Analysis of NMR Spectra for Rotamer Populations of Dimethoxyamphetamines

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Abstract □ The side chain of amphetamines gives an NMR spectrum analyzed as an *ABX* pattern. The method used for obtaining relative populations of rotamers about the α,β-bond from the spectrum is described, and results are presented for dimethoxyamphetamines. The data do not show any correlation between psychotropic activity and relative rotamer populations.

Keyphrases □ Amphetamines, dimethoxy-, rotamers—NMR spectroscopy, analysis □ Dimethoxyamphetamine rotamers—NMR spectroscopy, analysis, *ABX* pattern □ Psychotropic activity—dimethoxyamphetamine conformational behavior □ Conformational analysis, NMR spectroscopy—dimethoxyamphetamine rotamers □ NMR spectroscopy—analysis, dimethoxyamphetamine rotamers

Methods for the conformational analysis of organic molecules by consideration of their NMR spectra are well known (1, 2). Among biologically important open-chain compounds, the conformations of acetylcholine (3) and some isologs (4) have been studied. Diastereoisomers with protons on adjacent asymmetric carbons have received attention (5–11); for such compounds, the ratio of that rotamer with *trans*-disposition of the vicinal protons to the two rotamers with *gauche*-arrangement may be estimated from the observed mean vicinal coupling constant (1, 5). The effects of intramolecular hydrogen bonding on conformational behavior have been considered for ethane-1,2-diols (7), ephedrines (9, 10), and chloramphenicols (11). Interest in amphetamines led to the attempt to measure their relative rotamer populations using NMR data. Intramolecular hydrogen bonding between an *ortho*-methoxyl oxygen atom and the amino protons has been suggested (12) as modifying the conformational behavior of such psychotropic compounds.

DISCUSSION

In principle, it is possible to estimate relative populations of the three rotamers, 1, 2, and 3, shown in Newman projection (Fig. 1) for amphetamines $\mathrm{ArCH_2CH(CH_3)NH_2}$, provided that the diastereotopic methylene protons can be identified and distinguished from one another in the NMR spectrum. Let the mole fraction of Rotamer 1 be a, of 2 be b, and of 3 be c (Fig. 1). In every rotamer, all *trans*-$J\alpha,\beta$ are approximately equal (to Jt), and all *gauche*-$J\alpha,\beta$ are approximately equal (to Jg) (2). Then, where $J\alpha_1,\beta$ and $J\alpha_2,\beta$ are the two observed (mean) vicinal couplings:

$$J\alpha_1,\beta = a \cdot Jt + b \cdot Jg + c \cdot Jg \quad \text{(Eq. 1)}$$

$$J\alpha_2,\beta = a \cdot Jg + b \cdot Jt + c \cdot Jg \quad \text{(Eq. 2)}$$

$$1 = a + b + c \quad \text{(Eq. 3)}$$

Rearrangement gives:

$$a = \frac{J\alpha_1,\beta - Jg}{Jt - Jg} \quad \text{(Eq. 4)}$$

$$b = \frac{J\alpha_2,\beta - Jg}{Jt - Jg} \quad \text{(Eq. 5)}$$

$$c = \frac{Jt + Jg - (J\alpha_1,\beta + J\alpha_2,\beta)}{Jt - Jg} \quad \text{(Eq. 6)}$$

Using values for Jt and Jg obtained from suitable model compounds, c may be estimated; but unless the two observed $J\alpha,\beta$ couplings can be unambiguously assigned to the protons α_1H and α_2H, as depicted in Fig. 1, the values obtained for a and b can be assigned to either Rotamers 1 and 2 or 2 and 1. Secondary information from known steric preferences and/or observed chemical shifts assists in the definition. Data from the NMR spectra of five

