X-Ray Crystallography Studies and CP-MAS ^{13}C NMR Spectroscopy on the Solid-state Stereochemistry of Diphenhydramine Hydrochloride, an Antihistaminic Drug

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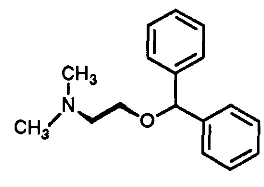
The solid-state structure of diphenhydramine hydrochloride [$(CH_3)_2NCH_2CH_2OCH(Ph)_2$·HCl], an antihistaminic drug, was determined by single crystal X-ray diffraction analysis. Diphenhydramine hydrochloride gave crystals belonging to the orthorhombic $Pn2_1a$ space group, and at ambient temperature: a = 10.592(2), b = 10.761(2), c = 14.280(2) Å, V = 1 627.6(8) Å^3, Z = 4, R(F) = 0.063, R_w(F) = 0.068. Since the molecule (1) is placed half-way between the a-glides perpendicular to c, and (2) its molecular conformation shows almost mirror symmetry {through N, C(4) [–CH_2O–], benzhydryl-C(5), and between the phenyls}, the *C*-face appears to act as a plane of pseudo-mirror symmetry enabling the unit cell to have pseudo-centring of the *B*-face [$Bb2_1m$ apparent symmetry]. The molecule shows an almost eclipsed geometry for the oxydimethyleneamino moiety [38(1)° O–C–C–N torsion angle] and a non-helical 'open book' disposition for the diphenylmethane moiety. The CP-MAS ^{13}C NMR spectrum for diphenyhydramine HCl is unusually simplified due to the pseudo-mirror symmetry of the structure. Internally diastereotopic pairs of nuclei, *e.g.* $(CH_3)_2N$, the two *ipso*-carbons, *etc.* appear to be pseudo-enantiotopic due to negligible differences in chemical shifts from pairs of what should be anisochronous carbons.

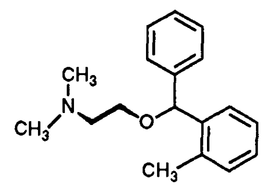
Diphenhydramine hydrochloride [2-diphenylmethoxy-*N,N*-dimethylethanamine hydrochloride] (1) is a well-known antihistaminic drug.[1] It is structurally related to the skeletal muscle relaxant orphenadrine (2)[2] and the non-narcotic analgesic nefopam (3).[3,4] Klohs *et al.*[4] have compared some of the pharmacological activities of the three drugs: the relative antihistaminic potencies of (1)–(3) are 1, 1/15, and 1/90, respectively; and the relative muscle relaxant potencies of (1)–(3) are 1, 2–3, and 10–30, respectively. Orphenadrine and histamine H_1 blockers such as diphenhydramine produce antinociception in mice,[5–7] and exhibit analgesic activity in clinical trials,[8] but are considerably less potent than nefopam.[8]

Stereochemical investigations[9–11] of nefopam hydrochloride (3) and modelling studies[12] on a hypothetical model for the serotonin (5-HT) re-uptake site have been reported by Glaser *et al.* Nefopam hydrochloride exists in the crystalline state in a boat-(flattened chair) conformation (3e), with an equatorial *N*-methyl group, and an *exo*-oriented phenyl ring.[9,10] Dissolution of either crystalline (±)-(3e) or (+)-(3e) results in a prototropic shift/nitrogen inversion diastereomerization process forming an equilibrium mixture of equatorial (e) and axial (a) *N*-methyl isomers (3) [e:a ratio *ca.* 1:1 (acidic D_2O, pD *ca.* 1), and *ca.* 2:3 (CD_2Cl_2)].[9,11] The (1*R*,5*R*)-(3e) and (1*R*,5*S*)-(3a) diastereoisomeric pair from the dissolution of crystalline (−)-(1*R*,5*R*)-(3e) is illustrated above.



•HCl

(1)



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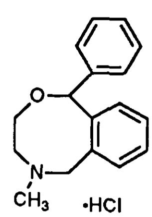

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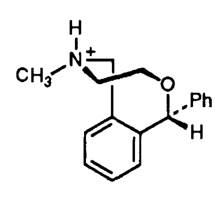
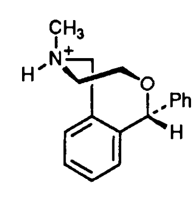
(3)



(3e)



(3a)

This paper reports the solid-state structure of diphenhydramine hydrochloride (1) and the CP-MAS ^{13}C NMR spectra of (1) and orphenadrine citrate [(2)-citrate] as part of a programme to correlate stereochemical structure with pharmacological activity in this family of molecules.

