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The Conformational Preferences of Isomeric Naphthaldehydes as Determined by NOE Experiments

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Abstract. The analysis of the NOE effects based upon the interproton distances obtained by MM2 calculations yields a quantitative assessment of the conformer population of 1- and 2-naphthaldehydes (Z-conformer 85% and 12% respectively).

The combined use of Nuclear Overhauser Enhancement (NOE) and Molecular Mechanics calculations to quantitatively determine the relative population of two conformers in rapid equilibrium seems a rather promising approach to conformational analysis, despite the number of inherent approximations that are inevitably required.

Rather accurate results have been recently obtained[1] in a simple case but additional examples need to be produced to test the reliability of this approach. The isomeric 1- and 2- naphthaldehydes (1 and 2 respectively) were selected for a test in that their conformational preferences had been determined with two independent, reliable techniques: a Lanthanide Induced Shift (LIS) analysis[2] at room temperature in $CDCl_3$ and a direct C-13 NMR observation[3] at very low temperature, in freon. Another attractive reason for this choice was the fact that in 1 the major conformer has a structure (Z) which is opposite to that (E) found for compound 2: to be reliable the NOE determination must register this reversal in a quantitative manner.

Results and Discussion

The NOE values, determined with a differential technique as shown in Fig 1, are reported in Table 1 together with the relaxation times T_1.

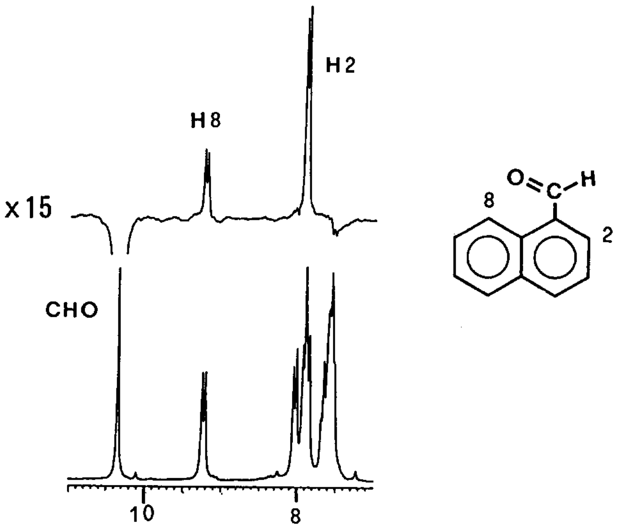

Figure 1. Differential NOE spectrum of 1 in $CDCl_3$ (upper trace 15-times enhanced) obtained on irradiation of the CHO signal. The control spectrum is shown underneath.

The ratio of the NOE's observed for the aldehyde signal, η(CHO), upon irradiation of the H2 and H8 signals in 1, and of the H1 and H3 signals in 2 can be considered, approximately, equal to the ratio of the cross relaxation rates that are proportional to the inverse 6th power of the average interproton distances.[4,5] Thus we have the relationship (1) for the case of 1:

$$2.9 \approx \eta^{H2}(CHO) \,/\, \eta^{H8}(CHO) \approx (\bar{r}_{H8,CHO})^6 \,/\, (\bar{r}_{H2,CHO})^6 \qquad (1)$$

An analogous equation, involving the distances between H3, H2 and CHO can be written for 2 where the corresponding ratio of NOE's is 5.6.

The NOE's experienced in 1 by the H2 and H8 signals on irradiation of the CHO signal yield a ratio $\left[\eta^{CHO}(H2) \,/\, \eta^{CHO}(H8) = 2.4_5\right]$ different from 2.9 in that, now, the observed protons have different relaxation times. However if the value is divided[5-7] by the ratios of the appropriate T_1 values, the same result is obtained (i.e. 2.8±.2) within the uncertainity due to T_1's. The fact that the same ratio is obtained from two independent measurements gives additional confidence to the internal consistency of the method, despite the assumed approximations. In the case of 2 the signals of H3 are buried under the lines of other protons: although a small NOE was detectable on irradiation of the CHO signal, its accurate quantitative determination was impossible.