Table I—NMR Spectral Data[a] for Dimethoxyamphetamines

Compound	β-CH_3 (Doublet)	NH_2	2αH (2 Double Doublets)	β-H (Multiplet)	$ArOCH_3$
2,3-Dimethoxyamphetamine	8.88 (6.0)	8.12	7.44 (−12.7, 8.7) 7.30 (−12.7, 4.1)	6.81	6.18, 6.16
2,4-Dimethoxyamphetamine	8.92 (6.0)	8.35	7.54 (−13.0, 8.2) 7.36 (−13.0, 4.6)	6.84	6.22, 6.22
2,5-Dimethoxyamphetamine	8.91 (5.8)	8.08	7.51 (−12.5, 8.4) 7.35 (−12.5, 4.4)	6.83	6.29, 6.29
3,4-Dimethoxyamphetamine	8.89 (6.0)	7.90	7.53 (−13.0, 8.4) 7.35 (−13.0, 4.5)	6.85	6.15, 6.15
3,5-Dimethoxyamphetamine	8.88 (6.0)	8.09	7.57 (−13.0, 8.5) 7.37 (−13.0, 4.3)	6.83	6.25, 6.25

[a] τ-values, measured with a Varian A-60A spectrometer using solutions about 15% in $CDCl_3$ at 40° containing tetramethylsilane as internal standard. Coupling constants (Hz., signs by analogy with known systems) calculated as described are thought accurate ±0.1 Hz. The NH_2 protons (τ-concentration dependent) exchanged with D_2O with no other change in τ or J values. Appropriate aromatic signals and integration ratios were observed. The (unreported) 2,6-dimethylamphetamine has not yet been obtained.

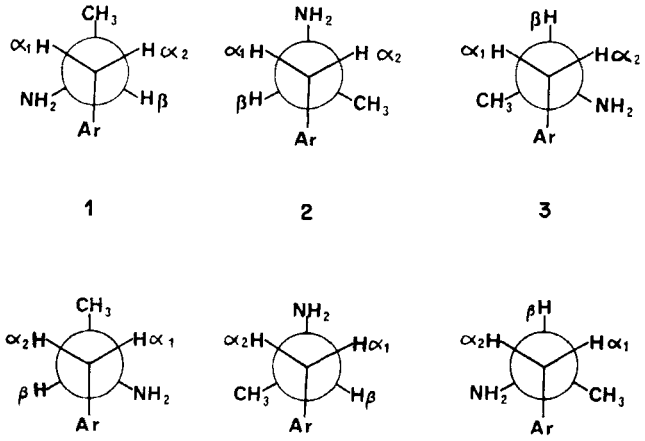
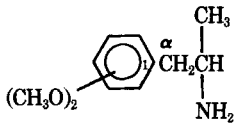


Figure 1—*Staggered rotamers for R (lower) and S (upper) amphetamines.*

dimethoxyamphetamines (two aromatic methoxyl groups) are summarized in Table I. The side-chain spectral type is that for fast rotation, unequal populations (2). The two α- (benzylic) protons and the β-proton give signals ($\alpha_1\alpha_2\beta$) analyzable as *ABX* (at 60 MHz., $\nu\alpha_1 - \nu\alpha_2 \simeq 20$ Hz.; $J\alpha_1, \alpha_2 \simeq -13$ Hz.; $\nu\alpha - \nu\beta \simeq 30$ and 40 Hz.). Only the eight-line *AB* ($\alpha_1\alpha_2$) portion was used here because the *X* (β-proton) part is complicated by further coupling with the β-CH_3 protons. The calculated *a*, *b*, and *c* are sensitive to $J\alpha_1\beta$ and to $J\alpha_2\beta$ (and to *Jt* and *Jg*), so a first-order analysis of the spectrum would give results in some error; thus, the two first-order $J\alpha,\beta$ are about 7.7 and 5.2 Hz., but calculation of the *ABX* type gives values of about 8.5 and 4.3 Hz. (Table I). The calculated *a*, *b*, and *c* of Table II (at once approximate because of the approximations made in deducing Eqs. 1 and 2) were obtained using 12 and 2 Hz. for *Jt* and *Jg*, respectively (5). Even if these chosen values are in error, the results will be of the right order and the direction of any observed changes will be correct[1]. If α_1H as shown is the proton with greater $J\alpha,\beta$ (observed at higher field), then on the average $a = 0.65$, $b = 0.23$, and $c = 0.12$ (Rotamer 1 dominates); if α_1H as shown is the proton with lower $J\alpha,\beta$ (observed at lower field), then $a = 0.23$, $b = 0.65$, and $c = 0.12$ (Rotamer 2 dominates). A *gauche*-β-CH_3 will have a weakly shielding effect (compared with H), and a *gauche*-β-NH_2 will have a more strongly deshielding effect on the α-protons (9, 13). Inspection of Rotamers 1, 2, and 3 (Fig. 1) and summing effects of either $b > a$ or $a > b$ shows that α_1H will be that at lower field *on this basis;* therefore, $J\alpha_1,\beta < J\alpha_2,\beta$ and, hence, $b > a > c$. The dominance of Rotamer 2 may be due to electrostatic repulsion between the electronegative amino and electronegatively substituted aryl groups, since CH_3 and NH_2 exert similar steric effects; this work seems to provide the first experimental confirmation of theoretical predictions (14) that the nitrogen atom of these compounds is antiplanar to the phenyl ring.