Results and Discussion

X-Ray Diffraction Studies.—Diphenhydramine hydrochloride gave crystals belonging to the orthorhombic $Pn2_1a$ space group, and at ambient temperature: a = 10.592(2), b = 10.761(2), c = 14.280(2) Å, V = 1 627.6(8) Å^3, Z = 4, R(F) = 0.063, R_W(F) = 0.068. Crystal data are provided in Table 1. The atomic parameters are listed in Table 2 [see structure (4) for numbering]. Intramolecular distances and angles are given in Table 3, and torsion angles are presented in Table 4.*

* *Supplementary material:* Tables of anisotropic thermal parameters for non-hydrogen atoms, fractional atomic co-ordinates for hydrogen atoms, and a list of observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre. For details see Instructions for Authors (1990), *J. Chem. Soc., Perkin Trans. 2*, 1990, Issue 1.

Table 1. Crystallographic details for diphenhydramine hydrochloride (**1**).

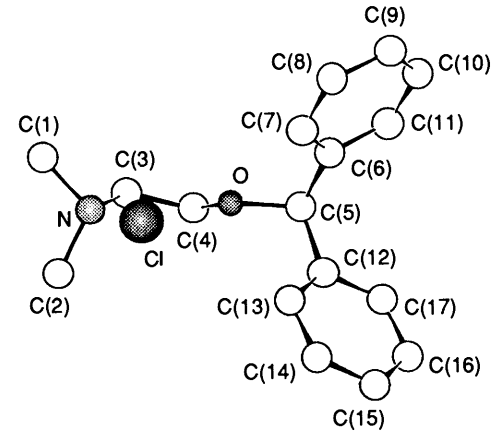
Formula	$C_{17}H_{21}NO{\cdot}HCl$
M_F/Da	291.82
Space group	$Pn2_1a$
a/Å	10.592(2)
b/Å	10.761(2)
c/Å	14.280(2)
V/Å^3	1 627.6(8)
Z	4
ρ_{calc}/g cm^{-3}	1.192
Linear abs. coeff./cm^{-1}	2.29
T/K	Ambient
Crystal size/mm^3	0.4 × 0.4 × 0.3
Radiation	Graphite-monochromated Mo-K_α (λ = 0.710 73 Å)
2θ limits	0.0° ≤ 2θ ≤ 56.0°
Scan type	ω
Scan width, deg	1.20 + 0.35 tan θ
Scan speed, deg min^{-1}	1–4
Background time/scan time	0.33
Unique data	2 059
Unique data with $I \geq 2\sigma(I)$	1 280
No. of variables	180
R(F)	0.063
R_W(F)	0.068
Weighting factor,[a] w	$4Lp{\cdot}I/\sigma^2(I)$; $\sigma^2(I) = \sigma^2(I)_{count} + (0.02I)^2$
Goodness of fit[b]	3.13

[a] Lp = Lorentz polarization factor. [b] Goodness of fit = SQRT[$(\Sigma_i\{w_i(|F_{obs}|_i - |F_{calc}|_i)\}^2)$/(No. of reflections − No. of parameters)].

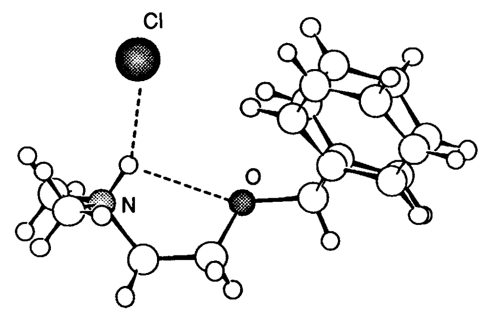
Table 2. Atomic parameters x, y, z, for diphenhydramine hydrochloride (**1**) non-hydrogen atoms. Esds in parentheses refer to the last digit printed.[a]

Atom	x	y	z
Cl	0.179 0(1)	0.500 [fixed]	0.006 33(2)
O	0.372 5(4)	0.232 1(4)	−0.021 8(4)
N	0.106 7(4)	0.232 3(5)	−0.009 8(3)
C(1)	0.013 2(7)	0.249(1)	−0.083 2(6)
C(2)	0.0477(8)	0.221(1)	0.081 3(5)
C(3)	0.184 0(7)	0.127 8(9)	−0.033 3(8)
C(4)	0.312 1(5)	0.129 9(7)	−0.012 6(5)
C(5)	0.505 9(6)	0.240 0(6)	−0.016 3(4)
C(6)	0.555 1(5)	0.311 9(5)	−0.095 4(4)
C(7)	0.492 4(5)	0.414 5(6)	−0.127 7(4)
C(8)	0.543 5(6)	0.485 5(5)	−0.201 3(4)
C(9)	0.656 7(7)	0.451 4(7)	−0.240 3(4)
C(10)	0.719 0(6)	0.347 6(8)	−0.209 0(5)
C(11)	0.668 4(5)	0.278 0(6)	−0.137 5(4)
C(12)	0.545 3(5)	0.298 8(5)	0.075 3(4)
C(13)	0.473 3(5)	0.388 8(6)	0.117 0(4)
C(14)	0.519 7(6)	0.450 4(6)	0.197 0(5)
C(15)	0.635 8(7)	0.421 4(7)	0.234 7(4)
C(16)	0.706 4(6)	0.331 6(7)	0.194 0(4)
C(17)	0.661 1(5)	0.270 4(6)	0.114 8(4)

