Nuclear Magnetic Resonance Study of the Conformations of Atropine and Scopolamine Cations in Aqueous Solution

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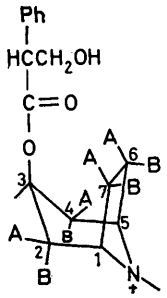
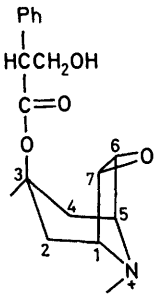
We have measured the ^1H and ^{13}C chemical shifts and ^1H–^1H coupling constants from the n.m.r. spectra of atropine and scopolamine cations. For both species, nuclei in symmetrical positions in the tropane ring shown non-equivalence because they experience different shielding effects from the aromatic substituent. We have estimated the different ring current shift contributions at the tropane ring nuclei for a wide range of conformations (varying the torsion angles ϕ_2—ϕ_5) and searched for the conformations which give the best fit to the measured chemical shift differences for the symmetrical pairs of nuclei. We find that the aromatic ring in atropine and scopolamine occupies approximately the same region of conformational space in both the crystal and solution states. In this special case where we are calculating several shielding differences (which can be measured accurately) attributed to ring current shifts this method of conformational analysis would be expected to give reliable results.

ATROPINE (I) and scopolamine (II) are powerful muscarinic antagonists of acetylcholine acting at the autonomic parasympathetic post-ganglionic junction.



(I)



(II)

Pauling and Petcher [1,2] have determined the crystal structures of these antagonists and compared them with the crystal structure of acetylcholine. Similarities in the conformational structures of all three molecules in the crystal state led them to the tentative conclusion that atropine analogues and acetylcholine bind to the muscarinic receptor in similar ways and at the same binding site. The rationale behind this reasoning assumes first that the crystal structures are maintained in aqueous solution and secondly that it is molecules in these conformations which bind to the receptor. While it is sometimes possible to test the first assumption by obtaining solution conformations from n.m.r. spectroscopy and potential energy calculations, it is more difficult to comment on the second assumption in the absence of information about the conformations of the molecules when bound to the receptor sites. Acetylcholine and most of its analogues have been shown by n.m.r. methods to have the same synclinal O–N^+ *gauche*-structure in solution as found in the crystal state. The purpose of this present study is to examine the ^1H and ^{13}C n.m.r. spectra of atropine sulphate and scopolamine hydrobromide in aqueous solution in order to establish their solution conformations. To understand fully the energetics of the interactions of the molecules with their receptors it will be necessary to determine their conformations both in solution and in the bound state. Thus there is considerable interest in determining the solution conformation of such molecules even though the full potential of the results will not be realised until the conformations in the bound states are also measured.

EXPERIMENTAL

Scopolamine hydrobromide (B.D.H. Ltd.) and atropine sulphate (Sigma Chemicals Ltd.) were obtained commercially and used without further purification. The ^1H n.m.r. spectra were obtained at 100, 220, and 270 MHz using Varian (HA100, HR220), Perkin-Elmer (R34), and Bruker (WH 270) spectrometers and the ^{13}C spectra at 25.2 MHz using a Varian XL-100 instrument equipped with proton noise decoupling facilities. The ^{13}C spectra and some of the ^1H spectra were recorded using the Fourier transform mode of operation.

The compounds were examined as 10% w/w solutions in D_2O using DSS (sodium 4,4-dimethyl-4-silapentane-1-sulphonate) as an internal reference for the ^1H spectra and dioxan as a reference material for the ^{13}C studies. Some ^1H n.m.r. measurements were also made at lower concentrations (5 and 50mM) to assess the effects of intermolecular interactions on the chemical shifts. The effects on the shielding differences for symmetrical pairs of protons in the tropane ring were negligible (<0.02 p.p.m.).

Most of the measurements were made at 28 °C but some were made at 70 °C where better resolved spectra were obtained. The effects of temperature on the shielding differences for tropane ring protons are negligible except for the H(2)–H(6) difference which for scopolamine decreases from 0.71 (28 °C) to 0.61 p.p.m. (70 °C).

