^{13}C NMR Spectra and Structure of Mono-, Di- and Trimethoxyphenylethylamines and Amphetamines

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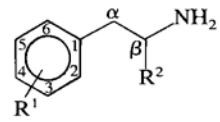
Carbon-13 and proton chemical shifts of mono-, di- and trimethoxylated phenylethylamines (PEAs) and their hydrochlorides were determined and the signals were assigned and are reported. The data are interpreted to indicate that the side-chains of PEA derivatives and amphetamine salts have the amino and aromatic moieties predominantly *trans* (antiperiplanar), that 'sandwiched' OCH_3 groups and side-chains are forced out of the ring plane and that planar *ortho*-OCH_3 groups have their electron lone pairs oriented toward the side-chain and partially stabilize *gauche* rotamers. It is suggested that the location and density of electronic charges just outside the aromatic ring will significantly affect interactions with putative receptors.

Substituted amphetamines and phenylethylamines (phenethylamines, PEA) have been the subject of extensive investigations into structure–activity relationships.[1,2] Some compounds of this type are endogenous and associated with neurotransmission; others, such as mescaline (3,4,5-TMPEA, Fig. 1, where TMP = trimethoxyphenyl), are hallucinogenic and subject to abuse. ^{1}H NMR spectra of substituted PEA[3] and amphetamines[4,5] have been reported and interpreted in terms of changes in the conformational behaviour of the side-chain. As part of a programme of authentication of reference materials for forensic drug analysis, we determined the ^{13}C NMR spectra of the fifteen mono-,[6] di-[6] and trimethoxyamphetamines[7] (MA, DMA and TMA, respectively). We have now extended this to an examination of PEA and its mono-, di- and trimethoxy derivatives (MPEA, DMPEA, and TMPEA, respectively; Fig. 1). An examination of systematic trends and variations in the data reveals effects that are indicative of structural changes related to the changes in substitution. The findings may be relevant to studies that have attempted to relate conformational changes to the differing activities of these compounds.[1]



Phenethylamine, PEA; $R^1 = R^2 = H$
Amphetamine, A; $R^1 = H$, $R^2 = CH_3$
Methoxy-PEA; $R^1 = (OCH_3)_n$, $R^2 = H$
Methoxy-A; $R^1 = (OCH_3)_n$, $R^2 = CH_3$

Figure 1. Structures of phenylethylamines and amphetamines.

RESULTS AND SIGNAL ASSIGNMENTS

Data from the ^{13}C NMR spectra of the PEA derivatives are presented in Table 1. The series is complete except for 2,3,5-TMPEA, for which no sample was available. Data from PEA itself and 2,3-DMPEA have been reported previously.[6] Assignments of C-α (range 27.0–40.4 ppm) and C-β (range 41.5–43.5 ppm) were made by simple comparison with the corresponding amphetamines.[6,7] The methoxy signals appeared between 55.3 and 59.3 ppm, except for signals between 60.7 and 64.1 ppm that arose among compounds having 'sandwiched' methoxy groups. Assignments were tentatively made (Table 1) by best-fit comparisons with the MPEA, 2,6-DMPEA, 3,5-DMPEA, 2,4,6-TMPEA and 3,4,5-TMPEA results, as these are unambiguous.

The assignments of the aromatic carbon signals were made by an internally consistent analysis based on approximately additive shielding effects of the substituent groups. Examples of the method have been fully described for corresponding methoxyamphetamines,[6,7] methoxynitrostyrenes[8] and methylamphetamines.[9] Some provisional assignments for closely similar chemical shifts are discussed in more detail below. Proton decoupling experiments were not helpful in these cases, because the carbons under consideration were either both substituted or the ^{1}H NMR signals overlapped and could not be assigned.

In the case of PEA itself, the stepwise addition of a chemical shift reagent (total 85 mg) resulted in progressively increasing downfield shifts of the signals ascribed to C-4, C-3,5, C-2,6 and C-1 (of 0.49, 0.46, 0.21 and 0.21 ppm, respectively), in agreement with their proximity to the site of pseudo contact (the amino function[10]). This confirms the similarity of the chemical shifts at C-3 and C-5 (*meta* to the side-chain) in PEA and amphetamine that was contended previously.[6] This principle[11] strongly supports the following assignments tentatively proposed in the amphetamine series: C-3 and C-5 of 3,4-DMPEA and 3,4-DMA,[6]

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Table 1. Data from the ^{13}C NMR spectra of methoxyphenylethylamines[a]