In the crystalline state, diphenhydramine hydrochloride is bent into a shallow −38(1)° *gauche*(synclinal) N–C(3)–C(4)–O torsion angle conformation in which N-*H* participates in a bifurcated hydrogen-bonding arrangement, see structure (**5**). This involves the chloride anion and an intramolecular oxygen: N ··· Cl 2.990(3) Å, N*H* ··· Cl 2.129(6) Å, angle N–N*H* ··· Cl 149.9(5)°, and N ··· O 2.821(6) Å, N*H* ··· O 2.398(6) Å, angle N–N*H* ··· O 106.6(5)°, while the Cl, N, N*H*, and O atoms are approximately coplanar [−1(1)° torsion angle



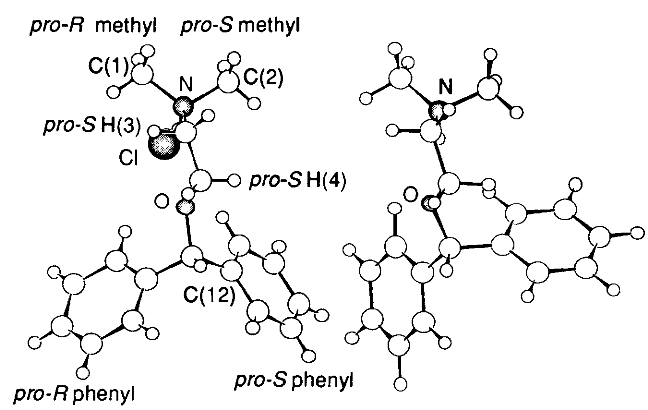
(**4**)



(**5**)

N*H*–N ··· O ··· Cl]. The (*M*)-sign of the N–C(3)–C(4)–O torsion angle will be arbitrarily chosen to provide a conformational descriptor for the (**1**)-enantiomer depicted in structure (**4**). In this conformation, C(1)—the *pro-R* methyl—is anticlinal to C(4) [143.3(9)° C(1)–N–C(3)–C(4)], the *pro-S* H(3,4) protons are antiperiplanar [−155(1)° *pro-S* H(3)–C(3)–C(4)–*pro-S* H(4)], and *pro-R* H(4) is synclinal to the benzhydrylic proton H(5) [−34(1)° *pro-R* H(4)–C(4) ··· C(5)–H(5)], see Figure 1.

Since the molecule (**1**) is placed half-way between the *a*-glides perpendicular to *c*, and (**2**) its molecular conformation shows almost mirror symmetry [through N, C(4), C(5), and between



(1) (6)

Figure 1. Comparison of X-ray determined structure of diphenhydramine hydrochloride [(*M*)-conformation] with that of the molecular mechanics energy optimized model (**6**).

the phenyls], the *C*-face appears to act as a plane of pseudo mirror symmetry enabling the unit cell to have pseudo-centring of the *B*-face [$Bb2_1m$ apparent symmetry]. This is in accord with the observation that the intensities of $h + l = 2n + 1$ are *generally weak* (*but not extinct*), inferring a pseudo-centring of the *B*-face. Consistent with the pseudo mirror-plane, the aromatic rings exhibit a non-helical 'open book' conformation in the diphenylmethane moiety as evidenced by the 4(1)° C(7)–C(6) ··· C(12)–C(13) and 6(1)° C(11)–C(6) ··· C(12)–C(17) synperiplanar torsion angles. Diarylmethane moieties, and $Ar_2ZX^1X^2$ systems in general, usually show helical dispositions giving the appearance of either a right- or left-handed two-bladed propeller subunit.[13,14]

