Tetrahedron Letters, Vol.28, No.41, pp 4883-4886, 1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

CONFORMATIONAL ENERGIES OF TRANS-1,4-DIFLUORO- AND TRANS-1-CHLORO-4-FLUOROCYCLOHEXANE. THE ROLE OF ELECTROSTATIC INTERACTIONS.

Lars-Gunnar Hammarström
Department of Organic Chemistry,
University of Umeå, S-901 87 Umeå, Sweden

Ulf Berg and Tommy Liljefors*
Department of Organic Chemistry 3, Chemical Center,
University of Lund, P.O. Box 124, S-221 00 Lund, Sweden.

Abstract: The conformational energies of the title compounds were extrapolated from solution ^{19}F NMR measurements to vapour phase dielectric medium. Vapour phase values were satisfactorily reproduced by MM2 computations including electrostatic interactions between charges obtained by the PEOE method.

The ring inversion of <u>trans</u>-1,4-dichlorocyclohexane (1) and <u>trans</u>-1,4-dibromocyclohexane (2) has been investigated experimentally by electron diffraction (ED) in the vapour phase[1] and by ^{1}H NMR in various solvents.[2] The equilibrium amount of diaxial (aa) conformer is larger than expected from an extrapolation of data from the mono-substituted compounds. This has been attributed to a pronounced electrostatic component of the conformational energies.[2] Molecular mechanics (MM2)[3] calculations using dipole-dipole interactions fail to predict the conformational preferences of these compounds. The diequatorial (ee) conformations are calculated to be preferred by 0.48 and 0.72 kcal/mol, respectively. By substitution of the dipole-dipole interaction term with a coulombic term for interactions between a complete set of partial charges obtained by a modified PEOE procedure[4], the energy differences between the conformers compare reasonably well with experimental data.[5]

$$\Delta E(1)_{aa-ee} = -0.22 \text{ kcal/mol (exp. } -0.17 \text{ kcal/mol)}^{1}$$

$$\Delta E(2)_{aa-ee} = 0.05 \text{ kcal/mol (exp. } 0.17 \text{ kcal/mol)}^{1}$$

We now present conformational data of two related compounds, <u>trans</u>-1,4-difluorocyclohexane (3) and <u>trans</u>-1-chloro-4-fluorocyclohexane (4)[6], the first of which not earlier prepared.[7] The conformational equilibria of 3 and 4 in various solvents were studied by ^{19}F NMR. At ca -90°C the ring inversion was slow on the NMR time scale, and the fluorine signal had split into two signals with the resonance from axial fluorine appearing at higher field ($\Delta\delta$ 15.1 ppm for 3 and 14.3 ppm for 4). Equatorial fluorine gave rise to a doublet, which was broadened due to unresolved gauche three-bond couplings, whereas axial fluorine appeared as a multiplet of various shape in different solvents due to larger trans couplings. The conformer populations were determined by integration and bandshape analysis. The results are summarized in Table 1. ^{1}H NMR studies in acetone agreed completely with the results obtained by ^{19}F NMR. The barrier to ring inversion for 3 in acetone was determined as 9.8 kcal/mol at -67°C.

The solvent effect on the conformational equilibria was estimated independently by two different methods. An extrapolation metod (PEM) was proposed by Zefirov[8], which relates the free energy difference in solution to the dielectric constant (ε) of the solvent through a parabolic expression.

$$\Delta G^{o} = A + B\,(0.5 - X)^{\frac{1}{2}} \qquad X = (\varepsilon - 1)/(2\varepsilon + 1)$$

A plot of ΔG^{o} of 3 in four different solvents against the square root expression provides a straight line, which on extrapolation to vapour phase conditions ($\varepsilon = 1.0$, $(0.5-x)^{\frac{1}{2}} = 0.707$) gives the vapour phase energy difference (Figure 1). A corresponding extrapolation has been done for 4 in two different solvents. From these extrapolations the values obtained for $\Delta G^{o}(3)_{aa-ee}$ and $\Delta G^{o}(4)_{aa-ee}$ are -1.14 and -0.90 kcal/mol respectively (Table 1). These vapour phase estimates are in good agreement with those calculated (ΔE_{vap}) by the MM2/PEOE method, -1.13 and -0.64 kcal/mol respectively. Standard MM2 gives -0.38 and 0.05 kcal/mol respectively.

In the more elaborate reaction field calculations of solvent effects[9], the solvation energy is built up by three terms, a dipole term (DT), a quadrupole term (QT) and a polar term (PT), accounting for the specific interactions between solvent and solute.

$$\Delta E_{solv} = DT + QT + PT$$

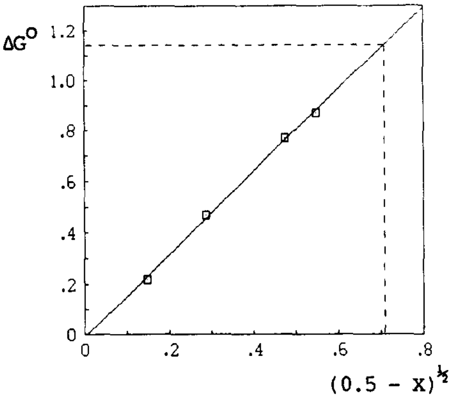
For the compounds and solvents under consideration QT dominates[10], while DT is vanishing or negligable since 3 has no net dipole moment and that of 4 is small (approx. 0.2 D). The calculated solution conformational energies ($\Delta E_{calc} = \Delta E_{vap} - \Delta E_{solv}$) summarized in Table 1 are in excellent agreement with experimental values.