RESULTS

^1H *Studies.*—In the 270 MHz ^1H n.m.r. spectra of the cations of atropine and scopolamine all the tropane ring protons were found to be magnetically non-equivalent. This is illustrated in the ^1H spectrum of scopolamine hydrobromide shown in Figure 1. The protons on the C(1)—(3) and C(3)—(5) fragments give separate ABMX type spectra from which we have calculated the chemical shifts and coupling constant shown in Tables 1 and 2. As noted previously [3-5] the non-equivalent H(6) and H(7) in the epoxide ring of the scopolamine cation appear as two AB doublets (J 3.6 Hz) broadened by a small coupling to the adjacent protons ($J_{56} < 1$ Hz).

The ^1H spectrum of the atropine cation is much more complicated and it was not possible to do a detailed analysis

[1] P. J. Pauling and T. J. Petcher, *Chem. Comm.*, 1969, 1001.
[2] P. J. Pauling and T. J. Petcher, *Nature*, 1970, **228**, 673.
[3] S. R. Johns and J. A. Lamberton, *Chem. Comm.*, 1965, 458.
[4] M. Ohashi, I. Morishima, K. Okada, T. Yonezawa, and T. Nishida, *Chem. Comm.*, 1971, 34.
[5] N. Mandava and G. Fodor, *Canad. J. Chem.*, 1968, **46**, 2761.

of all the tropane ring proton signals; however, the ABMX spin systems for protons on C(1)—(3) and C(3)—(5) could be analysed (see Table 2). The shifts of the signals from the remaining ring protons (ABCD system) were estimated from the centres of their multiplets. The coupling constants measured for the atropine cation are given in spectra of these cations and have shown that each of the non-equivalent tropane ring carbons leads to a separate ^{13}C signal. For atropine, it is difficult to make unambiguous assignments for the C(2) and (4) and C(6) and (7) and it appears that the original assignments should be reversed. Simeral and Maciel [7] based their assignments mainly on the

TABLE 1

The ^1H and ^{13}C chemical shifts in the tropane rings of the atropine and scopolamine cations

	Atropine				Scopolamine	
	NMe equatorial		NMe axial		NMe axial	
	^1H Chemical shift (δ)	Difference			^1H Chemical shift (δ)	Difference
H(1)	3.71	0.12			3.82	0.12
H(5)	3.83				3.94	
H(2)	2.28				2.40	
	1.88	0.06			1.82	0.07
H(4)	2.34	0.21			2.47	0.22
	2.09				2.04	
H(3)	5.04				5.05	
H(7)	1.54				3.07	0.73
	1.95	0.53				
H(6)	2.07	0.13			3.80	
	2.08					
	^{13}C Chemical shift (δ)	Difference	^{13}C Chemical shift (δ)	Difference	^{13}C Chemical shift (δ)	Difference
C(1)	62.94	~0.10 *	59.37	~0	58.13	0.14
C(5)	62.94		59.37		58.27	
C(2)	35.04	0.14	28.56	~0.1 *	25.20	~0.15 *
C(4)	35.18		28.56		25.20	
C(6)	24.01	0.25	26.02	0.24	53.92	0.35
C(7)	23.76		25.78		53.57	
C(3)	66.33				64.68	
NCH_3	39.33		32.4		25.72	

^1H Shifts referenced to DSS. ^{13}C shifts were measured from a dioxan reference and transferred to a Me_4Si reference scale. Errors in ^1H chemical shifts ±0.01 p.p.m. except for the H(6) and H(7) of atropine (±0.05 p.p.m.). Errors in ^{13}C chemical shifts ±0.03 p.p.m.

* Estimated from line widths.

Table 2 and are seen to be similar to the corresponding coupling constants in scopolamine hydrobromide.