The MMX88[15] molecular mechanics program (an enhanced version of Allinger's MM2/MMP1 programs[16,17]) was used to model the solid-state diphenhydramine conformation. Crystallographic co-ordinates were used for the input structure, and the geometry of the final energy optimized model was found to be similar to that of the initial structure. Selected non-hydrogen torsion angles for the molecular mechanics model (6) are given in Table 4 for comparison with those from the X-ray determined structure. Figure 1 shows a pictorial comparison between the X-ray and MMX models. Clearly, the pseudo-mirror plane in the solid-state molecule is no longer present in the molecular mechanics model since the *pro-S* phenyl ring [C(12–17)] has been pushed closer to pseudo-axial *pro-S* H(4), and the *pro-S* H(4) and C(12) atoms appear to have a *cis*-1,3-diaxial type relationship now. This is seen by the following: torsion angle C(3)–C(4)–O–C(5) −170.2(7)° [X-ray] *versus* +169.8° [MMX], *pro-S* H(4) ··· C(12) internuclear distance 3.18 Å [X-ray] *versus* 2.59 Å [MMX], and ∠C(12)–C(5) ··· C(4) 115.4(4)° [X-ray] *versus* 97.5° [MMX]. As a result, the *pro-S* phenyl ring appears to be more twisted about the C(5)–C(12) bond to relieve interactions between the *ortho* H(13) and *pro-S* H(4) −33.4(7)° torsion angle C(5)–O–C(12)–C(13) [X-ray] *versus* −52.1° [MMX]. Primarily as a result of this increased twisting of the *pro-S* phenyl ring, the diarylmethane moiety now shows some helicity in the MMX model: −19.0 and −19.7° torsion angles C(7)–C(6) ··· C(12)–C(13)/C(11)–C(6) ··· C(12)–C(17), respectively. Another way of looking at this change in pitch of the phenyl rings is to use atoms C(5,6,12) as a reference plane. A ring tilt angle[18] will be defined as the dihedral angle between the average plane of the aromatic ring and a line which passes through the central C(5) atom normal to the reference plane. The 6(1)° tilt angle [X-ray] of the C(6)–C(11) *pro-R* phenyl ring opens slightly to 9.8(1)° [MMX], while that for the C(12)–C(17) *pro-S* phenyl ring shows a larger increase: 3(2)° [X-ray] *versus* 18.7(1)° [MMX].

The bond lengths and angles reported in Table 2 are reasonable with the exception of some of those involving C(4) and O [*e.g.* 1.389(6) and 1.279(5) Å for the C(3)–C(4) and C(4)–O bonds, respectively]. Inspection of the ORTEP plot in Figure 2 shows that C(3,4) and O undergo considerable thermal motion perpendicular to the pseudo-mirror plane, while C(2) undergoes thermal movement parallel to the pseudo-plane. As a result of these librations, the N–C(3)–C(4)–O torsional angle can attain values having some synperiplanar character.

NMR Studies.—The ^{13}C NMR spectral parameters of (1) and (2) measured in the solution and solid-states are listed in Table 5. The DEPT (135° pulse angle) sequence was used to ascertain the multiplicities of protonated carbon resonances.[19] The NCH_3 and quaternary carbon resonances in the CP-MAS ^{13}C NMR spectra were confirmed by a dipolar dephasing experiment[20] based on less efficient solid-state

Table 3. Non-hydrogen bond distances and angles for diphenhydramine hydrochloride (1), esds in parentheses refer to the last digit printed.

Distances/Å			
C(1)–N	1.452(6)	C(8)–C(9)	1.372(6)
C(2)–N	1.449(5)	C(9)–C(10)	1.372(6)
N(3)–C(3)	1.431(6)	C(10)–C(11)	1.374(6)
C(3)–C(4)	1.389(6)	C(12)–C(13)	1.369(5)
C(4)–O	1.279(5)	C(12)–C(17)	1.384(5)
O–C(5)	1.418(4)	C(13)–C(14)	1.409(6)
C(5)–C(6)	1.465(5)	C(14)–C(15)	1.378(6)
C(5)–C(12)	1.512(5)	C(15)–C(16)	1.353(6)
C(6)–C(7)	1.368(5)	C(16)–C(17)	1.395(6)
C(6)–C(11)	1.391(5)	Cl ··· N	2.990(3)
C(7)–C(8)	1.408(6)		
Angles/°			
C(1)–N–C(2)	111.3(4)	C(7)–C(8)–C(9)	119.6(5)
C(1)–N–C(3)	108.6(5)	C(8)–C(9)–C(10)	120.4(5)
C(2)–N–C(3)	113.0(5)	C(9)–C(10)–C(11)	119.9(4)
N–C(3)–C(4)	119.8(4)	C(6)–C(11)–C(10)	121.0(4)
C(3)–C(4)–O	118.7(4)	C(5)–C(12)–C(13)	121.2(3)
C(4)–O–C(5)	122.9(3)	C(5)–C(12)–C(17)	120.3(3)
O–C(5)–C(6)	110.0(3)	C(13)–C(12)–C(17)	118.3(4)
O–C(5)–C(12)	110.4(3)	C(12)–C(13)–C(14)	119.4(4)
C(6)–C(5)–C(12)	110.4(3)	C(13)–C(14)–C(15)	121.4(4)
C(5)–C(6)–C(7)	120.9(4)	C(14)–C(15)–C(16)	119.2(5)
C(5)–C(6)–C(11)	120.1(4)	C(15)–C(16)–C(17)	119.7(4)
C(7)–C(6)–C(11)	118.9(4)	C(12)–C(17)–C(16)	122.1(4)
C(6)–C(7)–C(8)	120.2(4)		

