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CALCULATION OF ALCOHOL CONFORMATIONS BY MOLECULAR MECHANICS

ULRICH BURKERT
Universität Konstanz, Fachbereich Chemie Postfach 7733, D-7750 Konstanz, West Germany

Abstract—The geometries and energies of simple alcohols were calculated with a molecular mechanics force field. The force field requires the application of the charge interaction model with charges calculated by the CNDO/2 method, the importance of electrostatic interactions for the equilibrium of rotamers about the C–O bond exceeds that of van der Waals interactions. The calculated rotamer populations are discussed with regard to the value of ^1H NMR coupling constants $^3J_{HCOH}$ and other experimental data.

Molecular mechanics calculations have been applied in the past years frequently to problems of conformational analysis, but although several force field parameterizations are available for the calculation of the geometry and energy of hydrocarbons,[1] only little work has been reported about the development of force fields capable of handling molecules containing heteroatoms.[2,3] We are concerned with a systematic extension of a hydrocarbon force field to molecules containing the ether and alcohol oxygen. The main problems of non-bonded interactions in ethers (the oxygen lone pairs and electrostatic interactions) have been discussed in an earlier paper.[3] Electrostatic interactions are included in our force field as monopole interactions between point charges (from CNDO/2 calculations) positioned at the nuclei, and lone pairs with a very weak van der Waals potential are placed on oxygen. This force field gave good results for simple ethers and 1,3-dioxanes. Now we report calculations with this force field of the rotamers of simple alcohols.

Force field

Our force field is based on the 1973 hydrocarbon field of Allinger.[4] Parameters for the alcohol function to be added to this force field have been reported by Allinger and Chung,[5] fitting the geometry and rotation barrier in methanol. No further calculations were reported with this alcohol force field, so it was disappointing to find that ethanol was calculated to be more stable in the gauche, 2-propanol in the symmetrical conformation, although the opposite is established from several experimental studies.

The high calculated energy of the anti conformation of ethanol comes from the fact that 1–4 H…H van der Waals interactions are more repulsive than 1–4 H…CH_3. The inverted order of stability must be explained by another interaction term, and our earlier successful application of monopole instead of dipole interactions for electrostatic interactions[3] induced us to use the same approach for alcohols. In the Allinger force field, which uses the dipole approximation, bond dipoles are assigned to all bonds between a heteroatom (here oxygen) and its next neighbors (here carbon, hydroxyl hydrogen and lone pairs). Electrostatic interactions are not included in the conformational energy calculation when the bond dipoles end at the same atom, no electrostatic interaction terms appear therefore in calculations of monoalcohol rotamers. On the other side quantum mechanical calculations reveal considerable charges at the atoms bound to the oxygen and their neighbors,[6] which shows that the dipole approximation as described is too rough here. A modified dipole interaction scheme using transferable small bond dipoles in the hydrocarbon moiety too has been reported for the calculation of alkyl halides,[7] but this method also seems not fully satisfactory as CNDO/2 calculations show a complicated behaviour of electron densities in alkyl halides which cannot be described by invariant bond dipoles.[6] The monopole (charge) interaction scheme was therefore employed in our calculations using charges from CNDO/2 calculations. In our calculations the structure is optimized initially with the force field using the dipole approximation, the resulting geometry serves for the CNDO calculation to determine the charges, which are used in the final force field calculation with the monopole approximation (with an effective dielectric constant of 1.0). Only minor changes of the geometry are observed in the final calculation, although the energies change considerably.

Table 1. Force field parameters for alcohols

Stretching:		
O-H	k_s=4.60 mdyn A^{-1}	r_o=0.945 A
Bending:		
C-O-H	k_b=0.43 mdyn A^{-1}	Θ_o=106.50°
van der Waals interactions:		
$H_{(OH)}$	ε=0.043 kcal mol^{-1}	r_o=1.20 A
Torsion:		
H-C-O-H	V_3=0.38 kcal mol^{-1}	
C-C-O-H	V_3=0.38 kcal mol^{-1}	

The parameters for non-bonded interactions of the oxygen atoms as well as the treatment of the lone pairs are taken over unchanged.[3] The van der Waals center of hydrogen atoms bound to carbon is relocated in Allinger's force field along the C–H bond so that it is only 92.5% of the bond distance from the carbon.[8] We have now transferred this to the hydroxyl hydrogen. Finally the torsional potential constant V_3 for H–C–O–H was adjusted to fit the rotational barrier in methanol,[9] and the V_3 constant for C–C–O–H was given the same value.