Table 1. Conformational energies (aa-ee) in kcal/mol of **3** and **4** in different solvents.

Compound	Solvent	Diel. const.[a]	Temp.(K)	ΔG^{o}_{exp} [b]	ΔE_{calc} [c]
(3)					
	Vapour	1.0		(-1.14)[d]	-1.13
	$n\text{-}C_5H_{12}$	2.01	184	-0.87	-0.87
	CS_2	2.83	184	-0.77	-0.75
	$(C_2H_5)_2O$	8.6	186	-0.47	-0.47
	CD_3COCD_3	34.1	182	-0.22	-0.10
(4)					
	Vapour	1.0		(-0.90)[d]	-0.64
	CS_2	2.83	184	-0.46	-0.36
	CD_3COCD_3	33.6	186	0.16	0.12

[a] Diel. const. at the temperature of measurement. [b] Estimated error ±0.05 kcal/mol. [c] MM2/PEOE (vapour) and reaction field calculations.[9] [d] By the PEM method according to Zefirov.[8]

Figure 1. Solution conformational energies of **3**, extrapolated to vapour phase by the PEM procedure.[8]



The data of compounds **1**–**4** confirm that substitution of the standard MM2 interactions between the two C-X (X = halogen) dipoles in trans-1,4-dihalocyclohexanes by coulomb interactions between partial charges obtained by a modified PEOE method greatly improves the predictive capability of MM2. Discrepances between vapour phase energies obtained by direct gas phase measurements (i.e. ED) and vapour phase data obtained from solution measurements might be due to solvent internal pressure effects on the conformational equilibria[11]. Applied to trans-1,4-dihalocyclohexanes, the gas phase stability of the aa conformer may be estimated to be exaggerated by 0.1 - 0.4 kcal/mol. The largest discrepancy is expected for the dibromo compound.

Acknowledgements. We are grateful to the Swedish Natural Research Council for financial support.

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7. Prepared by the action of 3.5 eqv. of fluoride ion bound to anion-exchange resin (Amberlyst-A 26)[12] on pure trans-1,4-cyclohexanediol dimethanesulfonate (m.p. 137°C, dec.) in dry triglyme at 50 - 70°C. Volatile products were collected in a dry ice/acetone trap at 10 mm Hg during 5 days. After treatment with bromine in the dark to remove large amounts of unsaturated material, volatile products were subjected to preparative vapour phase chromatography (on OV 351). Since the yield of difluoride **3** was low (< 0.5 %), the compound was not isolated in the pure state but was trapped in the solvents proper for the NMR measurements. The fluorochloride **4** was obtained in the same preparation as a consequence of trace amounts of chloride remaining in the resin.
   trans-1,4-difluorocyclohexane: ^{1}H NMR (acetone-d_6) δ 1.71 (m, 4H), 1.91 (m, 4H, $^3J_{HF}$ = 29 Hz), 4.76 (p of d, 2H, $^2J_{HF}$ = 48.8 Hz, $^3J_{HH}$ = 2.8 Hz); ^{19}F NMR (acetone-d_6, ppm from C_6F_6) -19.95; MS (70 eV) m/z 120(M^+, 2.1 %), 100(25), 85(50), 80(46), 72(40), 59(100), 55(46), 54(42), 46(57), 41(95), 39(70), 33(35).
   trans-1-chloro-4-fluorocyclohexane: ^{1}H NMR (acetone-d_6) δ 1.72 (m, 4H), 2.10 (m, 4H), 4.28 (m, 1H), 4.72 (m of d, 1H, $^2J_{HF}$ = 48.7 Hz); ^{19}F NMR (acetone-d_6, ppm from C_6F_6) -16.07; MS (70 eV) m/z 138(0.5 %), 136(M^+, 1.5), 118(0.6), 116(2.0), 100(17), 85(24), 81(100), 80(49), 72(24), 59(36), 55(27), 54(41)), 53(25), 41(77), 39(65).
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10. $QT = [9q^2/2a^5][X/(5-X)]$ where q may be considered as the molecular quadrupole moment (origin at the center of charge), $X = (\varepsilon-1)/(2\varepsilon+1)$ and a is the radius of a spherical cavity enclosing the molecule. The estimation of a is crucial. This was done by placing the molecule in a rectangular box, allowing the vdW-surfaces of periferal atoms to touch the walls, and equalizing the volume of the box with the volume of a sphere with radius a.
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(Received in UK 23 July 1987)