Conformational Pseudopolymorphism and Solid-State CPMAS NMR Studies for Determination of Solvent-Dependent Solution-State Conformational Preferences for (−)-Scopolamine Hydrobromide/Hydrochloride Salts

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Crystalline (−)-scopolamine hydrohalide (bromide and chloride) salts exist in two conformational families for the tropate ester moiety: the *compact* conformation (hydrates, phenyl ring underneath the scopine moiety), and the *extended* conformation (anhydrates, phenyl ring ca. *antiperiplanar* to oxiranyl O-atom). CPMAS ^{13}C NMR solid-state spectra of anhydrates and hydrates are different. In both tertiary and quaternary scopolammonium salts, phenyl rings are immobile in *compact* conformation crystals having ca. 2.5 Å close lateral neighbors on both faces of the planar moiety. Phenyl rings undergo a π-flip in *extended* conformation crystals having ca. 3.0 Å close lateral neighbors on either face of the aromatic plane. Due to different O=C−Cα−*C*H_2OH dihedral angles [*synperiplanar* (*eclipsed*, in *compact*) and (+)-*synclinal* (gauche, in *extended*)], the methylol carbon chemical shifts of crystalline tertiary and quaternary scopolammonium salts and analogues are diagnostic markers for the tropate ester solid-state conformation [δ*C*H_2OH downfield from alkoxy δC(3) for *extended* conformations and upfield of δC(3) in *compact* conformations]. These solid-state model $\Delta\delta$ relationships were used to deconvolute weighted time-averaged chemical shifts in different solvents: e.g., one *axial N*-methyl scopolammonium bromide phenyl-ring face is solvent exposed in the *compact* conformation predominating in D_2O medium, while both faces are solvent accessible in the *extended* major conformational contributor in CD_2Cl_2 solution.

Introduction

The constraints of the crystalline lattice usually trap conformationally flexible molecules into one of the multiple low-energy conformers existing in solution. Efficient molecular packing within the extended array is usually a very important factor. Polymorphism (or in the case of solvate adducts, pseudopolymorphism) is a well-known crystallographic phenomenon. While these differently packed polymorphic crystals usually result from disparate crystallization conditions, sometimes they can even be found within conglomerates of crystals grown within the same vessel. Like the phenomenon of multiple molecules in the asymmetric unit of a crystal, polymorphism need not involve different conformations. However, when polymorphs or pseudopolymorphs do show different conformations (i.e., conformational polymorphism), this provides an opportunity to search for solid-state CPMAS conformationally diagnostic ^{13}C (or ^{15}N, ^{31}P, ^{29}Si, etc.) chemical shift values. Some of these conformationally correlated solid-state chemical shifts can be significantly different from the isotropic ^{13}C NMR chemical shift values measured for corresponding nuclei in the solution-state spectrum. This is due to the fact that, in solution, weighted time-averaging of the NMR spectral parameters (chemical shifts and coupling constants) arises at the fast exchange limit (FEL) for conformational interconversion. On the other hand, the solution-state isotropic ^{13}C NMR chemical shift values of rigid molecules are usually very similar to those found in solid-state CPMAS spectra. Solid-state CPMAS NMR spectroscopy of X-ray crystallographically determined conformational polymorphs, and pseudopolymorphs, can provide a useful tool for deconvolution of the weighted time-averaged solution-state chemical shifts and, thus, enable a determination of the major conformational preference of the solvated molecule.

(−)-Scopolamine hydrobromide [(−)-hyoscine hydrobromide, **1**] is a well-known anticholinergic drug and is also used in the treatment of motion sickness.[1] (−)-Hyoscine is a tropane alkaloid natural product isolated from the belladonna plant *Hyoscyamus niger* (henbane) and consists of the (*S*)-(−)-tropic acid ester[2] of scopine, a

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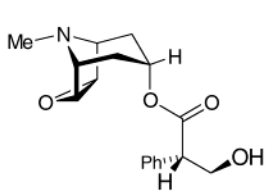
3-endo-substituted amino alcohol. NMR spectroscopy has been shown to be a useful tool to determine the stereochemistry of scopolamine and related compounds. On the basis of the time-averaged ^{13}C NMR *N*-CH_3 chemical shift in $CDCl_3$ solution, the *equatorial N*-methyl diastereomer of scopolamine free base was reported to be the predominant form at the fast exchange limit (FEL) for nitrogen-inversion.[3] While a recent nuclear Overhauser effect study was undertaken to ascertain the solution-state conformation about the tropate ester linkage in the free base,[4] it is still an open question due to the rapid interconversion of conformers.[5] Scopolamine has two stereogenic chirotopic[6] atoms: the relatively stereostable α-carbon and the stereolabile nitrogen. The important role of cis 1,3-diaxial interactions involving the *equatorial N*-methyl with the oxiranyl oxygen or the *axial N*-methyl with the piperidinyl-ring *axial* protons was recently studied by ab initio molecular modeling techniques.[7]