dimethoxyamphetamine

According to the model of Snyder and Richelson (12) for psychotomimetic activity of methoxyamphetamines, hydrogen bonding of the amino protons with a 2-methoxyl group favors a side-chain conformation approximating ring C of LSD. Such hydrogen bonding may occur in Rotamers 1 and 3 (possibly with some deformation) but not 2. An additional 3-methoxyl group will hinder this (12). Consequently, the model predicts that Rotamers 1 and 3 may contribute more to the mean for both 2,4- and 2,5-dimethoxyamphetamine than they do for 2,3-, 3,4-, or 3,5-dimethoxyamphetamine. Any marked changes in the true rotamer populations would be reflected in the observed coupling constants and, hence, the calculated rotamer populations in Table II (*e.g.*, a 10% change in Rotamer 1 or 2 would alter the corresponding *J* by about 1 Hz.). Differences in these figures are very small and about the same as the estimated error (arising in $J\alpha,\beta$) using the present technique; the results indicate little difference in the conformations of the dimethoxyamphetamines as free bases in an aprotic medium. This approach will be extended using different amphetamines, solvents, pH's, *etc.* Since the benzylic protons are distinguishable, such analyses may help in evaluating structure–activity relationships in the nature of the enzymic process in amine-β-hydroxylation of amphetamines to norephedrines, *etc.*

Table II—Calculated Rotamer Populations (Percent) for Dimethoxyamphetamines[a]

Compound	Rotamer 1	Rotamer 2	Rotamer 3
2,3-Dimethoxyamphetamine	21 (67)	67 (21)	12
2,4-Dimethoxyamphetamine	26 (62)	62 (26)	12
2,5-Dimethoxyamphetamine	24 (64)	64 (24)	12
3,4-Dimethoxyamphetamine	25 (64)	64 (25)	11
3,5-Dimethoxyamphetamine	23 (65)	65 (23)	12

[a] Solutions about 15% in $CDCl_3$ at 40°. Figures in parentheses apply if α_1H and α_2H, as shown in Fig. 1, are oppositely assigned.

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[1] During the preparation of this communication, J. E. Forrest, R. A. Heacock, and T. P. Forrest, *J. Pharm. Pharmacol.*, **22,** 512(1970), reported data for some adrenalin derivatives, neglecting rotamers of type 3. A first-order analysis was made, although $\nu\beta_1 - \nu\beta_2 \simeq 5$ Hz. and $J\beta_1,\beta_2$ (not reported) would be $\simeq -13$ Hz. Values of 9 and 2.5 Hz. for *Jt* and *Jg*, respectively, were obtained from the spectrum of adrepine which was assumed to exist as one rotamer of the 1 or 2 type.