RESULTS

Experimental information about alcohol rotamers is very scarce. Gas phase structure information has only been obtained from microwave spectroscopy, electron diffraction gives averaged data. Infrared spectra have

Table 2. Calculated and experimental structures of ethanol

	Force field	Microwave[14]	X-ray[15]
anti			
C-C	1.530A	1.530$\pm$0.002A	1.487$\pm$0.004A
C-O	1.412A	1.425$\pm$0.0025A	1.424$\pm$0.003A
O-H	0.946A	0.945$\pm$0.002A	0.97A
C-C-O	109.72°	107.33°	113.0°
C-O-H	109.61°	108.53°	109°
gauche			
C-C	1.529A		
C-O	1.410A	1.427$\pm$0.006A	
C-C-O	110.97°	112.35$\pm$0.5°	

been employed frequently; the hydroxyl band is symmetrical only if the alkyl group has C_3 symmetry as in methanol, *tert*-butanol and 1-adamantanol, in most cases unsymmetrical bands are observed as superimposition of the bands of different conformers.[10] The band position is determined by the groups in gauche position to the hydroxyl proton. This paper uses the nomenclature derived herefrom by Joris *et al.*,[10] who have determined the conformational equilibrium by decomposition of the hydroxyl band into symmetrical component bands.

In ^{1}H-NMR spectra observed $^3J_{HCOH}$ coupling constants are averaged values of all conformers, as rotation about the CO bond is fast on the NMR time scale. The equilibrium can therefore be determined if the coupling constants for the single isomers are known.[11–13] The dominating factors which influence the value of the coupling constants of one conformation are the electronegativity of the substituents on the carbon, and the HCOH torsion angle. It has been assumed that the effect when a hydrogen atom is replaced by an alkyl group is negligable, which makes it possible to use only one Karplus equation for all monoalcohols bearing no other heteroatoms.[11–13] In most of the cases we have studied, we find good agreement of the equilibria derived from the NMR coupling constant with experimental data from other sources and with the results of the force field calculation.

The structure and rotation barrier of methanol were used for the parameterization and are therefore calculated correctly. The next molecule studied was *ethanol* whose structure is known from microwave studies (in which some structural data of methanol were taken over unchanged however)[14] and X-ray structure determinations of ethanol adducts.[15] The calculated structures agree well with the experimental ones, the largest deviation being in the CCO angle of both conformations. The calculated *gauche* CCOH torsion angle (54.6°) agrees well with the experimental value (54 ± 6°).[14] The anti conformation A is calculated to be 0.54 kJ mol^{-1} more stable than the *gauche* isomer B; as we had expected, the electrostatic attraction between the positive hydroxyl hydrogen and the *negative*[6] α-hydrogens stabilizes A sufficiently. It is interesting to note that in ethanthiol, where charges are much less pronounced, the *gauche* isomer is more stable,[16] and the molecular mechanics calculation employing the dipole interaction model reproduces this correctly.[17] From the IR spectrum and the NMR coupling constant, which is smaller (5.07 Hz)[12] than in methanol (5.19 Hz),[12] an energy difference of 0.4 kJ mol^{-1} in favor of A can be derived for ethanol. Quantum mechanical *ab initio* calculations (STO4-31G) indicate greater stability of A (2.74 kJ mol^{-1}).[18]

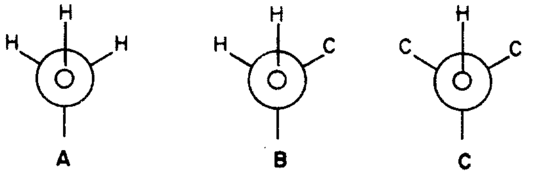

Fig. 1. Nomenclature of alcohol rotamers.[10]

In 2,2-*dimethyl*-1-*propanol* the hydroxyl hydrogen can be *gauche* or anti to a *tert*-butyl group instead of a methyl as in ethanol. The force field calculation predicts an energy difference of 0.74 kJ mol^{-1} favoring A, only slightly more than in ethanol. One would then expect that the NMR coupling constant would further decrease, but it was found to increase to 5.41 Hz.[13] This can be explained with the calculated structures: While the torsion angles ω_{CCOH} are similar in the A conformation of both alcohols, it increases to 67° in the B conformer of 2,2-dimethyl-1-propanol due to repulsion from the *tert*-butyl group. This makes the *gauche* HCOH torsion angle much smaller (ethanol 68°, 2,2-dimethyl-1-propanol 56°), increasing the coupling constant, whereas the anti HCOH torsion angle remains nearly unchanged (Fig. 2), and the observed coupling constant $(J_g + J_a)/2$ is considerably increased.[12]

In secondary alcohols the hydroxyl hydrogen can either be *gauche* to two alkyl groups (conformer C) or to one alkyl group and one hydrogen atom (conformer B). Our force field predicts that 2-*propanol* prefers the B conformation by 1.04 kJ mol^{-1}, again electrostatic interactions are essential for the results. Our value agrees well with a value of 1.16 kJ mol^{-1} which was deduced

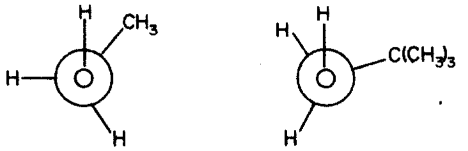

Fig. 2. *Gauche* isomers of ethanol and 2,2-dimethyl-1-propanol.

from quantitative microwave measurements,[19] and with the value obtained from the NMR coupling constant[12] (1.37 kJ mol^{-1}). The B conformer is calculated to have the same *gauche* CCOH torsion angle (56°) as ethanol. The energy obtained from quantum mechanical calculations[20] of 2.9 kJ mol^{-1} is in qualitative agreement.