The NMR observation of *N*-methyl diastereomers of scopolamine is linked to the time-scale of measurement. Scopolamine hydrobromide in D_2O gave a dynamic ^{13}C NMR spectrum with decidedly broadened peaks (especially for the *N*-methyl carbon).[3] The relatively low 7.55 pK_a of scopolammonium cation vis-à-vis the more characteristic pK_a = 9.25 of atropine HBr[8] was probably behind the inconsistent *N*-CH_3 chemical shift values of 53.4,[9] 34.3,[10] and 25.7[11] ppm reported for the single species of **1** in D_2O. We noted that addition of three drops of trifluroacetic acid to a 3 mL D_2O solution of **1** markedly sharpened the peaks in the spectrum and now afforded two species in a ca. 9:1 ratio.[3] These were shown to be the respective *axial* and *equatorial N*-methyl diastereomers (**2a**,**2e**) at the slow exchange limit (SEL) for epimerization via prototropic-shift/nitrogen-inversion. Surprisingly, a dramatic reversal of ca. 2:9 was measured for these same diastereomers in CD_2Cl_2.[3] However, the relative disposition of the scopine alkoxy moiety relative to the tropate ester phenyl group was not forthcoming from these studies.

Crystalline (−)-hyoscine hydrobromide (**1**) was first reported as a hemihydrate, but no atomic coordinates were presented nor were any to be found in the Cambridge Crystallographic Data Base.[12] It was depicted pictorially with an *axial N*-methyl group, a "*compact*" conformation (phenyl-ring under the oxiranyl moiety), and an *antiperiplanar* (ca. 180°) phenyl-to-methylol OH arrangement.[12] Other stereochemical studies of this molecule, its derivatives, and analogues made use of this early X-ray determined structure.[11,13−17] Recrystallization of **1** from ethanol/acetone afforded an anhydrous conformational pseudopolymorph [(N*r*,Cα-*S*)-(−)-scopolamine hydrobromide anhydrate, **3**] with an "*extended*" solid-state conformation, i.e., a different conformation from that in the illustration depicted for the hemihydrate.[18]

Slow recrystallization of **1** from water produced a stable sesquihydrate (**4**),[19] as opposed to the trihydrate form which is listed in the *United States Pharmacopeia 23 Official Monographs*.[20] The crystal [unit cell parameters (293 K)] and molecular (293, 213, and 180 K data sets) geometries of **4** were *identical* in all respects to those of the *compact* conformation hemihydrate[12] form reported earlier by Pauling and Petcher. Crystals of our sesquihydrate belonged to the tetragonal $P4_32_12$ space group and the 293 K data set structure refined to an *R(F)* value of 0.051,[19] while those of the hemihydrate were reported as



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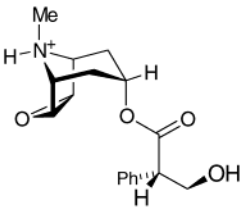

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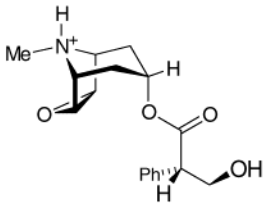

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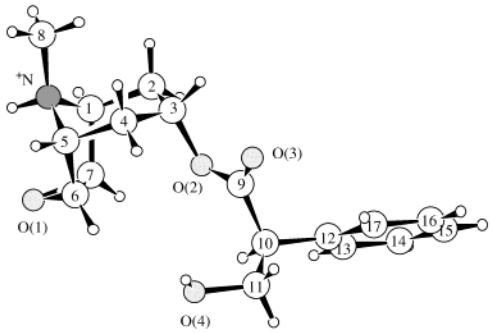