Table 4. Non-hydrogen torsion angles (°) for diphenhydramine hydrochloride (1), esds in parentheses refer to the last digit printed.[a]

C(1)–N–C(3)–C(4)	143.3(9) [142.7]	C(11)–C(6)–C(7)–C(8)	−1.2(9)
C(2)–N–C(3)–C(4)	−93(1) [−89.9]	C(5)–C(6)–C(11)–C(10)	−177.0(6)
N–C(3)–C(4)–O	−38(1) [−44.4]	C(7)–C(6)–C(11)–C(10)	1.6(9)
C(3)–C(4)–O–C(5)	−170.2(7) [+169.8]	C(6)–C(7)–C(8)–C(9)	0(1)
C(4)–O–C(5)–C(6)	131.7(7) [167.4]	C(7)–C(8)–C(9)–C(10)	1(1)
C(4)–O–C(5)–C(12)	−106.2(7) [−70.6]	C(8)–C(9)–C(10)–C(11)	−1(1)
O–C(5)–C(6)–C(7)	38.5(7) [24.3]	C(9)–C(10)–C(11)–C(6)	−1(1)
O–C(5)–C(6)–C(11)	−142.9(5) [−156.1]	C(5)–C(12)–C(13)–C(14)	−173.3(5)
C(12)–C(5)–C(6)–C(7)	−83.6(6) [−98.6]	C(17)–C(12)–C(13)–C(14)	1.0(9)
C(12)–C(5)–C(6)–C(11)	95.1(6) [80.9]	C(5)–C(12)–C(17)–C(16)	173.5(6)
O–C(5)–C(12)–C(13)	−33.4(7) [−52.1]	C(13)–C(12)–C(17)–C(16)	−0.9(9)
O–C(5)–C(12)–C(17)	152.4(5) [128.0]	C(12)–C(13)–C(14)–C(15)	0(1)
C(6)–C(5)–C(12)–C(13)	88.5(6) [71.2]	C(13)–C(14)–C(15)–C(16)	0(1)
C(6)–C(5)–C(12)–C(17)	−85.7(6) [−108.7]	C(14)–C(15)–C(16)–C(17)	0(1)
C(5)–C(6)–C(7)–C(8)	177.4(6)	C(15)–C(16)–C(17)–C(12)	0(1)

[a] Values calculated by molecular mechanics are given in square brackets.

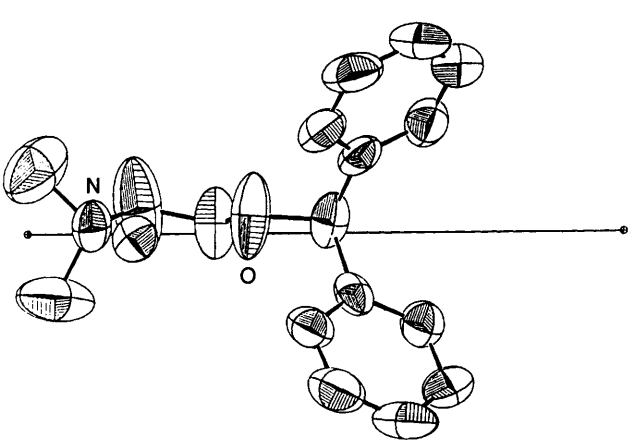


Figure 2. ORTEP drawing of the diphenhydramine hydrochloride (M)-(**1**) conformation in the $Pn2_1a$ unit cell [the a-axis appears as a solid line in the background].