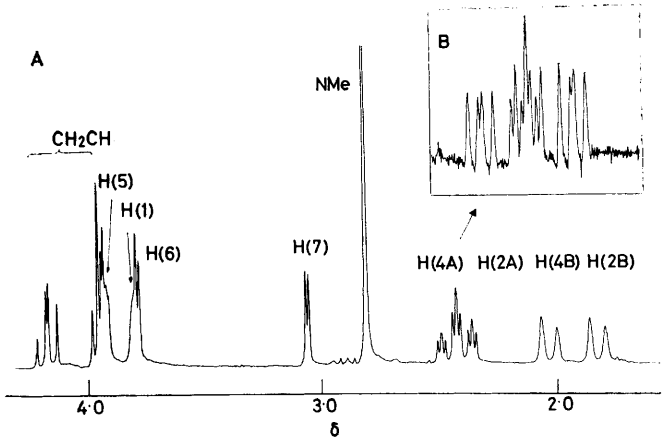


FIGURE 1 The high field region of the 270 MHz ^1H spectrum of scopolamine (5mM) at 70 °C

The spectra of the CH_2CH fragments in both molecules were analysed as ABC systems and gave chemical shifts and coupling constants in good agreement with each other and also with those observed previously for tropic acid.[6]

^{13}C *Studies.*—Simeral and Maciel [7] have studied the ^{13}C

[6] V. S. Dimitrov, S. L. Spassov, T. Zh. Radeva, and J. A. Ladd, *J. Mol. Structure*, 1975, **27**, 167.

similarity in chemical shift between the high field signals in the stropine cation (23.76 and 24.01 p.p.m.) and that for the scopolamine cation (25.2 p.p.m.) which can be assigned unequivocably to C(2) and (4). However, the *N*-methyl group has a different configuration in the two cations and this will influence the shielding of the tropane ring carbons. For example, a methyl group *syn* to a carbon as found for

TABLE 2

The ^1H–^1H spin coupling constants for the tropane ring nuclei in the atropine and scopolamine cations

Coupling constant (Hz)	Scopolamine	Atropine
$J_{3,2A}$	1.0	<2
$J_{3,2B}$	3.8	4.4
$J_{2A,2B}$	17.3	16.8
$J_{1,2B}$	4.8	4.2
$J_{5,4B}$	4.8	4.7
$J_{1\,2A}$	1.3	
$J_{5,6A}$	<2.0	
$J_{6A,7A}$	3.6	
$J_{1,7A}$	<2.0	

Errors: scopolamine ±0.1, atropine ±0.2 Hz.

NMe and C(2) and (4) in the *N*-methyl axial isomer can cause large upfield shifts (*ca.* 5 p.p.m.).[8] For this reason we have also considered the ^{13}C chemical shifts of the small

[7] L. Simeral and G. E. Maciel, *Org. Magnetic Resonance*, 1974, **6**, 226.

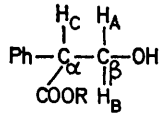
[8] J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972.

amount (*ca.* 9%) of the atropine *N*-methyl axial isomer which is present in the equilibrium mixture. The signal at 28.56 p.p.m. for this isomer and those at 35.04 and 35.18 p.p.m. in the spectrum of the *N*-methyl equatorial isomer can thus be assigned to C(2) and (4). Likewise the high field signal of the *N*-methyl equatorial form (23.76 and 24.01 p.p.m.) can be assigned to C(6) and (7) because its shift is to lower field (25.78 and 26.02 p.p.m.) of the corresponding signal of the *N*-methyl axial form.

For the scopolamine cation it is difficult to assign C(1) and (5) and C(6) and (7): the larger magnetic non-equivalence of the signals at 53.57 and 55.92 p.p.m. suggests that these correspond to C(6) and (7). In the ^1H spectrum of the scopolamine cation the largest chemical shift difference is observed for the protons on C(6) and (7) and one would expect similar effects for the carbon shielding difference since this also depends on ring current effects.

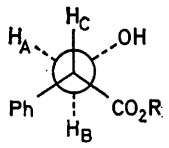
Determination of the Conformational Structures.—Several three-bond ^1H–^1H coupling constants have been measured for the cations of atropine and scopolamine (see Table 2) and by using Karplus type relationship between the coupling constants and torsion angles some information about the conformation is readily available.