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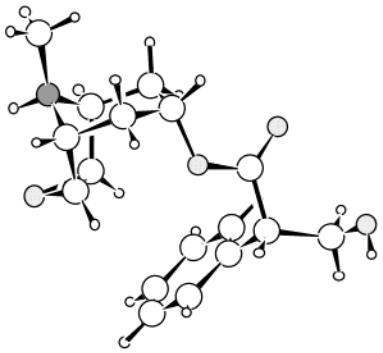

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belonging to the tetragonal $P4_12_12$ space group (containing a right-handed 4_1-screw) and only refined to an *R(F)* of 0.09.[12]

The structures of crystalline (−)-scopolamine hydrochloride anhydrate (**5**) and scopolamine hydrochloride 1.66 hydrate **(6)** were recently determined, and each was found to be similar to that of the corresponding hydrobromide analogue.[21] In addition to the hydrohalide anion, **6** differed from **4** in that an additional special C_2-positioned water molecule was present in ca. one-third of the unit cells of **6**. The hydrobromide "trihydrate" form was recently shown to be a conglomerate of **4** plus two or more hydrated forms, which undergo a temperature-induced phase-transition to yield only **4** when the 4 mm CPMAS rotor was spun at high speeds.[21] This paper illustrates the use of CPMAS ^{13}C NMR spectroscopy on

Table 1. Solid-State CPMAS ^{13}C NMR Spectral Parameters for Scopolamine Hydrohalide Salts and Related Compounds[a]

	scopolamine						(−)-hyoscamine
atom	HBr anhydrate (**3**)	HBr·1.5H_2O (**4**)	HCl anhydrate (**5**)	*eq*Bu^{n}Br MeOH (**7**)	MeBr (**8**)	*N*-oxide HBr (**11**)	HBr (**10**)
C(1)	56.6 (70)	56.5 (51)	56.0	65.5	63.7	70.1	61.5
C(2)	25.0 (73)	23.2 (50)	24.9	28.6	28.1	30.4	33.5
C(3)	63.7 (63)	64.1 (54)	63.4	61.6	61.4	62.7	65.5
C(4)	25.0 (73)	24.0 (49)	24.9	29.5	29.2	31.8	34.8
C(5)	56.6 (70)	57.2 (55)	56.4	66.8	65.5	70.6	61.5
C(6)	51.0 (85)	51.7 (62)	51.2	54.7	53.0	54.9	23.9
C(7)	51.0 (85)	51.0 (66)	51.2	54.7	52.7	54.9	23.0
C=O	173.2 (89)	171.4 (84)	173.2	175.6	171.4	171.0	172.8
C(α)	56.0 (56)	55.9 (37)	55.6	56.7	56.1	51.6	57.4
C(*β*)	64.6 (6)	60.5 (19)	64.3	65.5	59.7	63.4	61.5
NCH_3ax	32.7 (≤1)	32.5 (≤1)	31.9	45.5	47.7	45.0	
NCH_3eq					54.3		39.7
C(ipso)	134.6 (82)	138.3 (55)	134.4	137.4	139.0	134.4	136.1
C(ortho)	*π*-flip	128.0 (33)	*π*-flip	*π*-flip	127.5	127.4	128.2
C(ortho′)	*π*-flip	130.1 (35)	*π*-flip	*π*-flip	129.1	129.9	128.2
C(meta)	*π*-flip	130.6 (35)	*π*-flip	*π*-flip	131.0	129.9	132.7
C(meta′)	*π*-flip	133.3 (32)	*π*-flip	*π*-flip	131.7	131.6	133.0
C(para)	126.3 (73)	127.3 (31)	126.1	129.8	125.3	125.7	126.3
NCH_2eq			67.0				
NCCH_2			24.0				
NCCCH_2			19.0				
NCCCCH_3			12.0				
CH_3OH				48.4			
^{15}N	−330.5	−335.2					

[a] Ppm, 125.76 MHz (^{13}C) and 50.70 MHz (^{15}N), T_1 values (s) given in parentheses, external spectral references: glycine 176.03 δC=O and $^{15}NH_4{}^{+15}NO_3{}^-$ −5.25 $\delta^{15}NO_3{}^-$ ($CH_3{}^{15}NO_2$ scale), assignments within a diastereotopic pair are arbitrary.

scopolamine hydrobromide conformational pseudopolymorphs to ascertain the preferred conformations in D_2O and in CD_2Cl_2 solutions.

