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NMR ASSIGNMENT OF DIASTEREOTOPIC PROTONS IN AMPHETAMINE BY THE USE OF Eu(fod)$_3$

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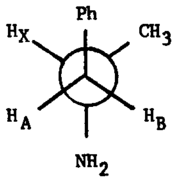
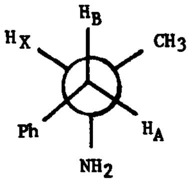
In the ABX nmr spectra of amphetamines and related compounds, a problem arises in the assignment of individual A and B protons since usually there is no a priori reason to assign one "quartet" to one or the other of the diastereotopic protons. (Suggestions have been made, however, that the A proton in (R)-amphetamines, as labelled in structures I and II, corresponds to the upfield signal in the nmr spectra of amphetamine hydrochlorides in deuterochloroform[1].) Conformational studies[1,2] based on nmr are, consequently, equivocal since the vicinal coupling constants, J_{AX} and J_{BX}, are not uniquely assigned. Because of the net difference between the distances and angles from a bound lanthanide atom and nearby diastereotopic protons, however, it should be possible to distinguish the individual diastereotopic protons by differential lanthanide induced shifts. Such differential induced shifts have recently been reported[3] for diastereotopic protons in some β-lactams.



I



II

Considering the two major[1] rotamers of (R)-1-amphetamine (I,II), the methylene proton A will be on the average closer to the amino group and, presumably, closer to a bound lanthanide atom than the B proton. This will be true regardless of the relative populations of the two conformers - the difference in magnitude of the induced shifts will be partially a function of the conformer distribution. The AB portion of the nmr spectrum[4] of 1-amphetamine in deuterochloroform is centered at 2.63 ppm and exhibits a chemical shift difference $|\nu_A-\nu_B|$ = 11.7Hz (calculated as ABX). Addition of incremental amounts of Eu(fod)$_3$ to the solution causes this difference to decrease until, at $\nu_A-\nu_B = 0$, the AB signals become a doublet. The lanthanide induced shifts of 1-amphetamine (extrapolated to 1:1 mole ratio) are: NH_2, 100.9 ppm; CH_3, 26.8 ppm; H_X, 26.4 ppm; H_A, 17.5 ppm, and; H_B, 11.7 ppm. Since the upfield AB proton is shifted to a greater extent than the downfield one, we conclude that it corresponds to proton A in the structures. A plot of $\nu_A-\nu_B$ vs mole ratio of Eu(fod)$_3$:amphetamine at very low (<.013 M) shift reagent concentrations gives 0.032 as the mole ratio where $\nu_A = \nu_B$. From the same plot, $\nu_A-\nu_B$ at 1:1 mole ratio turns out to be 6.45 ppm which compares reasonably well with the difference in extrapolated induced shifts (5.8 ppm). The difference in induced shifts is not linear at higher lanthanide concentrations since the rotamer distribution is undoubtedly changing. Furthermore, deductions of conformation based on purely pseudocontact interaction and simple 1:1 stoichiometry in shift reagent : substrate binding may not be strictly valid.[5] These aspects are being pursued further.

The assignment of the upfield AB signal as the A proton of 1-amphetamine allows unique assignment of J_{AX} and J_{BX} in this and related compounds. Thus, in the above case where $\nu_A-\nu_B$ = 11.7 Hz, J_{AX} = 9.22 Hz and J_{BX} = 4.78 Hz. Calculation[6] of conformer distribution gives 72% I and 28% II, in agreement with the magnitudes given by Bailey, et al.[1]

References

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2. G. A. Neville, R. Deslauriers, B. J. Blackburn and I. C. P. Suiter, J. Med. Chem. 14, 717 (1971).
3. A. K. Bose, B. Dayal, H. P. S. Chawla and M. S. Manhas, Tetrahedron Lett., 3599 (1972).
4. NMR spectra were determined at ambient temperature on a JEOL C60-HL spectrometer, external lock. 1-Amphetamine concentration was 0.63 M. TMS was used as internal standard. Eu(fod)$_3$ was purchased from Norell Chemical Co.
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6. The parameters used were those of ref. 1: J_t = 12.0 Hz and J_g = 2.0 Hz.