Conformation of the (Ph)(CO_2R)CH–CH_2OH *moiety.* We have measured the J_{AC} and J_{BC} vicinal coupling constants

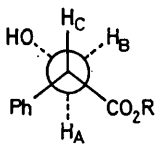


(III)

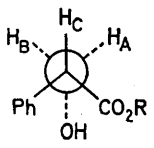
for the side-chain fragment (III) of both molecules in order to determine the conformation about the C_α–C_β bond. The coupling constants are found to be the same for both molecules (J_{AC} 6.5, J_{BC} 8.2 Hz) and also very similar to the values reported previously for tropic acid [6] (5.55, 8.88 Hz) indicating that all the molecules have similar side-chain conformations. It is usual to consider substituted ethanes of this type as rapidly interconverting mixtures of the three staggered rotamers (IV)—(VI) with



(IV)



(V)



(VI)

fractional populations $P_{(IV)}$, $P_{(V)}$, and $P_{(VI)}$ such that equation (1) applies. From consideration of coupling

$$P_{(IV)} + P_{(V)} + P_{(VI)} = 1 \qquad (1)$$

constants in model compounds and the effects of substituent electronegativity on their values we have estimated the component coupling constants in the rotamers to be J_{HH}^{gauche} 2.3 and J_{HH}^{trans} 12.1 Hz.* Thus the observed averaged vicinal coupling constants are given by equations (2) and (3). Equations (1)—(3) can be used to estimate the

$$J_{AC} = (P_{(IV)} + P_{(VI)})J_{HH}^{gauche} + P_{(V)}J_{HH}^{trans} \qquad (2)$$

$$J_{BC} = (P_{(V)} + P_{(VI)})J_{HH}^{gauche} + P_{(IV)}J_{HH}^{trans} \qquad (3)$$

fractional populations from the measured values of J_{AC} and J_{BC}. For these molecules it was found that only rotamers (IV) and (V) are significantly populated ($P_{(IV)}$ 0.60, $P_{(V)}$ 0.40, $P_{(VI)}$ 0.0). These results are essentially the same as those found previously for tropic acid.[6]

Conformation of the tropane ring. The tropane ring configurations and conformations for scopolamine (VI) has been determined previously using coupling constant and chemical shift data. Mandava and Fodor [5] have pointed out that the small observed coupling constants between H(2) and H(3) (1.0 and 3.8 Hz in the scopolamine cation) show that H(3) occupies an equatorial position. They have interpreted the remaining ring coupling constants in terms of a distorted chair conformation. In their 60 MHz studies they did not observe the non-equivalence of the pairs of protons at C(2) and (4) and C(2) and (5) positions seen in this present work. Fortunately there are no differences in coupling constants between the non-equivalent nuclei and their neighbours. We have estimated the torsion angles in the tropane ring of the scopolamine cation from the crystal structure and found that the values ($\chi_{C(1)-C(2)}$ = 60 ± 5, 60 ± 5°; $\chi_{C(1)-C(7)}$ = 70 ± 5°; $\chi_{C(2)-C(3)}$ = 40 ± 5, 80 ± 5°) are consistent with the small vicinal coupling constants observed in the n.m.r. studies. Thus the tropane ring appears to have a similar conformation in the solution and in the crystal state. For atropine only limited information about the coupling constants is available (see Table 2) but the values which could be measured are similar to those in scopolamine.

Crystal studies have shown that the configuration of the *N*-methyl group is different in the atropine (I) and scopolamine (II) cations.[1,2] N.m.r. studies have confirmed that the predominant configurations found in solution are the same as those in the crystal state.[5,7]

Overall molecular conformation using ring current shifts. Three-bond coupling constants can only provide local conformational information about the particular torsion angle characterised by the coupling constants. For non-rigid acyclic molecules containing several bonds it is usually impossible to construct the overall molecular conformation from such measurements. Other n.m.r. methods of conformational analysis such as studies of relaxation, nuclear Overhauser enhancements, lanthanide induced shifts, and shielding effects of anisotropic shielding groups are better suited to determining the relative positions in conformational space of non-bonded groups in the molecule. For example, in the structures of both atropine and scopolamine there is an aromatic residue which will cause appreciable ring current shifts of neighbouring nuclei in a manner which depends on the positions of the nuclei with respect to the ring. In principle this offers a method of conformational analysis which could lead to the overall shape of the molecules. In practice the method is difficult to apply and the results are of a somewhat qualitative nature. One of the main problems encountered is that of isolating the shielding contributions arising solely from ring current effects. Ideally one requires a model compound which lacks the aromatic ring but retains the same conformation. For the molecules under consideration here this problem can be circumvented by considering the shielding differences between corresponding nuclei in the tropane ring rather than the individual shifts. These shielding differences are given in Table 1 and arise from the unequal