Results and Discussion

Solid-State NMR Spectroscopy of Scopolamine Tertiary and Quaternary Salts. ^{13}C CPMAS NMR spectroscopic parameters of scopolamine HBr pseudopolymorphs **3**, **4**, the HCl anhydrate salt (**5**), and related compounds are presented in Tables 1 (solid-state) and 2 (solution-state). Carbon nuclei multiplicities were determined by the following protocol of four solid-state experiments: regular CPMAS (all carbons seen), NQS (nonquaternary and nonmethyl carbon suppression−a 50 μs dipolar dephasing T_2 delay experiment affording signals from inefficiently T_2 relaxed quaternary and methyl nuclei), CPPI[22] (cross-polarization/polarization-inversion, signals seen for methylene carbons only), and T_1 inversion−recovery delay (signals from efficiently T_1 relaxed methyl nuclei disappear after a 30 s delay). Complete determinations of T_1 relaxation values were made for pseudopolymorphs **3**,**4** (see Table 1). The numbering system is presented in structure **3**.

The two conformational pseudopolymorphs of scopolamine hydrobromide afford very different cpmas ^{13}C NMR (125.76 MHz) spectra. Since conformationally diagnostic chemical shifts from two pseudopolymorphs will be used to ascertain the conformational preference in solvents of high and very low dielectric constant, it is important to discuss the cpmas chemical shift assignments. Internally diastereotopic pairs of nuclei [C(1,5), C(2,4), and C(6,7)] in the scopine moiety and in the phenyl ring [C(13,17) and C(14,16)] are anisochronous, as expected, in the CPMAS spectrum of scopolamine HBr sesquihydrate **4**. Assignments for the C(2,4) methylene carbons versus that of methylol C(11) were readily made based upon the "methylene-only"[22] CPPI spectrum chemical shifts of δ 23.2, 24.0 versus a low-field resonance at δ 60.5, assigned to C(11). Depending upon the conformation, one (or the other) of the diastereotopic scopine methylene carbons [C(2,4)] has a *γ-gauche* effect: diastereotopic C(2) and C(4) are respectively gauche and *antiperiplanar* to carbonyl C(9) in the *compact* conformation, while their spatial dispositions are reversed in the *extended* conformation. Differential assignments will not be made for specific nuclei *within* a diastereotopic pair, and thus, assignments in such pairs are arbitrary. The methylol carbon T_1 value was the shortest (19 s) for the molecule after that of the δ 32.5 rotationally mobile *N*-methyl (<1 s). The six aliphatic methine carbons [tropate-C(10) and C(3) and diastereotopic C(1,5), C(6,7) scopine carbons], fall into three groups of chemical shifts which exhibit the following T_1 values: s, 66, 62 (for δ 51.0, 51.7); 37, 51, 55 (for δ 55.9, 56.5, 57.2); and 54 (for δ 64.1). This enabled δ 55.9 and 64.1 assignments for C(10) and alkoxy C(3), respectively. Furthermore, in addition to the T_1 argumentation, the almost equal intensity signals at δ 56.5 and 57.2 vis-à-vis the ca. 18% higher intensity signal at δ 55.9 are consistent with the lower field signals arising from an internally diastereotopic pair. One expects that chemical shift values for the rigid scopine moiety should bear a close similarity to those measured in solution. Differentiation of C(1,5) from C(6,7) was based upon comparison with the 2D-HMQC hetereonuclear $^1H/^{13}C$ correlated values of δ 56.7, 56.9,

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Table 2. Solution-State ^{13}C NMR Spectral Parameters for Scopolamine Hydrohalide Salts and Related Compounds[a]