	Signal												
	C-1	C-2	C-3	C-4	C-5	C-6	α-CH_2	β-CH_2	OCH_3[b]		OCH_3[b]		OCH_3[b]
PEA	139.99	129.05	128.75	126.44	128.75	129.05	39.84	43.24					
PEA·HCl	139.50	131.67	131.85	130.15	131.85	131.67	35.35	43.24					
2-MPEA	128.33	158.08	110.71	127.72	120.73	130.75	34.43	41.90	55.39	(2)			
2-MPEA·HCl	127.66	160.33	114.42	131.91	124.01	133.67	30.55	42.39	58.30	(2)			
3-MPEA	141.63	114.90	160.15	111.75	129.66	121.46	40.02	43.18	55.27	(3)			
3-MPEA·HCl	141.32	117.45	162.15	115.69	133.18	124.50	35.41	43.24	58.18	(3)			
4-MPEA	131.79	129.97	114.24	158.51	114.24	129.97	38.51	43.24	55.39	(4)			
4-MPEA·HCl	131.97	132.94	117.33	160.82	117.33	132.94	34.56	43.42	58.18	(4)			
2,3-DMPEA	133.79	147.88	153.16	111.02	124.07[c]	122.62[c]	34.19	42.69	60.73	(2)	55.81	(3)	
2,3-DMPEA·HCl	133.24	149.52	155.29	115.39	128.20	125.35[c]	30.06	42.69	63.65	(2)	58.67	(3)	
2,4-DMPEA	120.79	159.00[c]	98.99	159.97[c]	104.40	131.00	33.45	42.21	55.51	(2)	55.51	(4)	
2,4-DMPEA·HCl	120.43	161.42[c]	101.79	162.64[c]	108.41	134.22	30.00	42.57	58.42	(2)	58.42	(4)	
2,5-DMPEA	129.72	152.44[c]	111.81	111.81	153.95[c]	117.27	35.10	42.15	56.18[d]	(2)	55.87[d]	(5)	
2,5-DMPEA·HCl	129.18	154.88[c]	116.06[d]	116.48[d]	156.08[c]	119.76	30.61	42.39	59.21[e]	(2)	58.85[e]	(5)	
2,6-DMPEA	116.54	159.06	104.03	127.48	104.03	159.06	27.21	41.48	55.81	(2)	55.81	(6)	
2,6-DMPEA·HCl	115.51	161.18	107.56	131.91	107.56	161.18	23.20	42.01	58.73	(2)	58.73	(6)	
3,4-DMPEA	132.82	112.66[c]	149.46[d]	148.00[d]	111.93[c]	121.10	39.60	43.48	56.18[e]	(4)	56.06[e]	(3)	
3,4-DMPEA·HCl	132.52	115.33[c]	151.28[d]	150.19[d]	115.09[c]	124.38	35.04	43.42	58.55	(3)	58.55	(4)	
3,5-DMPEA	142.54	107.25	161.30	98.51	161.30	107.25	40.39	43.18	55.39	(3)	55.39	(5)	
3,5-DMPEA·HCl	142.23	110.17	163.43	101.91	163.63	110.17	35.59	43.06	58.24	(3)	58.24	(5)	
2,3,4-TMPEA	126.08	152.50[c]	142.84	152.74[c]	107.74	124.56	34.19	42.88	61.03[d]	(3)	60.85[d]	(2)	56.24 (2)
2,3,4-TMPEA·HCl	125.65	154.14[c]	144.48	155.35[c]	111.81	128.20	30.00	42.75	64.13[d]	(3)	63.77[d]	(2)	58.91 (4)
2,3,6-TMPEA	122.98	148.85[c]	147.52[c]	110.77	105.73	152.92	28.36	42.03	60.85	(2)	56.42[d]	(3)	55.99[d] (6)
2,3,6-TMPEA·HCl	122.13	150.31[c]	149.52[c]	115.45	110.23	154.99	24.11	42.21	63.89	(2)	59.09[d]	(3)	58.97[d] (6)
2,4,5-TMPEA	120.13	152.38	98.63	148.61	143.45	115.45	34.07	42.39	56.97[c]	(4)	56.48[c]	(5)	56.48[c] (2)
2,4,5-TMPEA·HCl	119.34	154.93	101.42	151.22	145.21	117.88	30.12	42.69	59.27[c]	(4)	59.27[c]	(5)	59.79 (5)
2,4,6-TMPEA	109.01	159.61	90.98	160.03	90.98	159.61	26.96	41.78	55.81	(2)	55.81	(6)	55.51 (4)
2,4,6-TMPEA·HCl	108.16	161.91	94.13	162.94	94.13	161.91	22.96	42.33	58.61	(2)	58.61	(6)	58.36 (4)
3,4,5-TMPEA	135.86[c]	106.28	153.65	137.07	153.65	106.28	40.39	43.30	60.97	(4)	56.30	(3)	56.30 (5)
3,4,5-TMPEA·HCl	136.34[c]	109.32	155.59	138.83	155.59	109.32	35.77	43.30	63.71	(4)	58.97	(3)	58.97 (5)

[a] The bases were examined in $CDCl_3$ and the salts in D_2O; see text for method of assignment.
[b] The numbers in parentheses refer to the assigned position of substitution.
[c,d,e] It is emphasized that these assignments may be reversed.

