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A REMARKABLE CONSISTENCY IN CONFORMATIONAL PREFERENCE FOR A SERIES OF 1,3-DISUBSTITUTED-2,2-DIMETHYLPROPANES

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ABSTRACT: ^{1}H NMR spectra at low temperatures for five 1,3-disubstituted-2,2-dimethylpropanes reveal a strong preference for one molecular geometry (C_2 symmetry) which is qualitatively consistent with empirical force field calculations.

1,3-Interactions are ubiquitous in small molecules and polymers. The relative contributions of van der Waals, electrostatic, and other energy terms to medium-range 1,3-interactions in acyclic systems continue to be of interest. Studies of conformational preference in 1,3-dichloro-2,2-dimethylpropane have appeared in previous papers.[1-3] Dipole moment measurements at 298K estimated 56% of geometry **6** (X=Cl, see Figures).[1] Gas-phase electron diffraction studies at 333K revealed three conformations: 56% of **6** (X=Cl), 37% of **7** and 7% of **8**.[2] Vibrational spectroscopy indicates the presence of three conformations (**6**, **7** , and **8** ; X=Cl) in solution and only one geometry (**6**) in the crystalline solid at 80K.[3] Using ^{1}H NMR spectroscopy, we have observed the apparently exclusive presence of one molecular geometry for 1,3-dibromo-2,2-dimethylpropane (**6**, X=Br) in solution ($CBrF_3$) at 121K.[4]

This paper concerns ^{1}H dynamic NMR (DNMR) and empirical force field (EFF) studies of a series of 1,3-disubstituted-2,2-dimethylpropanes (**1**-**5**; Table I). The results indicate an apparently exclusive or at least very strong preference at low temperatures for that conformer having C_2 symmetry (i.e., **6**) whether the substituent (X; Table I) is polar or non-polar.

^{1}H DNMR data for **1** - **5** (2% v/v in $CBrF_3$; 270 MHz) under conditions of fast DNMR interchange (170-180K) and slow DNMR exchange (100-130K) are listed in Table I. In each case, the spectra decoalesce at low temperatures to reveal only two methylene proton signals, while the gem-dimethyl signal remains a relatively sharp singlet. Of the four possible conformations (**6**-**9**), each slow exchange spectrum is consistent only with geometry **6** . Conformer **9** possesses an energetically unfavorable 1,3-di-X-interaction[5] and would give an NMR spectrum which is inconsistent with the observed slow-exchange spectrum. Geometry **7** should display non-equivalence for both the CMe_2 and CH_2 signals, and **8** should show NMR equivalence for both CMe_2 and CH_2 signals at all temperatures. Figure 1 illustrates the diastereotopic methylene protons signals for compounds **2**-**5** at slow DNMR exchange. The spectrum for the methylene protons (i.e., two signals with a typical geminal coupling constant) and the CMe_2 singlet are consistent only with geometry **6** . Furthermore, the spectra in Figure 1 are virtually free of any distortion indicating that if minor conformations are indeed present, they are beyond the lower NMR detection limit, i.e., about 3% of the total peak area.

Although temperatures low enough to reach the DNMR "slow-exchange" limit were not achieved in compounds **1** and **5** , theoretical line shape analysis allowed the verification of the reported spin systems (Table I). The spectrum of the ethyl groups of **1** at 105K is readily simulated using an $ABX_3 \rightleftharpoons BAX_3$ exchange model with a rate constant of 50 sec^{-1} (Figure 2). The methylene protons spectrum of **5** (see asterisks in Figure 1) was successfully modeled as an AB

⇄ BA exchange system with a rate constant of 60 sec^{-1} at 100K. The OCH_3 singlet overlaps the low field methylene proton signal.