	scopolamine						atropine mesylate[d] (hemisulfate)	
atom	HBr[b] *ax*Me (**2a**) CD_2Cl_2 (D_2O)	HBr[b] *eq*Me (**2e**) CD_2Cl_2 (D_2O)	*eq*Bu^{n}Br (**7**) $CDCl_3$ (D_2O)	MeBr (**12**) D_2O	*ax*Bu^{n}Br (**8**) $CDCl_3$ (D_2O)	free base[c] (**17**) $CDCl_3$	*ax*Me (**10a**) CD_2Cl_2 (D_2O)	*eq*Me (**10e**) CD_2Cl_2 (D_2O)
C(1)	56.70 (59.49)	61.86 (64.02)	63.44 (65.83)	68.12	65.15 (67.64)	57.8	58.31 (61.14)	62.29 (64.80)
C(2)	24.99 (26.33)	30.27 (32.91)	28.99 (30.70)	31.04	28.83 (30.65)	30.8	28.49 (30.31)	34.53 (36.94)
C(3)	62.65 (66.26)	64.46 (66.95)	63.70 (66.03)	65.07	61.42 (65.19)	66.9	64.21 (68.41)	65.07 (68.32)
C(4)	25.11 (26.22)	30.43 (33.10)	29.09 (30.70)	31.04	28.93 (30.65)	31.0	28.61 (30.41)	34.70 (37.10)
C(5)	56.90 (59.65)	62.01 (64.20)	63.57 (65.84)	68.26	65.47 (67.76)	57.9	58.41 (61.26)	62.39 (64.80)
C(6)	52.76 (55.52)	54.40 (56.53)	53.94 (56.75)	56.75	53.59 (56.27)	56.4	25.80 (27.93)	24.05 (25.93)
C(7)	52.27 (55.17)	54.15 (*e*)	53.64 (56.47)	56.46	53.20 (55.99)	56.0	25.44 (27.71)	23.59 (25.68)
C=O	*e* (175.05)	171.54 (*e*)	171.63 (175.02)	175.02	171.65 (175.09)	171.8	*e* (*e*)	171.88 (175.77)
C(α)	*e* (56.17)	53.6 (*e*)	54.26 (56.08)	56.09	54.21 (56.09)	54.4	*e* (*e*)	54.50 (56.37)
C(*β*)	64.22 (64.64)	64.07 (*e*)	62.36 (64.53)	64.58	63.96 (64.54)	64.0	64.13 (64.94)	63.97 (64.93)
N*C*H$_3$*ax*	32.12 (32.83)		46.10 (47.24)	50.08			31.95 (34.13)	
N*C*H$_3$*eq*		45.06 (46.85)		59.23	53.83 (56.50)	42.2		39.27 (41.26)
C(*ipso*)	*e* (138.28)	136.01 (*e*)	135.63 (138.16)	138.16	135.33 (138.12)	135.8	*e* (*e*)	135.80 (138.07)
C(*ortho*)	*e* (131.04)	128.46 (*e*)	128.07 (131.00)	131.02	128.05 (130.99)	128.1	*e* (*e*)	128.45 (131.08)
C(*meta*)	*e* (131.93)	129.46 (*e*)	128.92 (131.89)	131.90	128.99 (131.91)	129.0	*e* (*e*)	129.93 (131.92)
C(*para*)	*e* (130.99)	128.46 (*e*)	127.89 (130.95)	130.96	128.05 (130.99)	127.9	*e* (*e*)	128.12 (130.93)
N*C*H$_2$*ax*			− (−)		59.25 (61.75)			
N*C*H$_2$*eq*			68.73 (71.66)					
NC*C*H$_2$			24.74 (26.77)		25.30 (26.86)			
NCC*C*H$_2$			19.48 (21.56)		20.02 (22.01)			
NCCC*C*H$_3$			13.59 (15.49)		13.83 (15.51)			

[a] Ppm, 125.76 MHz, CD_2Cl_2 or $CDCl_3$, D_2O measurements given in parentheses, internal spectral references: tetramethylsilane or 4,4-dimethyl-4-silapentanesulfonate sodium salt; assignments within a diastereotopic pair are arbitrary. [b] Acidic D_2O (10 drops of trifluoracetic acid in 0.5 mL of D_2O), 90:10 ratio of axial/equatorial *N*-methyl diastereomers in D_2O, 18:82 ratio of axial/equatorial *N*-methyl diastereomers in CD_2Cl_2. [c] Data taken from ref 4. [d] Data for mesylate taken from ref 3 (DEPT-135) with exception of δC=O and δCipso measured in $^{13}C\{^1H\}$ spectrum, $CH_3SO_2O^-$ δ 39.42, 8:92 ratio of axial/equatorial *N*-methyl diastereomers in D_2O, 5:95 ratio of axial/equatorial *N*-methyl diastereomers in CD_2Cl_2. [e] Not measured.

52.8, and 52.3 for the corresponding chemical shifts of *axial N*-methyl diastereomer methine nuclei C(1,5,6, and 7) in CD_2Cl_2 solution, while δC(3) in this solution-state spectrum was 62.7.