C-3 of 2,5-DMPEA and 2,5-DMA[6] and C-3 of 2,3,6-TMPEA and 2,3,6-TMA.[7]

The position of attachment of the methoxy groups was marked by the lowest field signals. Tentative assignments (Table 1) were made by comparisons with the unambiguous results for the MPEA derivatives and symmetrically substituted DMPEA and TMPEA derivatives. The important assignments of C-2 and C-3 of 2,3-DMPEA were based on the proposition that the shielding effects of the C-2 substituent should be approximately equal at C-1 and C-3.[6,8] If C-2 absorbs at 147.88 ppm and C-3 at 153.16 ppm, the 2-methoxy group shields C-1 and C-3, relative to 3-MPEA, by 7.84 and 6.99 ppm, respectively; with the reversed assignments the shieldings would be 7.84 and 12.27 ppm, respectively. The former assignment is therefore strongly favoured (Table 1).

The assignments of C-1 and C-4 of 3,4,5-TMA were proposed on the basis of the best fit to predicted chemical shifts, and those for 3,4,5-TMPEA were made initially by simple comparison. Supporting evidence was obtained by determining the spectra of benzaldehyde (B), 4-methoxybenzaldehyde (4-MB) and 3,4,5-trimethoxybenzaldehyde (3,4,5-TMB), in which the C-1 and C-4 signals were unambiguously identified at 136.74 and 134.67, 130.30 and 164.98, and 132.09 and 144.15 ppm, respectively. Thus, there is a relative shielding of 1.79 ppm at C-1 and a deshielding of 20.83 ppm at C-4 for 4-MB in comparison with 3,4,5-TMB. The corresponding differences for these signals are 4.07 and 21.44 ppm in 4-MPEA relative to 3,4,5-TMPEA (5.28 and 22.65 ppm with the reversed assignments) and 3.64 and 21.50 ppm in 4-MA relative to 3,4,5-TMA (5.04 and 22.90 ppm with the reversed assignments). Similarly, the C-1 and C-4 signals of 3,4,5-TMB are shifted upfield by 4.65 ppm and downfield by 9.48 ppm, respectively, from their positions in B. The corresponding differences for 3,4,5-TMPEA vs PEA are 4.13 and 10.63 ppm (2.92 and 9.42 ppm with the reversed assignments) and for 3,4,5-TMA vs amphetamine are 4.20 and 10.63 ppm (2.80 and 9.23 ppm with the reversed assignments). Similar calculations can be made from data published for methoxybenzenes.[11] The minimum discrepancies are obtained using the assignments proposed in Table 1, which are in agreement with those deduced for 3,4,5-TMPEA.HCl by Levy *et al.*[12]

SPECTRAL PARAMETERS AND STRUCTURAL EFFECTS

Comparisons among isomers and between series reveal differences which are the net result of several

Table 2. Effect of γ-CH_3 on chemical shifts (ppm)[a]

Substituent[b]	C-1	C-2/6 (ortho)	C-3/5 (meta)	C-4 (para)	C-α	C-β
None	*−0.06*	0.49/0.49	0/0	0.06	6.80	5.16
2-	*0.12*	*0.06*/0.67	0/−0.06	0.12	6.69	5.17
3-	*0*	0.43/0.49	*0*/0	0.06	6.74	5.10
4-	*0.30*	0.54/0.54	0/0	*0.12*	7.22	5.28
2,3-	*0*	*0.18*/0.54	*0.07*/−0.06	0.06	6.56	5.11
2,4-	*0.06*	*0.06*/0.67	−0.06/−0.12	*0*	6.56	4.98
2,5-	*0*	*0.06*/0.43	−0.06/*−0.12*	−0.06	6.20	4.98
2,6-	*0.13*	*0.06*/*0.06*	0/0	0.06	6.19	5.71
3,4-	*−0.06*	0.36/0.48	*0*/−0.06	*0.06*	6.68	4.98
3,5-	*0*	0.43/0.43	*0*/*0*	0.06	6.74	5.10
2,3,4-	*−0.25*	*0*/0.49	*−0.06*/−0.19	*−0.06*	6.32	4.85
2,3,6-	*0.06*	*0.12*/*0.06*	*0*/−0.06	0.06	6.13	5.46
2,4,5-	*−0.19*	*0*/0.49	−0.06/*−0.06*	*0.06*	6.19	5.04
2,4,6-	*0.18*	*0.11*/*0.11*	0/0	*0.06*	6.20	5.53
3,4,5-	*−0.13*	0.42/0.42	*−0.13*/−0.13	*0.06*	6.61	5.04

[a] The chemical shift of the PEA was subtracted from that of the A. Negative signs indicate that upfield shifts result on introducing the γ-CH_3. Italicized figures refer to substituted aromatic positions.
[b] Numbers indicate position of OCH_3 attachment.

changes that occur in conjunction; nevertheless, examination of the very large data base now available does reveal effects that can be regarded as occurring independently.

