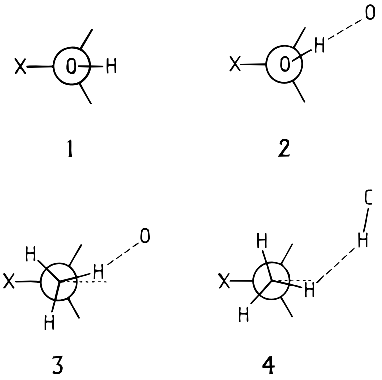


Figure 1. Distribution of torsion angles X−C−C−H in 134 C(sp^3)−CH$_3$ groups (only one of the three angles is given per methyl group).

SCHEME 1



effect in C(sp^3)−O−H···O hydrogen bonds is shown for comparison. Although strong and conventional, this effect is not well documented in the literature and is, therefore, briefly analyzed here. For a hydroxyl group of the kind C(sp^3)−OH, the minimum energy conformation is staggered, **1** (Scheme 1). If a hydrogen bond O−H···O is formed, the O−H vector is oriented at the acceptor O-atom, normally associated with rotation out of the staggered conformation, **2** (Scheme 1). For C(sp^3)−OH···O hydrogen bonds in neutron diffraction crystal structures, the correlation of the torsion angles X−C−O···O and X−C−O−H is shown in Figure 2 (details in the figure legend). The two torsion angles are strongly correlated over the whole angular range, showing that the main determinant of C(sp^3)−OH orientation is the donated hydrogen bond. Even eclipsed C(sp^3)−OH groups occur relatively frequently.

C−H···O Interactions. For methyl groups C(sp^3)−CH$_3$, the situation should differ from that for hydroxyl groups only in the magnitude of the effect, but not in the nature, **3** (Scheme 1). However, the situation is more complicated in the details because two or even all three methyl H-atoms can be involved in C−H···O interactions, which can have opposite influences on the methyl conformation. Furthermore, each of the C−H groups can form interactions with more than one acceptor atom at the same time ("bifurcated" or "three-center" hydrogen bonds), which also can influence methyl conformations in different ways.

In the first step of the analysis, methyl groups were used that form only one intermolecular C−H···O contact with clear hydrogen bond geometry. To make sure that no interactions of questionable geometries are included, the relatively restrictive cutoff criteria H···O < 2.8 Å and C−H···O > 135° were applied. These criteria yield 25 contacts in 17 diffraction neutron crystal structures [distance range 2.39−2.8 Å, average 2.61(2) Å]. The scatter plot of X−C−C−H against X−C−C···O shows that the two torsion angles are actually correlated, Figure 3; i.e., the methyl groups are rotated out of the staggered geometry to optimize the interaction with O. The linear correlation coefficient r is 0.72(14), more than 5 times above the standard uncertainty. The slope of the linear regression function is 0.23(3) (shown as a dashed line in Figure 3). This means that a deviation of X−C−C···O by, for example, 10° from 180° causes a methyl rotation of 2.3(3)° on the average.

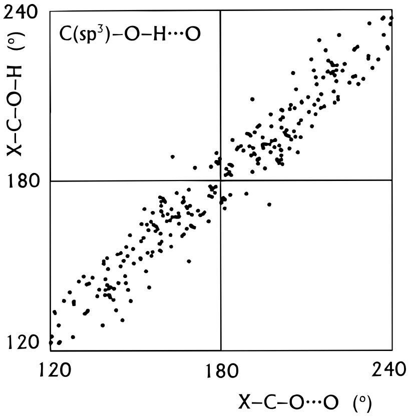


Figure 2. Scatter plot of torsion angles X−C−O−H against X−C−O···O in intermolecular hydrogen bonds C(sp^3)−O−H···O with H···O distances < 2.2 Å (148 hydrogen bonds in 54 neutron crystal structures). X is the atom most trans with respect to H. Because the handiness of the angles are meaningless here, the scatter plot is symmetrized with respect to X−C−O−H = X−C−O···O = 180°. In consequence, there are two data points for each hydrogen bond. The scatter of the correlation is probably to a large degree caused by interactions with second and third nearest neighbors.

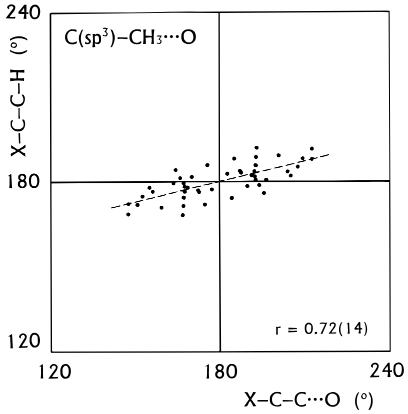


Figure 3. Symmetrized scatter plot of torsion angles X−C−C−H against X−C−C···O in intermolecular C(sp^3)−CH$_3$···O contacts with H···O distances < 2.8 Å and C−H···O angles > 135° (25 hydrogen bonds in 17 neutron crystal structures). X is the atom most trans with respect to H. The linear correlation coefficient is 0.72(14); and the linear regression line has a slope of 0.23(3).