While the solid-state spectrum of scopolamine HBr sesquihydrate **4** does not show any unusual features, that for the HBr anhydrate (**3**) has a number of aspects deserving comment. It is well-known that line widths in solid-state CPMAS spectra are considerably higher than those measured in high-resolution liquid-state spectra. Even the spherical-shaped adamantane shimming standard affords widths at half-height, $W_{1/2}$, of only ca. 7−10 Hz, while values for nuclei in more typical organic molecules are about 40−50 Hz. Chemical shift anisochronicity for internally diastereotopic pairs of nuclei is based upon symmetry argument, but Δδ magnitudes are not forthcoming from such argumentation. The *axial N*-methyl scopolamine HBr narrow line widths in the CD_2Cl_2 solution-state high-resolution spectrum permit resolution of C(1,5), C(2,4), and C(6,7) internally diastereotopic pairs having respective Δδ values of 0.20, 0.12, and 0.49. While Δδ values of 0.67, 0.89, and 0.67 for the respective C(1,5), C(2,4), and C(6,7) internally diastereotopic pairs in crystalline sesquihydrate **4** are large enough for adequate resolution, those for anhydrate **3** fall within the line-widths. For example, $W_{1/2}$ for the unresolved C(2,4) and unresolved C(6,7) peaks were 64 and 55 Hz, respectively, compared to a 58(6) Hz mean value measured for other carbons in the molecule. In the HCl anhydrate analogue **5**, 0.33 Δδ resolution of the diastereotopic C(1,5) nuclei was now observed (separate δ 56.0 and 56.4 peaks), while the broadened signals for the unresolved C(2,4) and unresolved C(6,7) peaks showed $W_{1/2}$ = 93 and 69 Hz, respectively [48(3) Hz mean value for other carbons].

It is well-known that weighted time-averaged chemical shifts for internally diastereotopic ortho or meta aromatic carbon pairs are a common occurrence in solution-state NMR spectra due to *rapid topomerization* (e.g., rapid rotation about the Cα−Cipso bond axis in **2**). A striking feature in the solid-state spectrum of the **3** and **5** anhydrates is that both sets of "off-axis" ortho and meta internally diastereotopic carbons [C(13,14), C(16,17] appear as one very low intensity broadened hump at ca. δ 131, while the δ 134.6 and 126.3 signals for the respective "on-axis" C(12) ipso and C(15) para carbons in **3** are sharp. This observation is different from that for sesquihydrate **4** where aromatic carbons appear as six sharp resonances (as noted above). The sets of anisothermal parameters for aromatic carbons in sesquihydrate **4** and in anhydrate **3** are both very similar, which suggests that continuous rapid rotation or libration is *not* occurring about the C(10)−C(12) bond of **3**; i.e., they are *not* free rotors as in the solution state.

This phenomenon for aromatic rings, appropriately packed within the crystal lattice, is referred to as a "π-flip" and has been observed before.[23−25] For example, in *N*,*N*,*N*-trimethyl-2-phenylethylammonium bromide, the CPMAS-observed π-flip free energy of activation at ambient temperature (293 K) was calculated to be 10.0 kcal mol^{-1}.[25] It has been noted that a π-flip "involves significant van der Waals contacts, highlighting the need for lattice deformations to permit ring dynamics".[24] The π-flip may be correlated with the perpendicular distance of nearest neighboring atoms to the phenyl-ring mean

(23) Henrichs, P. M.; Luss, H. R.; Scaringe, R. P. *Macromolecules* **1989**, *22*, 2731.
(24) Clayden, N. J.; Williams, D. W.; O'Mahoney, C. A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 729.
(25) Riddell, F. G.; Rogerson, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 249.

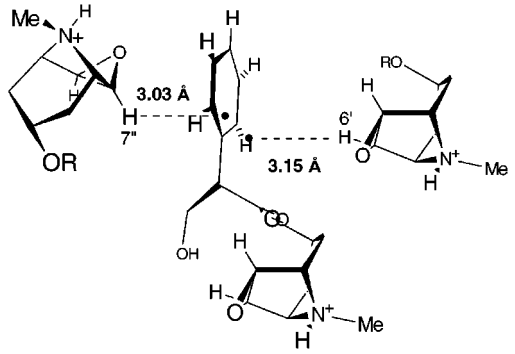


Figure 1. Iconic projection of X-ray crystallographically determined structures of (−)-scopolammonium cation of HBr anhydrate **3** and nearest neighbors on either side of the phenyl ring. In this *extended* conformation, the ca. 3.0 Å perpendicular minimum distances of lateral nearest neighbor atoms to the phenyl-ring plane are large enough for a phenyl-ring π-flip.