Table 5. ^{13}C NMR spectral parameters for diphenhydramine hydrochloride (**1**) and orphenadrine citrate [(**2**)-citrate].[a]

δ_C	(1) (D_2O)[b]	(1) (solid)[c]	(2)-citrate (D_2O)[d]	(2)-citrate (solid)[e]
C(1)	43.03	43.42	43.20 br	38.70
C(2)	43.03	43.42	43.20 br	43.86
C(3)	56.81	58.50	57.27	57.62
C(4)	62.35	61.50	62.59	62.70
C(5)	83.94	84.20	81.16	82.30
C(6)	141.33	146.17	139.08	139.70
C(12)	141.33	146.17	140.26	141.50
C-CH_3	—	—	136.42	136.69
C-*C*H_3	—	—	18.69	19.51
Internal *C*HCO_2	—	—	74.04	77.30
External *C*H_2CO_2	—	—	43.93	47.73 br
External *C*H_2CO_2	—	—	43.93	47.73 br
Internal CH*C*O_2	—	—	178.82	181.36
External CH*C*O_2	—	—	175.00	170.91
External CH*C*O_2	—	—	175.00	173.97

[a] ppm downfield from tetramethylsilane. [b] Other aromatic carbons (ppm): 126.92, 128.93, 128.16. [c] Other aromatic carbons (ppm): 127.99, 129.16. [d] Other aromatic carbons (ppm): 125.80, 125.87, 127.18, 127.69, 127.86, 128.39, 130.35. [e] Other aromatic carbons (ppm): 125.85, 127.84, 128.86, 129.84, 131.04, 132.28.

relaxation for these nuclei (*vis-á-vis* methylene and methine carbons). After a suitable delay period was introduced prior to FID acquisition, N–CH_3 and $C_{quaternary}$ magnetization was still noted in the spectrum. This technique has been used previously to assign *N*-methyl resonances in crystalline atropine sulphate (equatorial N–*C*H_3) and scopolamine hydrobromide (axial N–*C*H_3).[21]

In the ^{13}C NMR spectrum of (**1**) measured in solution, we expect only one *N*-methyl carbon resonance at the fast exchange limit for conformational interconversion (an enantiomerization process) since the internally diastereotopic *pro-R*/*pro-S* *N*-methyl carbons in the *gauche* (synclinal) (P)-(**1**) conformation undergo a rapid topomerization into externally enantiotopic[22] environments in (M)-(**1**), while they are internally enantiotopic in the antiperiplanar conformation, see Figure 3. If the pseudo-axial *pro-R* *N*-methyl is labelled a, and pseudo-equatorial *pro-S* *N*-methyl is labelled b in (P)-(**1**), then in (M)-(**1**) the pseudo-axial *pro-S* *N*-methyl becomes $\bar{a}$, and the pseudo-equatorial *pro-R* *N*-methyl is denoted as $\bar{b}$. The rapid topomerization affords what may be described as dynamically enantiotopic sets of nuclei, set[$a,\bar{b}$] *versus* set[$b,\bar{a}$] *via* the

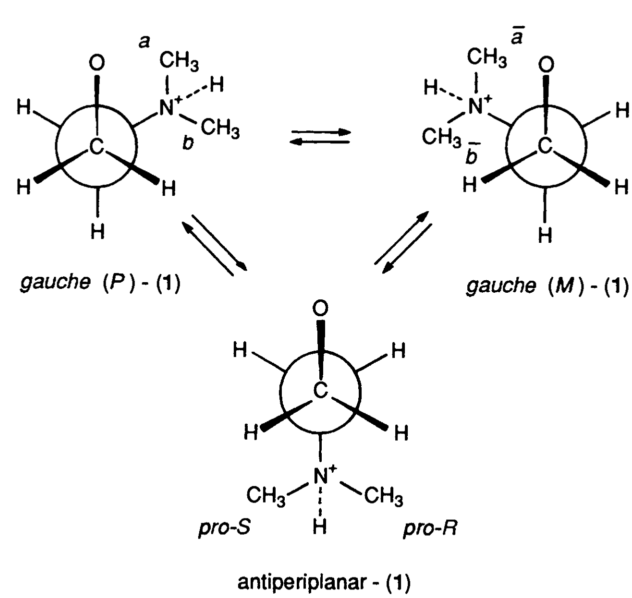
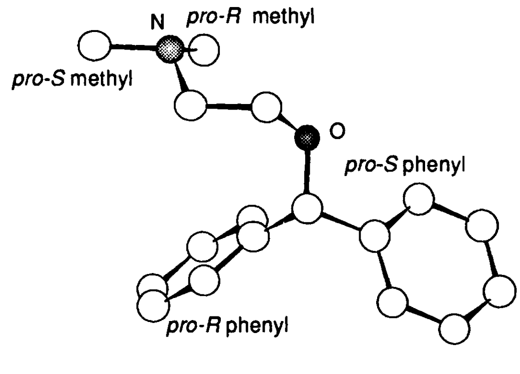