Effects of the γ-CH_3

Comparison of data from amphetamines and the corresponding phenylethylamines reveals little effect on C-1 of the bases (Table 2), but C-1 of the amphetamine salts is 0.4–0.8 ppm upfield (γ-shielding effect[13]). There is a consistent downfield shift at the *ortho* carbons in amphetamines with a definite gradation toward a larger effect at the non-substituted (more accessible) positions. This generalization supports the tentative assignments of C-2 and C-6 of 2,5-DMPEA (Table 1) and 2,5-DMA.[6] Similar results were obtained from the salts (not tabulated). This does not have a counterpart in any apparent influence of *ortho*-OCH_3 groups on the chemical shifts of C-γ, but seems to be an example of the deshielding δ effect (the γ-CH_3 is δ to the *ortho* carbons).[13,14] There are modest (<0.3 ppm) influences trending toward upfield *meta* and downfield *para* shifts in the amphetamines. Differential effects in the side-chain occur for C-β such that the amphetamine signal is relatively downfield and/or the phenylethylamine signal relatively upfield to a larger extent than usual in the 2,6-, 2,3,6- and 2,4,6-methoxylated compounds—both bases and salts. Since there seems to be no intermediate effect for the mono-*ortho*-methoxylated compounds, the observation might be a reflection of C-β being forced out of the aromatic ring plane (torsional rotation about the benzylic bond) by the two flanking OCH_3 groups to different extents—presumably greater in the amphetamine series. There is no obvious effect at C-α which is related to this structural change (Table 2).

Effects of OCH_3 groups

The data in Table 1 and the data from amphetamines[6,7] can be manipulated to give a very large set of data showing the effect of *ortho*-, *meta*- and *para*-OCH_3 groups on one another and on side-chain and aromatic carbon chemical shifts. There is little difference between the chemical shifts of methoxy groups that have one *ortho* methoxy substituent and those that have none (ranges 55.81–56.97 and 55.27–56.48 ppm, respectively; Table 1). Methoxy groups that are sandwiched between two *ortho* substituents are relatively deshielded by about 5 ppm (range 60.70–61.03 ppm; Table 1). While this manuscript was in preparation, Knittel and Makriyannis[15] reported data for the OCH_3 signals of 2-MPEA and 2,3,4- and 3,4,5-TMPEA (mescaline) hydrochlorides in D_2O. They obtained excellent evidence from relaxation time measurements that sandwiched OCH_3 groups are forced to adopt a conformation in which the O—CH_3 bond is essentially perpendicular to the ring plane; this is accompanied by downfield shifts of approximately 5 ppm. Our data, therefore, indicate that one *ortho* substituent has a minimal effect on the overall extent to which the methoxy group is in the ring plane.

The more notable side-chain data are given in Table 3. Since methoxylation has little effect at C-γ and *para* methoxylation has little effect at C-β, these data are omitted. *ortho*-Methoxylation results in upfield shifts of C-α and C-β, and the effects at C-α and C-β are relatively enhanced and diminished, respectively, when a second *ortho*-OCH_3 group is introduced (Table 3). Analogous results were found for methylation in a

Table 3. Effects of methoxy substitution on chemical shifts of side-chain carbon signals[a]

ortho Methoxylation:										
	2/0	2,3/3	2,4/4	2,5/3	2,6/2	2,3,4/3,4	2,3,5/3,5	2,3,6/2,3	2,4,5/3,4	2,4,6/2,4
C-α	−5.52−*5.41*	−6.01−*5.83*	−5.22−*4.56*	−5.46−*4.92*	−7.72−*7.22*	−5.77−*5.41*	−5.71[b]	−6.26−*5.83*	−6.02−*5.53*	−7.35−*6.99*
C-β	−1.33−*1.34*	−0.48−*0.49*	−1.33−*1.03*	−1.15−*1.09*	+0.12−*0.42*	−0.73−*0.60*	−0.48[b]	−0.31−*0.66*	−1.03−*1.09*	+0.12−*0.43*
meta Methoxylation:										
	3/0	2,3/2	2,5/2	3,4/4	3,5/3	2,3,4/2,4	2,3,5/2,3	2,3,5/2,5	2,3,6/2,6	2,4,5/2,4
C-α	+0.12+*0.18*	−0.37−*0.24*	+0.18+*0.67*	+0.55+*1.09*	+0.37+*0.37*	0.00+*0.24*	+0.67[b]	+0.12[b]	+1.09+*1.15*	+0.25+*0.12*
C-β	−0.12−*0.06*	+0.73+*0.79*	+0.06+*0.25*	−0.06+*0.24*	0.00 *0.00*	+0.54+*0.67*	0.00[b]	+0.67[b]	+0.30+*0.55*	+0.26+*0.18*
para Methoxylation:										
	4/0	2,4/2	3,4/3	2,3,4/2,3	2,4,5/2,5	2,4,6/2,6	3,4,5/3,5			
C-α	−0.91−*1.33*	−0.61−*0.48*	−0.48−*0.42*	−0.24 *0.00*	−1.04−*1.03*	−0.24 *0.25*	−0.12 *0.00*			