* This analysis assumes that the J_{HH}^{gauche} and J_{HH}^{trans} values are the same in all three rotamers and will lead to some errors in the estimated populations (*ca.* ±10%).

anisotropic shielding effects of the aromatic ring in the presence of hindered rotation about the bonds in the O–C–C(:O)–C fragment. By comparing these shielding differences with the values calculated for an extensive set of conformations it has proved possible to determine the position of the aromatic ring with respect to the tropane ring.

Johnson and Bovey [9] have estimated the ring current chemical shift contributions at various co-ordinate positions near to an aromatic ring using equation (4) where n is the

$$\delta_{\text{p.p.m.}} = \frac{ne^2}{6\pi mc^2 a} \cdot \frac{1}{[(1+p)^2+z^2]^{\frac{1}{2}}} \left[K + \frac{1-p^2-z^2}{(1-p)^2+z^2} \cdot E\right] \quad (4)$$

number of circulating electrons in a loop of radius a, p, and z are the cylindrical co-ordinates (see Figure 2) expressed in units of a, and K and E are elliptical integrals.

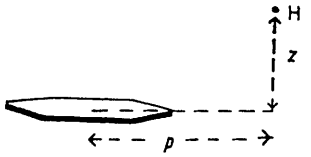
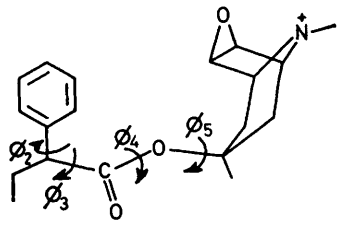


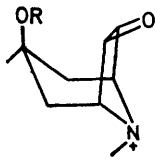
FIGURE 2 Cylindrical co-ordinates p and z of a proton with respect to an aromatic ring

We have written a computer program (RINGSCAN) which, starting from a set of Cartesian co-ordinates for an aromatic derivative, calculates the aromatic ring current shifts at any nucleus in the molecule. RINGSCAN first produces the required conformation of the molecule and then calculates the cylindrical co-ordinates z and p. The program allows the torsion angles [ϕ_2—ϕ_5 in structure (VIII)] to be varied systematically so that the ring current shifts (or shift differences) in any defined conformation can be calculated and then compared with experimental values to find the conformations which give the best fit to the observed data (as measured by the smallest value of the sum of the squares on the residuals Σr_i^2). In these calculations the tropane ring is considered to be rigid and in the same conformation as was found in the crystal structure. The elliptical integrals required in the Johnson and Bovey calculation were obtained using the rapidly convergent series of Bartky.[10] A Honeywell DDP 516 computer was used for the calculation of the chemical shifts (each conformation taking about 0.5 s).



(VIII)

In the case of atropine we were fitting eight values of shielding difference while for scopolamine we were dealing with seven values. Some additional information can be obtained by considering the ^{1}H shifts of scopine (IXa) and scopolamine (IXb) in $CDCl_3$: [5] these data indicate that H(6) and (7) of scopolamine have upfield shift contributions of 0.23 and 0.76 p.p.m. respectively which can be assumed to arise mainly from aromatic ring current effects. Although there will be some error in assuming these values are the same for the scopolamine cation in aqueous solution we have ensured that the solutions found using the shielding differences in Table 1 are also generally consistent



(IX)

(a) Scopine, R = H, $\delta_{H(6)} = \delta_{H(7)} = 3.6$

(b) Scopolamine, R = $COCH(CH_2OH)Ph$, $\delta_{H(6)}, \delta_{H(7)} = 2.84, 3.37$

with the approximate values of the total ring current shift contributions estimated above.