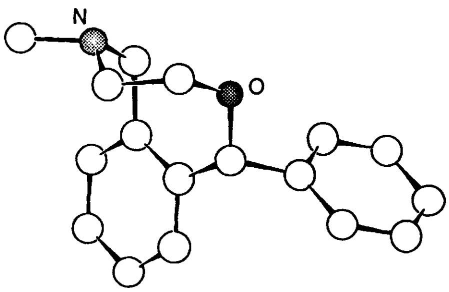
Figure 3. Interconversion of *pro-R* *N*-methyl in site a of gauche conformation (P)-(**1**), into site $\bar{b}$ of *gauche* conformation (M)-(**1**), and of *pro-S* *N*-methyl in site b of *gauche* conformation (P)-(**1**), into site $\bar{a}$ of *gauche* conformation (M)-(**1**).

permutation ($a\bar{b}$)($b\bar{a}$), *i.e.* a interconverted into $\bar{b}$ and b interconverted into $\bar{a}$. Thus, the interconversion results in two dynamic sets that are enantiotopic and hence isochronous to each other. Therefore, one isochronous resonance (43.03 ppm) for both carbons is found in solution. Strictly speaking, the chiral molecular conformation of diphenhydramine hydrochloride in the crystal results in the existence of sets of internally diastereotopic[22] pairs of nuclei [internal or intramolecular comparison], *e.g.* the *N*-methyl carbons C(1,2), the *ipso*-carbons C(6,12), etc. We expect to be at the slow exchange limit for (M)-/(P)-(**1**) conformational interconversion in the solid state. While symmetry arguments tell us that diastereotopic nuclei are anisochronous in NMR spectra, the magnitude of the spectral differences are not forthcoming from the argument. The pseudo-mirror symmetry of the molecule in the crystal, coupled with the thermal librational motions therein can cause these differences to be negligibly small in magnitude in the solid-state spectrum. A simplified CP-MAS ^{13}C NMR spectrum of (**1**) was indeed observed in which diastereotopic pairs of nuclei appeared to be pseudo-enantiotopic due to negligible differences in chemical shifts from pairs of what should be anisochronous carbons. Only one sharp signal was noted for the two $(CH_3)_2N$, and one for both *ipso*-carbons, while only two peaks were seen for remaining aromatic carbons.

Orphenadrine citrate [(**2**)-citrate] has a chirotopic stereogenic[23] benzhydryl C(5) atom. ^{13}C NMR spectroscopy was used to investigate solutions containing the racemic modification of (**2**)-citrate. Rotation about the C(3)–C(4) bond is a diastereoisomerization process in this case, and now the diastereotopic *N*-methyl carbons remain anisochronous even at the solution state fast exchange limit (broad 43.20 ppm signal). The achiral anion from $CHCO_2H(CH_2CO_2H)_2$ still shows enantiotopic prochiral pairs of nuclei (one isochronous resonance for the two citrate methylene carbons at 43.93 ppm, and two carbonyl carbon signals with *ca.* 2:1 intensity). In the solid-state, the citrate anion does not occupy a special position of mirror symmetry (m) in the unit-cell since the methylene carbons are now anisochronous (broad 47.73 ppm signal), and three carbonyl carbon resonances were found.



(7)



(3e)

Figure 4. Comparison of X-ray determined structure of (1*R*,5*R*)-nefopam HCl (**3e**) with molecular mechanics energy optimized diphenhydramine cation twisted into a similar conformation [(*M*)-conformation model-(**7**)]. Hydrogen atoms have been omitted for clarity.

Conformational Comparison of Diphenhydramine and Nefopam.—A major difference between the two compounds appears to be the antiperiplanar −170.2(7)° C(3)–C(4)–O–C(5) torsion angle in crystalline (*M*)-(**1**) as opposed to the corresponding *gauche* (synclinal) angle in nefopam (**3**). While both drugs show *gauche* N–C(3)–C(4)–O torsion angles in the crystalline state, the −38(1)° value for (*M*)-(**1**) is clearly smaller than the −57.7(2)° and −48.0(3) values for (±)-(**3**)[(1*R*,5*R*)-enantiomer, (**3e**)] and (−)-($3\cdot H_2O$), respectively (X-ray crystallography[10]). Molecular mechanics was also used to provide an estimate for the energy required to fold the molecule into a conformation similar to that for nefopam. Torsion angles in model (**6**) were changed to provide input values similar to those found in (**3e**). The *pro-S* phenyl group in (**3e**) and in the resulting energy optimized diphenhydramine structure [model (**7**)] are both similarly oriented [O–C(5)–C(12)–C(13): −59° (**3e**) and −24° (**7**)], see Figure 4. The two structures differ primarily in the twist of the *pro-R* phenyl group, which is not unexpected since this cycle becomes the benzo moiety upon ring-closure to the 2,5-benzoxazocine ring of (**3e**). Non-bonded interactions between the H(7) aromatic *ortho*-proton and the *pro-R* methyl protons in (**7**) open up the O–C(5)–C(6)–C(7) torsion angle to 59° from the 6° value in (**3e**). The two *gauche* torsion angles N–C(3)–C(4)–O and C(3)–C(4)–O–C(5) are also larger in model (**7**) [−83 and −79°, respectively] relative to the corresponding −58 and −64° values in (**3e**). The higher energy calculated for model structure (**7**) (*ca.* 3.0 kcal mol^{-1}) *vis-á-vis* (**6**) suggests that it is highly unlikely that the former is the major conformational species in solution.