[a] Values in italics are for PEA derivatives, the remainder for amphetamines; the symbolism 2/0, etc., indicates that the chemical shift of the unsubstituted compound ('0') was subtracted from that of the 2-OCH_3 compound ('2') and so on. Positive and negative signs indicate that downfield and upfield shifts, respectively, result from the substitution.
[b] 2,3,5-TMPEA not available.

Table 4. Directional *ortho* shielding effects of OCH_3 groups in phenylethylamines

Compound	C-2		C-3		C-4		C-5		C-6		
	C-1	C-3	C-2	C-4	C-3	C-5	C-4	C-6	C-5	C-1	Σ-effects
2-MPEA	11.66	18.04									29.70
3-MPEA			14.15	14.69							28.84
4-MPEA					14.51	14.51					29.02
2,3-DMPEA	7.84	6.99	10.20	16.70							14.83, 26.90
2,4-DMPEA	11.00	15.25			11.72	16.33					26.25, 28.05
2,5-DMPEA	11.91	17.85					15.91	13.48			29.76, 29.39
2,6-DMPEA	11.79	16.70							16.70	11.79	28.49, 28.49
3,4-DMPEA			17.31	10.51	10.69	17.73					27.82, 28.42
3,5-DMPEA			14.21	13.24			13.24	14.21			27.45, 27.45
2,3,4-DMPEA	6.74	6.62	6.50	7.23	10.32	16.33					13.36, 13.73, 26.65
2,3,6-TMPEA	6.74	6.43	10.21	16.71					18.34	10.81	13.17, 26.92, 29.15
2,4,5-TMPEA	12.69	13.30			13.18	10.50	11.36	15.55			25.99, 23.68, 26.91
2,4,6-TMPEA	11.78	13.42			13.05	13.05			13.42	11.78	25.20, 26.10, 25.20
3,4,5-TMPEA			14.82	10.93	7.65	7.65	10.93	14.82			25.75, 15.30, 25.75

series of methylamphetamines.[9] These observations can be related to the torsional effects in the side-chain suggested previously, since less shielding of C-β is expected if it is forced out of the ring plane. An OCH_3 group introduced between the side-chain and an existing 3-OCH_3 group (e.g. 2,3/3, Table 3) has diminished effective shielding at C-β. Sandwiched OCH_3 groups of this type are thought to be forced out of the ring plane.[15]

The introduction of a *meta*-OCH_3 group generally results in downfield shifts of C-α and C-β (Table 3). The effect at C-β is usually largest in the *ortho* methoxylated pairs, e.g. 2,3/2, which is probably associated with secondary effects due to the 2-OCH_3 group being forced out of plane.

para-Methoxylation results in an upfield shift of C-α (Table 3), with a variation in magnitude that is the same in both series. Data for the salts (not tabulated) are similar to those for the bases, and show the alternating effect of upfield, downfield and upfield shifts resulting in the side-chain following *ortho*, *meta* and *para* methoxylation, respectively.

Effects on the ring carbons are very interesting and have been commented on previously for mono- and dimethoxyamphetamines and corresponding nitrostyrenes.[8] The data on *ortho* shielding effects which can be derived for the phenylethylamines are presented in Table 4; the observations essentially duplicate those on amphetamines.[8] Methoxy groups which can freely rotate into the aromatic ring plane shield the two *ortho* positions by a total of approximately 26–30 ppm; there is a shielding of 14–15 ppm at unhindered (non-substituted) *ortho* positions which is diminished to approximately 10–12 ppm at a substituted (by a side-chain or OCH_3) position, but simultaneously enhanced to about 15.5–18.5 ppm in the direction away from such a substituent. Sandwiched OCH_3 groups shield each *ortho* position by approximately 6–8 ppm. It can also be seen from Table 4 and other data[8] that *ortho* shielding is slightly (about 1 ppm) diminished toward a *meta* substituent and that there is a compensatory enhancement in the shielding away from it. This effect is greater for OCH_3 groups than for the side-chain (see the shieldings towards C-2 and C-4 of the 3-OCH_3 groups in 3-MPEA and 3,5-DMPEA; Table 4).