Scopolamine conformation. A global search of conformational space was conducted using RINGSCAN to examine all sterically allowed torsion angles of ϕ_2, ϕ_3, and ϕ_5 at 6° intervals, assuming the ϕ_4 torsion angle (the ester CO–O bond) to be the same as in the crystal structure. All the allowed solutions of this search had their ϕ_5 angle fairly close to the crystal values and when we plotted the structures the aromatic ring was found in conformations quite similar to that in the crystal structure. We then undertook a more detailed search of the conformations

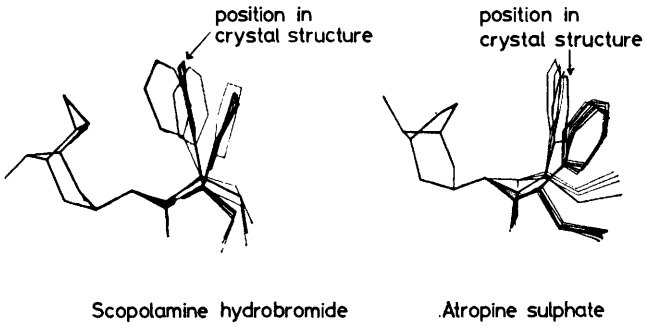


FIGURE 3 The family of conformations which show good agreement between observed and calculated ring current shielding contributions for the tropane ring nuclei in scopolamine and atropine. The positions of the aromatic rings in the crystal structures are also shown

around the crystal structure co-ordinates allowing all four torsion angles to vary in steps of 3° over a range of ±30° of the torsion angles in the crystal structure (20^4 conformations). The conformations of the scopolamine cation which gave best agreement between observed and calculated shielding differences for corresponding pairs of nuclei are given in Table 3. The close agreement between observed and calculated chemical shift differences can also be seen in Table 3. Some of the conformations together with the crystal structure conformation are plotted in Figure 3. It is interesting that the aromatic ring and the tropane ring always occupy the same general region of

[9] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

[10] W. Bartky, *Rev. Mod. Phys.*, 1938, **10**, 264.

conformational space near where the groups are in the crystal structure.

Atropine conformation. A detailed search of the conformations around the crystal co-ordinates of atropine was undertaken using RINGSCAN. All four torsion angles were varied in steps of 3° over a range of ±30° of the angles in the crystal structure. Table 2 and Figure 3 summarise the data for the conformations which showed the best fit between calculated and observed shielding differences. Again the aromatic ring is generally in the same region of conformational space in both the crystal and solution conformations.

would be a mixture of interconverting conformers especially involving rotation about the ϕ_2 and ϕ_3 torsion angles. It is not possible to incorporate such effects into the calculations. However, in view of the broad agreement between the positions of the aromatic ring in the crystal and 'solution' structures it does indicate that the dominant solution conformations are similar to the crystal structure conformation.

Conclusions.—The aromatic ring in the atropine and scopolamine cations occupies approximately the same region of conformational space in both the crystal and solution states. The CH_2OH side-chain exists as a mixture

TABLE 3

The families of conformations giving best agreement between calculated and observed shielding differences for the nuclei in the tropane ring of scopolamine and atropine cations

Scopolamine

Torsion angles *				Calculated shielding differences								
ϕ_2	ϕ_3	ϕ_4	ϕ_5	|H(1) − H(5)|	|C(2) − C(4)|	|H(2B) − H(4B)|	|H(2A) − H(4A)|	|H(6) − H(7)|	|C(6) − C(7)|	|C(1) − C(5)|	Σr_i^2	Distance (Å) ring–N-atom †
−30	21	−6	18	0.17	0.11	0.05	0.24	0.75	0.24	0.13	0.017	6.88
−30	24	−6	15	0.17	0.11	0.05	0.23	0.74	0.24	0.13	0.017	6.90
−30	24	−3	15	0.19	0.12	0.06	0.26	0.75	0.25	0.14	0.017	6.85
−30	21	−9	18	0.17	0.11	0.05	0.24	0.75	0.24	0.13	0.017	6.93
−27	21	−9	18	0.16	0.11	0.06	0.24	0.74	0.24	0.13	0.017	6.92
−27	27	−6	12	0.18	0.12	0.06	0.25	0.72	0.24	0.14	0.018	6.91
−18	−30	−12	6	0.17	0.12	0.06	0.25	0.74	0.24	0.13	0.017	5.82
−9	27	−18	6	0.17	0.12	0.07	0.26	0.74	0.23	0.13	0.018	7.00
Observed shifts				0.12	0.15	0.07	0.22	0.73	0.35	0.14		