In conclusion, the antiperiplanar value for torsion angle C(3)–C(4)–O–C(5) observed in crystalline (**1**) is obviously mutually exclusive with C–C bond formation between *N*-methyl and *ortho*-benzo carbon atoms to yield the benzoxazocine ring system of nefopam. The higher energy calculated for the nefopam-like conformation in model (**7**) relative to that found for model (**6**) might provide a rationalization for the lower analgesic and higher antihistaminic potencies noted for diphenhydramine relative to nefopam.

Experimental

Diphenhydramine hydrochloride was purchased from the Sigma Chemical Co., Inc. Orphenadrine citrate was obtained as a gift from 3M Riker UK. Dissolution in absolute ethanol followed by vapour diffusion of acetone yielded clear, colourless, crystalline prisms, belonging to the orthorhombic system $Pn2_1a$. M.p. 166.1–168.7° (uncorr.) (lit.,[1] 166–170 °C) was determined on a Wild Heerbrugg stereo-microscope equipped with a Mettler model FP-52 hot stage.

Intensity data were collected at ambient temperature on an Enraf-Nonius CAD4 automatic diffractometer. Table 1 provides crystallographic and data collection details. The unit-cell dimensions were obtained by a least-squares fit of 25 centred reflections in the range of $18° \leqslant 2\theta \leqslant 31°$. Reflections were measured with a variable scan speed of 1–4° min^{-1}. During data collection, the intensities of three standard reflections were monitored after every 120 min. Decay was observed, and was corrected accordingly.

The structure was solved by the Patterson method and refined by full-matrix least squares using the Enraf-Nonius SDP-87 programs. An absorption correction was applied.[24] Hydrogen positions were geometrically placed. The final refinement included anisotropic thermal parameters for the non-hydrogen atoms, and hydrogen atoms were included but not refined. At convergence the final discrepancy indices on F were $R(F) = 0.063$ and $R_W = 0.068$ for the 1 280 reflections with $I \geq 2\sigma(I)$ and 180 variables.* The residual positive and negative electron density in the final map was +0.29 and −0.32 e $Å^{-3}$, respectively, while the maximum shift/esd was 0.01.

^{13}C NMR spectra (4.7 T, D_2O broad-band proton decoupling and DEPT-135°) were recorded at 50.3 MHz on a Bruker WP-200-SY Fourier transform spectrometer equipped with an Aspect 2000 data system. Acetone (30.5 ppm) was used as an internal secondary reference, and the deuteriated solvent was used as an internal lock. Solid-state ^{13}C NMR spectra (75.4 MHz) were recorded on a Varian VXR-300 Fourier transform spectrometer operating in the CP-MAS mode using the TOSS (total suppression of spinning sidebands)[25] technique. Hexamethylbenzene (132.1 ppm) was used as an external secondary reference for the solid-state spectra. Evolution delay periods of 30 and 50 μs were used in solid-state dipolar dephasing experiments.

The minimized energy geometry of the molecular mechanics calculated model compounds were determined by the MMX88 program,[15] and were performed on a Micro VAX-II computer under MicroVMS V4.5. MMX88[15] is an enhanced version of Allinger's MM2 program[16] with MMP1 π-subroutines[17] incorporated for localized π-electron systems. Structures (**4**)–(**11**) and those in Figures 1 and 4 were drawn with the BALL AND STICK 2.0 program.[26]

* The final discrepancy index R(F) is defined as: $R(F) = (\Sigma_i||F_{obs}|_i - |F_{calc}|_i|)/(\Sigma_i|F_{obs}|_i)$; the weighted value R_W is defined as: $R_W(F) = \mathrm{SQRT}[(\Sigma_i\{w_i(|F_{obs}|_i - |F_{calc}|_i|)\}^2)/(\Sigma_i\{w_i(|F_{obs}|_i)\}^2)]$, and the particular weighting factor w_i used is given in Table 1.

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