meta-Shielding effects are small and *para* effects are highly variable and trends are not easily discerned. Table 4 can be used to predict chemical shifts provided that an analogue with appropriate *meta* and *para* substituents is chosen for the carbon under consideration.[7]

Table 5. Effect of protonation and solvent change on chemical shifts of aromatic carbon signals of methoxyphenylethylamines and methoxyamphetamines (ppm)[a]

	C-1	C-2/6 (ortho)	C-3/5 (meta)	C-4 (para)
PEA	*−0.49*	2.62/2.62	3.10/3.10	3.71
Amphetamine	*−0.98*	2.73/2.73	3.10/3.10	3.71
2-MPEA	*−0.67*	*2.25*/2.92	3.71/3.28	4.19
2-MA	*−1.46*	*2.19*/2.98	3.59/3.16	4.13
3-MPEA	*−0.31*	2.55/3.04	*2.00*/3.52	3.94
3-MA	*−0.79*	2.67/3.16	*2.00*/3.52	3.94
4-MPEA	*+0.18*	2.97/2.97	3.09/3.09	*2.31*
4-MA	*−0.43*	3.16/3.16	3.21/3.21	*2.49*
2,3-DMPEA	*−0.55*	*1.68*/2.73	*2.13*/4.13	4.17
2,3-DMA	*−1.10*	*1.64*/2.86	*2.18*/4.07	4.37
2,4-DMPEA	*−0.36*	*2.42*/3.22	2.80/4.01	*2.67*
2,4-DMA	*−1.22*	*2.30*/3.21	2.61/3.88	*2.67*
2,5-DMPEA	*−0.54*	*2.44*/2.49	4.25/*2.13*	4.67
2,5-DMA	*−1.33*	*2.43*/2.79	4.00/*2.01*	4.73
2,6-DMPEA	*−1.03*	*2.12*/*2.12*	3.53/3.53	4.43
2,6-DMA	*−1.77*	*2.24*/*2.24*	3.34/3.34	4.49
3,4-DMPEA	*−0.30*	2.67/3.28	*1.82*/3.16	*2.19*
3,4-DMA	*−0.67*	2.86/3.41	*1.88*/3.22	*2.31*
3,5-DMPEA	*−0.31*	2.92/2.92	*2.13*/*2.13*	3.40
3,5-DMA	*−0.79*	3.03/3.03	*2.07*/*2.07*	3.46
2,3,4-TMPEA	*−0.43*	*1.64*/3.54	*1.64*/4.07	*2.61*
2,3,4-TMA	*−0.85*	*1.70*/3.82	*1.70*/4.13	*2.79*
2,3,5-TMA	*−0.91*	*1.76*/3.40	*2.19*/*2.49*	3.58
2,3,6-TMPEA	*−0.85*	*1.46*/*2.07*	*2.00*/4.50	4.68
2,3,6-TMA	*−1.52*	*1.52*/*2.07*	*1.94*/4.44	4.80
2,4,5-TMPEA	*−0.79*	*2.55*/2.43	2.79/*1.76*	*2.61*
2,4,5-TMA	*−1.33*	*2.50*/2.67	2.85/*1.76*	*2.67*
2,4,6-TMPEA	*−0.85*	*2.30*/*2.30*	2.91/2.91	*2.91*
2,4,6-TMA	*−1.63*	*2.31*/*2.31*	2.97/2.97	*2.97*
3,4,5-TMPEA	*+0.48*	3.04/3.04	*1.94*/*1.94*	*1.76*
3,4,5-TMA	*+0.06*	3.16/3.16	*2.00*/*2.00*	*1.82*

[a] The chemical shift of the base in $CDCl_3$ was subtracted from that of the salt in D_2O. Negative signs indicate that upfield shifts result. Italicized figures refer to substituted positions.

Table 6. Effect of protonation and solvent change on chemical shifts of side-chain carbon signals (ppm)[a]

(A) Compounds with *ortho*-OCH_3:

Substitution	C-α	C-β	C-γ
2-M	−3.58/*−3.88*	+3.92/*+0.49*	−3.28
2,3-DM	−3.58/*−4.13*	+3.46/*0.00*	−3.40
2,4-DM	−3.59/*−3.95*	+3.76/*+0.36*	−3.34
2,5-DM	−3.59/*−4.49*	+3.82/*+0.24*	−3.34
2,6-DM	−3.34/*−4.01*	+3.82/*+0.52*	−3.15
2,3,4-TM	−3.40/*−4.19*	+3.47/*−0.13*	−3.40
2,3,5-TM	−4.01/	+3.27/	−3.89
2,3,6-TM	−3.46/*−4.25*	+3.52/*+0.18*	−3.41
2,4,5-TM	−3.15/*−3.95*	+3.83/*+0.30*	−2.98
2,4,6-TM	−3.28/*−4.00*	+3.89/*+0.55*	−3.22