Table I $X-CH_2-CMe_2-CH_2-X$ Chemical Shifts[a] and Coupling Constants[b]

Compd.	X	Temp.	Me_2C	CH_2	X	J_{HH}
1	Me	170^c	0.84 (s)[e]	1.24 (q)	0.82 (t)	7.8 (HCCH)
		105^d	0.85 (s)	1.40,1.04	0.79 (t)	7.8 (HCCH) -12.0 (HCH)[f]
2	Cl	180^c	1.09 (s)	3.45 (s)		
		110^d	1.14 (s)	3.74, 3.23		-10.8 (HCH)
3	Br	170^c	1.19 (s)	3.39 (s)		
		121^d	1.21 (s)	3.61, 3.19		-10.2 (HCH)
4	I	180^c	1.29 (s)	3.25 (s)		
		130^d	1.32 (s)	3.36, 3.17		- 9.8 (HCH)
5	OMe	180^c	0.84 (s)	3.04 (s)	3.25 (s)	
		100^d	0.86 (s)	3.26, 2.80	3.29 (s)	-10.8 (HCH)[f]

(a) for ^1H in ppm, TMS reference, (b) Hz, proton-proton coupling, (c) fast exchange, (d) slow exchange, (e) s-singlet, t-triplet, q-quartet, (f) assumed value of $^2J_{HCH}$

A further point of interest in the spectra depicted in Figure 1 is the relative behavior of the low field and high field methylene protons chemical shifts for **2**-**4**. The top three spectra of Figure 1 are all plotted within the same frequency range. The low field shift is much more sensitive to substituent than the upfield counterpart. Indeed, we feel that this observation allows for assignment of specific protons in these systems. It is reasonable to expect that the proton positioned 1,3-syn to the remote halogen will encounter the greatest deshielding. Therefore in **6**, the methylene proton positioned 1,3-syn to a halogen atom is assigned to the low field peak and the proton positioned gauche to both of the gem-dimethyl groups is assigned to the high field resonance. These assignments are consistent with similar data for 2-(chloromethyl)-2-methyl-1,3-dichloropropane in which four of the six methylene protons of the major conformer (C_s symmetry) are 1,3-syn to chlorine atoms and are found to be downfield from the signal due to the remaining two protons which are 1,3-syn to other protons.[6]

One is tempted to employ electrostatic models to explain the observed predominance of **6** in compounds **2**-**5**.[4] Such models have been invoked in order to rationalize conformational preferences in cyclohexyl[7] and heterocyclic[8] systems. Attractive electrostatic interactions between protons and electronegative atoms positioned 1,3-syn to each other have been proposed to explain the unusually high population of diaxial trans-1,4-dichlorocyclohexane.[7] Similar arguments have been suggested as responsible for conformational preferences in ethers analogous to **5**.[9] The significant populations of axial conformers of 5-halomethyl-1,3-dioxanes was rationalized in terms of an electrostatic attraction between the electropositive halomethyl carbon and the electronegative oxygen atoms.[8c] However, these interactions are not expected to play a major role in the observed preference of **1** for conformer **6**.

In contrast to previous studies of **2** at high temperatures,[1-3] and in spite of the fact that **1** is a non-polar compound and **2**-**5** possess polar bonds, there is a strong consistency in conformational preference in **1** - **5** at least at very low temperatures. The conformation with C_2 symmetry (**6**) is thermodynamically favored in all five cases. In order to rationalize these observations, it may be useful to invoke an optimized combination of bond angle bending and van der Waals interactions if not dipole-dipole interactions.[10] If the flexibility of the propane chain plays a significant role in determining conformation, then one might examine the central CCC bond angle ($XH_2C-C-CH_2X$) as a function of conformation. Conformations in which this angle is allowed to open, thus relieving strain, may lead to lower energy. For example, if the angle is opened in **8**, both X substituents will be forced into the area gauche to both gem-dimethyl groups. This results in increased vicinal interactions at the expense of angle opening. Rotamer **7** possesses only one such interaction on angle opening, and **6** has none. It is noteworthy that optimized EFF calculations done in our laboratory using the MM2 method[11] are consistent with this rationale. The relative MM2 energies in kcal/mole for conformers **6**-**9** in