The C−H···O interactions in Figure 3 have a relatively broad distance range, and it must be anticipated that there is a distance dependence of the effect. To study such a distance dependence, the H···O distance cutoff must be expanded, and several subsets with different distance ranges must be formed. Unfortunately, when using the condition that there is only one C−H···O contact per methyl group, the small data quantity does not allow such a differentiation. Therefore, a rougher method has to be used where more than one C−H···O contact per methyl group is allowed. This inevitably leads to some smearing of the effect, reflecting in a reduction of the correlation coefficient. The angular criterion C−H···O > 135° is maintained. Under these conditions, C−H···O contacts were retrieved to a maximal

TABLE 1: Correlation between the Torsion Angles X−C−C···O and X−C−C−H in $C(sp^3)-CH_3\cdots O$ Contacts with H···O < 3.2 Å and C−H···O > 135° [a]

H···O range	*n*	mean H···O	*r*	*b*
<2.6	15	2.48(1)	0.60(19)	0.21(5)
2.6−2.8	24	2.71(1)	0.71(15)	0.20(3)
2.8−3.0	22	2.89(1)	0.56(16)	0.13(3)
3.0−3.2	12	3.11(2)	0.25(22)	0.08(7)

[a] Unlike in Figure 2, more than one contact per methyl group is allowed. H···O distances are given in Å; r = linear correlation coefficient with its standard uncertainty. Linear regression is described as X−C−C−H − 180° = b (X−C−C···O − 180°).

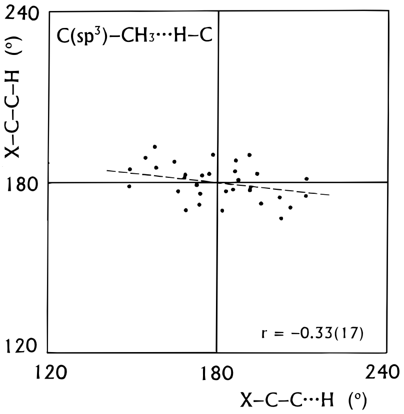


Figure 4. Symmetrized scatter plot of torsion angles X−C−C−H against X−C−C···H in short intermolecular $C(sp^3)-CH_3\cdots H-C$ contacts with H···H < 2.2 Å (18 contacts in 13 neutron crystal structures). X is the atom most trans with respect to H. The linear correlation coefficient is −0.33(17), and the linear regression line has a slope of −0.11(6), showing the repulsive nature of the interaction.

distance of H···O = 3.2 Å, and analyzed in 0.2 Å distance steps in the same way as shown in Figure 3. The results are summarized in Table 1. As to be expected, the slope of the regression line falls systematically with increasing distance. In the distance range H···O = 2.8−3.0 Å, the slope is still significantly positive, 0.13(3). In the distance range 3.0−3.2 Å, it has fallen to 0.08(7), which is not significantly above zero.

C−H···H−C Repulsions. The results given above show that the C−H···O interaction of methyl groups is a bonding interaction, at least in the geometrical regime analyzed. It is of interest to see if the analytical method is of more general applicability, in particular if it can be used also to characterize intermolecular *repulsions*. As a test example, C−H···H−C repulsions in short intermolecular contacts are selected, because they occur relatively frequently in crystals. If significantly repulsive, a short H···H contact must rotate the methyl group out of the way, **4** (Scheme 1).

In the sample of neutron diffraction crystal structures studied, 18 intermolecular $C(sp^3)-CH_3\cdots H-C$ contacts are found with H···H distances < 2.2 Å, which should be in the repulsive regime of the van der Waals interaction (the formal van der Waals radius of H is given as 1.2 Å by Bondi[12] and as 1.1 Å by Rowland and Taylor[13]). For these contacts, the correlation diagram of the torsion angles X−C−C−H and X−C−C···H is shown in Figure 4. A weak negative correlation is discernible just at the significance limit. The correlation coefficient is −0.33(17), and the slope of the regression line is −0.12(6), both negative and differing from zero by two standard uncertainties. These data at least suggest that short H···H contacts are sufficiently repulsive to influence methyl conformations to a small degree.

IV. Discussion

Based on neutron diffraction crystal structures, the data in Figure 3 and Table 1 clearly show an effect of C−H···O interactions on the torsional conformation of methyl groups. The effect, however, is relatively small for $C(sp^3)-CH_3$, which has rotation barriers around 3 kcal/mol. The effect must be larger for methyl groups with lower rotation barriers, such as those bonded to $C(sp^2)$, and to O.

In neutron diffraction studies, there is no example of an eclipsed $C(sp^3)-CH_3$ group. However, there is a famous case of an eclipsed $C(sp^3)-CH_3$ group in the X-ray crystal structure of a hydrated tricyclic orthoamide (reported by Dunitz and coworkers).[4] The eclipsed methyl conformation was found associated with $C-H\cdots OH_2$ interactions of all three methyl C−H groups. This can be explained only because the potential of methyl torsion is exceptionally shallow in this compound (calculated as around 1.5 kcal/mol),[14] and donor and acceptor groups are strongly activated when compared to the methane−water dimer. For normal $C(sp^3)-CH_3$ groups with rotational barriers ≥ 3 kcal/mol, C−H···O interactions are not able to cause an eclipsed conformation, even if all three H-atoms of the methyl group are involved.

The present analysis has been restricted to *inter*molecular interactions. Related intramolecular effects can be anticipated, but must be shown separately.

Finally, it is pointed out that analysis of methyl torsional conformation is a sensitive tool to determine whether an intermolecular interaction in a given geometry is attractive or repulsive (in terms of forces). It is applicable to many other interaction types than those shown here. At least in principle, it would even be possible to map out the potential energy surface of intermolecular interactions. Related analysis can be performed also on $X-YZ_3$ groups in general, such as $C(sp^2)-CH_3$, O/N−CH_3, X−CF_3, and so on.

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