(B) Compounds without *ortho*-OCH_3:

Substitution	C-α	C-β	C-γ
A/*PEA*	−3.95/*−4.49*	+3.34/*0.00*	−3.34
3-M	−4.01/*−4.61*	+3.46/*+0.06*	−3.34
4-M	−3.71/*−4.95*	+3.53/*+0.18*	−3.22
3,4-DM	−3.89/*−4.56*	+3.53/*−0.06*	−3.34
3,5-DM	−4.19/*−4.80*	+3.34/*−0.12*	−3.52
3,4,5-TM	−3.95/*−4.62*	+3.46/*0.00*	−3.46

[a] Values in italics are for PEA derivatives, the remainder for amphetamines; the chemical shift of the base in $CDCl_3$ was subtracted from that of the salt in D_2O. Positive and negative signs indicate that downfield and upfield shifts, respectively, result from protonation. 2,3,5-TMPEA was not available.

Effects of protonation

The effects of protonation and change of solvent from $CDCl_3$ to D_2O on the PEA and amphetamine series aromatic ^{13}C shifts are presented in Table 5. Several general features emerge. The effects in both series are of similar magnitude except that the upfield γ-shift at C-1 on protonation is consistently less in the PEA series; as observed in methylamphetamines,[9] there is a greater downfield shift on protonation progressing across the ring from C-1 to C-4; the downfield shift at methoxylated positions is less than at corresponding unsubstituted positions, and the smallest downfield shifts are seen at those carbons bearing the sandwiched OCH_3 groups, whether this be an *ortho*, *meta* or *para* position. The effects in the side-chain are to shift C-γ upfield by 3.0–3.9 ppm, and C-α upfield by 3.2–4.2 ppm (amphetamines) or 3.9–5.0 ppm (phenylethylamines), respectively (Table 6). In the case of compounds without an *ortho*-OCH_3 group and the seven that have 2,3-dimethoxy-type substitution, C-β shifts downfield on protonation by 3.3–3.5 ppm (amphetamines) or ±0.2 ppm (PEA derivatives); normally, *ortho*-methoxylated compounds shift downfield by 3.8–3.9 ppm (amphetamines) or 0.3–0.6 ppm (PEA derivatives). There is no clear structure–shift relationship in the C-α and C-γ data.

DISCUSSION

There are now sufficient NMR data available for several inferences to be drawn about the solution conformation of methoxylated amphetamines and PEA derivatives. First, from ^{1}H NMR data the side-chain of PEA derivatives (bases) exists with approximately equal populations of the *trans* (NH_2 and aromatic moieties antiperiplanar) and two *cis* rotamers.[3] In addition to previous data, the proportion of *trans* rotamer in the DMPEA.HCl and TMPEA.HCl derivatives has now been obtained as before (the bases gave poor quality spectra at 60 MHz, several of which could not be solved; Table 7).[3] The proportion of the *trans* rotamer increases on protonation in water to a greater extent when there are unfavourable and less when there are favourable (hydrogen bonding?) interactions with *ortho*-OCH_3 substituents.[3] The side-chain of amphetamine bases was shown[4] to be approximately 15% in the least stable rotameric conformation (C, Fig. 2) in which the aryl, NH_2 and γ-CH_3 groups are all *gauche* about the α—β bond, and either approximately 65% and 20% in the *trans* (A) and remaining *cis* (B) rotamers, respectively, or vice versa. Subsequent stereospecific deuterium labelling experiments by Jacobus and co-workers[16] and more recently by Makriyannis and Knittel[17] have identified the diastereotopic α-protons, from which it now seems that the antiperiplanar rotamer (A) of the bases is present only to 20–40%.[4,5,16,17]

^{1}H NMR spectra of amphetamine salts show that, as with PEA derivatives, the proportion of the antiperiplanar form (A) is increased, to approximately 60–75% in $CDCl_3$.[4,17] The ^{1}H NMR data suggest that this increase in proportion is greater in amphetamines, and this may be associated with the observed larger magnitude of the ^{13}C shielding at C-1 on protonation (see above). There is strong evidence that an *ortho*-OCH_3 group increases the population of the *gauche* form (B) by approximately 10%.[4,5] A re-examination of our earlier data[4] shows that this effect is diminished for 2,3-DMA.HCl and 2,3,4-TMA.HCl. The same conclusion can be drawn from PEA data (Table 7 and previous work[3]). The ^{13}C NMR data now presented for C-β support this interpretation, especially the observation that the effects following protonation of compounds having sandwiched *ortho*-OCH_3 groups are similar to those in non-*ortho*-methoxylated compounds. It is evident that a considerable proportion of the 2,3,6-trimethoxy salt assumes a rotameric conformation in which the amino side-chain is directed towards C-6.