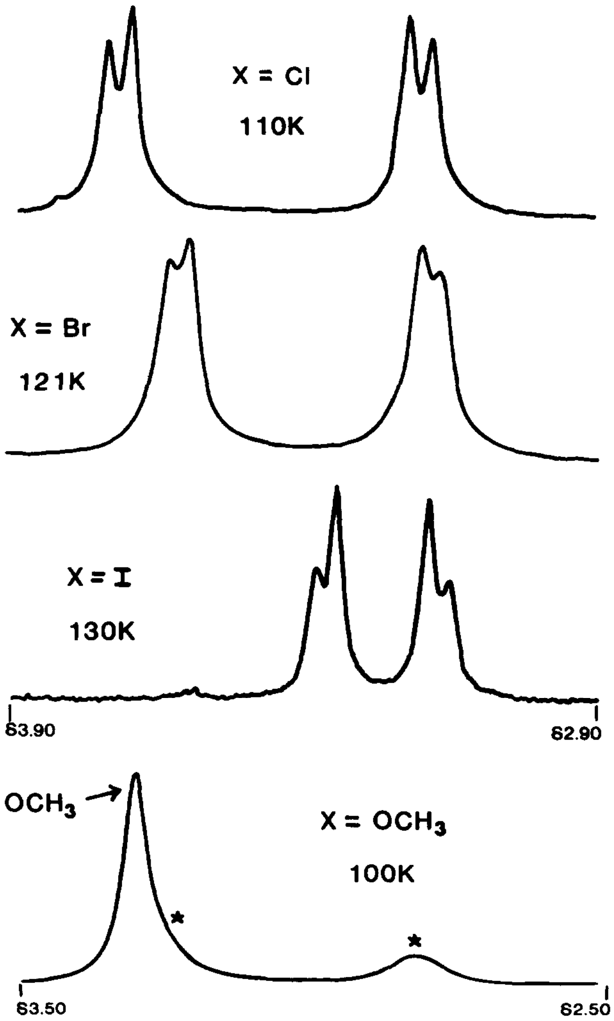


Figure 1.

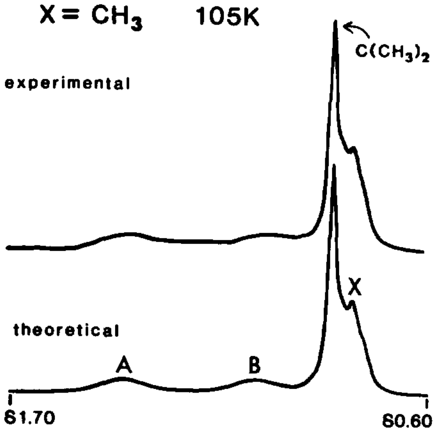
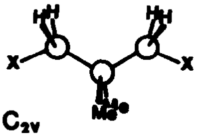


Figure 2.



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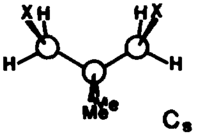

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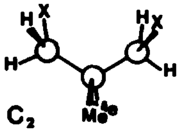

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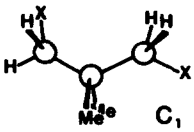

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compounds **1**-**5** are compiled in Table II. The MM2 method consistently predicts the conformer with C_2 symmetry (**6**) to be the most stable in agreement with our NMR data. In addition, the central C-C-C bond angles consistently optimize at or near 113°, 110°, and 106°, respectively, for **6**, **7**, and **8** in compounds **1**-**4** and 111°, 109°, and 108° for **6**, **7**, and **8** in **5**. This corroborates to some degree the intervention of an optimized combination of central C-C-C bond angle bending and van der Waals interactions in determining conformational preference.

Table II. Relative Energies Computed Using the MM2 Method

Compd.	Rotamer **6**	Rotamer **7**	Rotamer **8**	Rotamer **9**
1	0.00	0.35	0.68	2.03
2	0.00	0.51	1.79	3.37
3	0.00	0.45	1.52	3.64
4	0.00	0.39	1.15	3.24
5	0.00	0.54	1.72	4.73

However, the agreement between the MM2 calculations and our NMR data is only qualitative. In all instances (Table II), the population of **7** estimated from the MM2 energy is too large, i.e., about 10-25% at 100K. Populations of this magnitude would be DNMR-visible and we do not observe them. One reasonable explanation for the discrepancy might lie in the differential solvation energies of **6** and **7**. However, current solvation theory which employs both dipolar and quadrupolar terms,[12] allows the approximation of no more than 0.1 kcal/mole stabilization of **6** over **7**. This improves the agreement with the NMR data slightly but still predicts a significant population of **7**. These results suggest that conformational preferences for **1**-**5** in solution apparently are dominated by factors other than electrostatic interactions.

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