Atropine

Torsion angles				Calculated shielding differences								
ϕ_2	ϕ_3	ϕ_4	ϕ_5	|H(1) − H(5)|	|C(2) − C(4)|	|H(2B) − H(4B)|	|H(2A) − H(4A)|	|H(6A) − H(7A)|	|C(6) − C(7)|	|C(1) − C(5)|	|H(6B) − H(7B)|	Σr_i^2	Distance Å ring–N-atom
−9	12	−18	21	0.15	0.11	0.06	0.23	0.55	0.17	0.12	0.15	0.009 9	7.10
−3	9	−27	21	0.13	0.11	0.05	0.21	0.55	0.16	0.11	0.14	0.009 7	7.10
−6	12	−21	21	0.15	0.12	0.06	0.23	0.54	0.17	0.12	0.15	0.010 0	7.12
−9	6	−24	−30	0.14	0.11	0.05	0.22	0.53	0.16	0.11	0.14	0.009 8	6.52
−15	9	−15	27	0.14	0.11	0.05	0.22	0.53	0.16	0.12	0.14	0.009 9	7.09
−18	6	−12	−30	0.15	0.11	0.05	0.22	0.55	0.17	0.12	0.14	0.009 8	6.19
3	21	−24	6	0.15	0.11	0.06	0.22	0.55	0.17	0.12	0.15	0.009 8	7.17
−3	12	−24	18	0.14	0.11	0.06	0.22	0.56	0.17	0.11	0.15	0.009 7	7.11
3	15	−27	12	0.14	0.11	0.06	0.22	0.55	0.17	0.11	0.15	0.009 7	7.14
0	24	−21	3	0.15	0.11	0.05	0.21	0.55	0.17	0.12	0.16	0.010 0	7.16
−9	6	−24	−30	0.14	0.11	0.05	0.22	0.53	0.16	0.11	0.14	0.009 8	6.52
−12	12	−15	21	0.15	0.11	0.05	0.22	0.56	0.17	0.12	0.15	0.010 0	7.07
−12	6	−18	−30	0.15	0.12	0.06	0.24	0.55	0.17	0.12	0.14	0.009 8	6.35
Observed shifts				0.12	0.14	0.06	0.21	0.53	0.25	0.10	0.13		

* Torsion angles in crystal structure taken as zero. † Distance from nitrogen atom to the centre of the aromatic ring.

Table 3 also contains the calculated values of the distance between the centre of the aromatic ring and the nitrogen atom: for both the atropine and scopolamine cations the distances are *ca.* 1 Å different from the crystal values (6.1 and 5.9 Å respectively).

An examination of the data in Table 3 reveals that for both atropine and scopolamine there are several combinations of torsion angles which result in the aromatic and the tropane rings being in the same positions relative to each other. Thus while this method can give us information about the positions of the rings it cannot give much useful information about the exact values of these torsion angles. This is not surprising since we have not used the shifts of any nuclei in the O–C(:O)–CH–C fragment in our fitting procedure.

In the calculations we have assumed a single conformation for the molecules although it seems likely that there of rotamers (IV) and (V) with fractional populations of 0.60 and 0.40 respectively.

Although the configuration of the *N*-methyl group is different in the atropine and scopolamine cations the overall conformations of the two species appear to be very similar.

The general agreement between the solution and crystal conformations strongly indicates that, in this special case where several shielding differences in a molecule can be attributed to ring current shifts, the method of conformational analysis (using RINGSCAN) discussed in this paper can be used with considerable confidence.

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