Secondly, OCH_3 groups are forced out of the ring plane by flanking substituents[15] (the downfield shift of the OCH_3 signal in similar compounds has been ascribed to a 'δ_1-type effect[18]), which apparently adds to the effective bulk of the aromatic moiety in the salts. In the case of amphetamines, owing to the asymmetric C-β, non-planarity at C-2 and/or C-3 results in different diastereotopic conformations, but no evidence for this has been observed in our spectra.

Thirdly, flanking 2,6-$(OCH_3)_2$ groups appear to force the side-chain largely into a conformation in which C-α—β is perpendicular to the ring plane. A similar suggestion was made following studies on nitrostyrenes.[8] Others have investigated torsional effects about the benzylic bond by NMR techniques, but interpretation of observations is difficult.[18] In any

Table 7. Molar fraction of *trans* rotamer in PEA derivatives[a]

	PEA	2M-	3M-	4M-	2,3DM-	2,4DM-	2,5DM-	
Base	0.36	0.36	0.33	0.36	[b]	0.17	[b]	
Hydrochloride	0.50	0.33	0.53	0.47	0.66	0.47	0.50	
	2,6DM-	3,4DM-	3,5DM-	2,3,4TM-	2,3,6TM-	2,4,5TM-	2,4,6TM-	3,4,5TM-
Base	[b]	0.41	0.33	0.41	[b]	0.17	[b]	0.39
Hydrochloride	0.09	0.61	0.69	0.56	0.36	0.47	0.14	0.56

[a] Bases in $CDCl_3$, hydrochlorides in D_2O; calculations following method published for PEA and 2-, 3- and 4-MPEA.[3]
[b] Spectral quality and parameters unsuitable for solving as AA'BB' spectra.

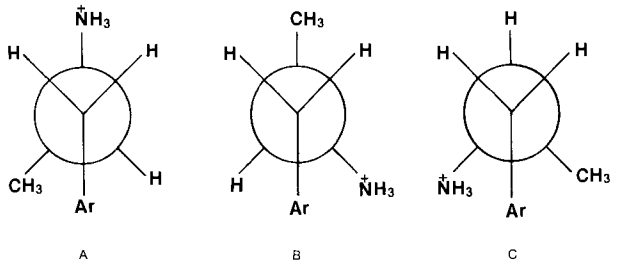

Figure 2. Rotameric conformations of amphetamines.

event, the hallucinogenic activity of 2,3,6-TMA[19] indicates that ground-state coplanarity of the C-α—β and/or O—CH_3 bonds are not essential features for activity.

Fourthly, the OCH_3 groups are predominantly in the ring plane and the O—CH_3 bond is directed toward unhindered positions. *ortho*-OCH_3 groups project their *n* electron lone pairs towards the side-chain. The interactions described above lead to differences in the electronic character of otherwise similar groups. For example, the lone pairs on the oxygens of 3,4-methylenedioxyamphetamine (3,4-MDA) are necessarily directed *away* from one another, but in 3,4-DMA our evidence is that they are largely directed *towards* one another.

It is evident that the conformational preferences of phenylethylamines and amphetamines at physiological temperatures in solution are not great. The locations of electronic charge, and of the electronegative atoms themselves, can be expected to have significant effects on interactions with putative biological receptors.

EXPERIMENTAL

Samples were prepared from the corresponding benzaldehydes via the nitrostyrenes using standard procedures.[20] Broad-band proton-decoupled ^{13}C NMR spectra were determined at 20.1 MHz on a Bruker WP80 Fourier transform spectrometer using a sweep width of 5000 Hz and an 8K data point system. Since the 4K output addresses are separated by 0.06 ppm, tabulated spectral differences of 0.12 ppm should not be regarded as necessarily significant. Spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock. Hydrochlorides were examined in deuterium oxide and free bases in deuteriochloroform, containing internal standards of sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) and tetramethylsilane (TMS), respectively. The solution concentration was approximately 100 mg per 1.7 ml of solvent in 10-mm tubes. The pulse widths were 1.5 μs (19.2° flip angle) with no pulse delay following data acquisition. The chemical shift reagent Eu-Resolve (Ventron Corp., Beverly, MA, USA) was added incrementally (5, 10, 20, 20 and 30 mg) to a solution of phenylethylamine (310 mg) in deuteriochloroform (1.7 ml), and ^{13}C NMR spectra were recorded at each stage. Proton spectra were determined at 60 MHz on a Varian A-60A spectrometer as described previously.[3]

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