Table 1. Selected NOE values (η), expressed as a percent of the original signals, and relaxation times T_1 determined in 1- and 2- naphthaldehydes in $CDCl_3$ at room temperature.

Compound	$T_1(s^{-1})$	Observed signals	Irradiated signals	NOE(η)
1	$4.9 \pm .15$	H2	CHO	9.8±.1
	$5.5_5 \pm .15$	H8	CHO	4.0±.1
	$4.1_5 \pm .15$	CHO	H2	10.2±.1
	$4.1_5 \pm .15$	CHO	H8	3.5±.1
2	$5.0 \pm .2$	H1	CHO	11.8±.1
	$6.5 \pm .3$	CHO	H1	14.6±.1
	$6.5 \pm .3$	CHO	H3	2.6±.1

The distances between the protons in each conformer were obtained by Molecular Mechanics calculations.[8] The relative energies computed for a pair of conformers may not agree with their relative stability in solution, owing to a variety of effects that can modify the situation with respect to the ideal case of an isolated molecule. On the other hand the bond lenghts and angles are much less affected, so that the computed distances can be confidently used to fit the experimental data. Thus, for instance, the H8,CHO distances are 3.56 and 2.19 Å and the H2, CHO distances 2.56 and 3.66 Å in the conformers Z and E, respectively, of compound 1.

The mean distance $\bar{r}_{H8,CHO}$ to be introduced in the equation (1) can be obtained by making the wheigthed average between the distances of the unequally populated conformers[9] (X being the amount of Z- and 1-X that of E-conformer):

$$\bar{r}_{H8,CHO} = \left[X \, (r^{Z}_{H8,CHO})^{6} + (1-X) \, (r^{E}_{H8,CHO})^{6} \right]^{1/6} \qquad (2)$$

A similar equation (3) exists for the H2, CHO distances.[10] By combining equations (1)-(3) the solution X ≈ 85% is obtained for 1 and, similarly, X ≈ 12% for 2. As shown in Table 2 the agreement with the previous values is quite good.

Table 2. Amount of the Z-conformer in 1 and 2 as determined by NOE experiments (this work) by LIS studies (Ref. 2) in the same solvent ($CDCl_3$) and temperature (25°) and by low temperature C-13 NMR in freon (Ref. 3).

Compound	This work	Ref. 2	Ref. 3
1 (Z)	85±2%	77%	90% (at -134°)
2 (Z)	12±2%	14%	20% (at -108°)

As observed in the case of ref. 1, also in these two examples the combined NOE and MM2 approach gives satisfactory quantitative results: the approximations assumed are probably not too unreasonable. The advantage of this method, with respect to other reliable techniques in solutions, lies in its simplicity, both on the experimental and computational side as well as in its vaste range of potential applications.

Experimental

The differential NOE experiments were carried out in nitrogen saturated $CDCl_3$ solutions at 200 MHz. The signals were presaturated for a time equal to 40 seconds. A program that accumulates the difference between two FID's (that of the preirradiated spectrum and the one with the irradiation far away) was employed. The T_1 values were obtained in the same sample with the inversion-recovery technique.

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9. Another analogous equation, linking the NOE ratio to the interproton distances, can also be used: [1,5,7] although both give essentially the same result we feel that the use of equation (2) is, in principle, more correct.
10. The MM2 computed distances of 2 are the following (in Å): r(3,CHO)= 3.84 and 2.41; r(H1,CHO)= 2.39 and 3.80 for E and Z respectively. The computed energy for the Z conformer of 2 is 0.12 Kcal/mol lower than that of the E conformer. As in the case of 1 (where E has a computed energy 0.5 Kcal/mol lower than Z) the calculated trend is opposite to the one found experimentally.