In *2,2,4,4-tetramethyl-3-pentanol* the hydroxyl hydrogen is vicinally neighbored to two *tert*-butyl groups. At first it is surprising that the force field calculation finds the C form as the more stable one (by 1.32 kJ mol^{-1}). The NMR coupling constant agrees however with this result, as it increases from 4.20 Hz (isopropanol) to 6.55 Hz.[12] Analyzing the different interaction terms in the calculation, one finds that the electrostatic interactions, which were very important in the other molecules studied, balance out in this highly alkylated molecule. The two conformations only differ in their van der Waals energies which favor C. In C the *tert*-butyl groups are rotated out of the ideal staggered geometry, as has been found for example in tri-*tert*-butylmethane,[21] which relieves the repulsion between the *tert*-butyl groups. The hydroxyl proton, pointing in the direction of the *tert*-butyl groups, follows this deformation (an example of a gear effect) to a position with $\omega_{HCOH} = 162°$, far from the ideal anti torsion angle. For a quantitative analysis of the coupling constant it is clearly misleading to use 60° and 180° coupling constants. With the torsion angles from the force field calculation and Fraser's equation for the NMR coupling constant[13] an energy difference of 2.1 kJ mol^{-1} results between the conformations of 2,2,4,4-tetramethyl-3-pentanol, in very good agreement with the calculated value from molecular mechanics in view of the assumptions involved in the Karplus equation.[13]

Finally the conformations of *cyclohexanol* were calculated. While the equatorial conformers are unexceptional (as in 2-propanol the B conformation is the preferred one), the axial hydroxyl group has been a matter of controversy. In the IR spectrum only one band is found, which was interpreted to indicate absence of the *endo* conformer.[22] Both conformations have however the same frequency for the hydroxyl band, and Joris *et al.* give a relative energy of the *endo* conformer of only 0.4–1.7 kJ mol^{-1} over that of the *exo* form. This is what we find as the result of the molecular mechanics calculation (0.41 kJ mol^{-1}). From the results obtained for 2,2,4,4-tetramethyl-3-pentanol it might even have been expected that the *endo* conformer comes out more stable, but in cyclohexanol the bulky alkyl groups, which escaped into an unsymmetrical conformation in the open chain alcohol, are held in place as members of the ring. The *endo* conformer is calculated to have C_s symmetry, the repulsions from the syn-axial hydrogen atoms cannot be relieved by a simple rotation, making the *exo* (B) conformer more stable. The NMR coupling constant in axial cyclohexanols however is surprisingly small (3.05 Hz), and employing one of the Karplus functions[12,13] one would conclude that the energy difference is in fact 2.6 kJ mol^{-1}. This is unacceptable, even with a hydroxyl hydrogen van der Waals potential as big and hard as that of the hydrocarbon hydrogen[4] the energy difference is calculated only to be 1.20 kJ mol^{-1}. The only explanations we can offer are that the Karplus equation does not apply for such small coupling constants, or that solvation of the hydroxyl proton (the coupling constants were measured in dimethylsulfoxide) shifts the equilibrium.

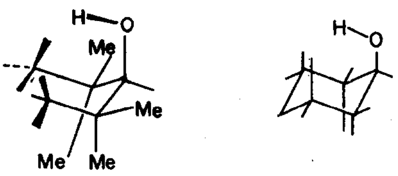

Fig. 3.

The calculated energy difference of equatorial and axial isomers of cyclohexanol is 2.15 kJ mol^{-1}, in good agreement with the "best value"[23] of 2.40 kJ mol^{-1} in aprotic solvents.

CONCLUSIONS

A molecular mechanics force field has been described which reproduces the rotamer behaviour of alcohols with various steric requirements very well. It seems most relevant that van der Waals interactions play only a secondary role for the conformational energies, and that instead electrostatic interactions are dominant. Unfortunately charges must be calculated by a quantum mechanical method, which is unfavorable for both the computer time required and the number of atoms which can be handled, empirical methods should however be in reach.[24]

The results of these and other molecular mechanics calculations illustrate that a first order prediction of conformational energies, which would rule out the C conformation of 2,2,4,4, - tetramethyl - 3 - pentanol and the *endo* conformation of axial cyclohexanols, is dangerous when molecular relaxation processes are important. The degree by which strain can be relieved by a deformation of the molecule can usually not be predicted and must be found from molecular mechanics calculations.

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