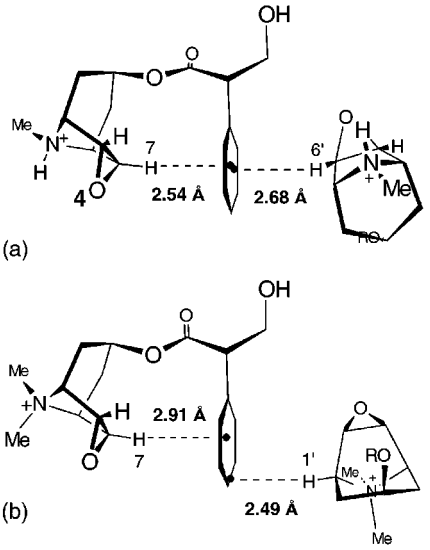


Figure 2. Iconic projection of X-ray crystallographically determined structures of (−)-scopolammonium cations of HBr sesquihydrate **4** (a) and of MeBr **8** (b) and nearest neighbors on either side of the phenyl rings. In these *compact* conformations, the ca. 2.5 Å perpendicular minimum distances of lateral nearest neighbor atoms to the phenyl-ring plane are too small for a phenyl-ring π-flip to occur.

best-plane. Figure 1 shows that oxiranyl-protons H(6′) and H(7″) are the nearest neighbors respectively 3.15 Å above and 3.03 Å below the anhydrate **3** phenyl ring best-plane (3.29 and 3.05 Å, respectively, in HCl anhydrate **5**). Immobile phenyl rings have closer nearest neighbors: oxiranyl protons H(6′) and H(7) are the nearest neighbors respectively 2.68 above and 2.54 Å below the sesquihydrate **4** phenyl ring best-plane (see Figure 2).

Other examples were investigated to probe the generality of the above observations regarding a correlationship between scopolamine tropate ester conformation and phenyl-ring ability to undergo a π-flip. Scopolamine *n*-butylbromide *equatorial N*-butyl diastereomer (Buscopan) is an antispasmodic drug.[26] CPMAS ^{13}C NMR spectroscopy shows two molecules in the asymmetric unit of the crystal and its molecular structure has not been reported. The structure of the crystalline methanol solvate adduct (**7**) has been determined by Carpy and coworkers[15] using X-ray crystallography. The single molecule in the asymmetric unit of adduct **7** has an *extended*

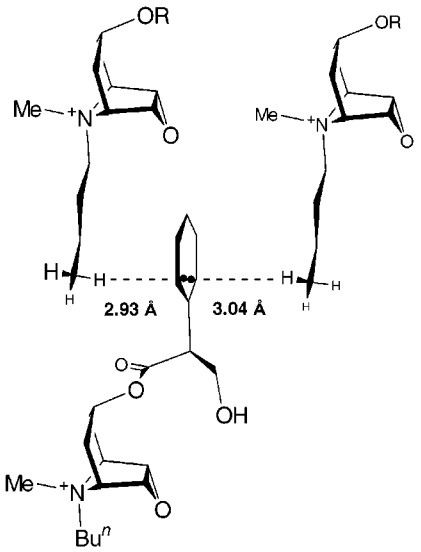


Figure 3. Iconic projection of X-ray crystallographically determined structure of (−)-*equatorial n*-butyl-scopolammonium cation of Bu^{n}Br methanol solvate adduct **7** and nearest neighbors on either side of the phenyl ring. In this *extended* conformation, the ca. 3.0 Å perpendicular minimum distances of lateral nearest neighbor atoms to the phenyl-ring plane are large enough for a phenyl-ring π-flip.

conformation very similar to that exemplified by **3** and **5** [superimposition of all similar heavy atoms of **5** and **7** on those of **3** gives a root-mean-square difference (rms) of 0.077 and 0.263 Å, respectively]. If ortho, meta, and para aromatic carbons are removed from the superimposition, the rms difference of **5** and **7** compared to **3** improves to 0.047 and 0.129 Å, respectively. Figure 3 shows that the phenyl ring lies between terminal methyl protons respectively 3.04 above and 2.93 Å below the phenyl-ring best plane. These are similar distances to those measured for **3** and **5**, and a π-flip is indeed observed in the CPMAS ^{13}C NMR spectrum also for **7** [δ 128.3 broadened hump "off-axis" ortho and meta carbons, δ 137.4 and 129.8 sharp peaks for respective "on-axis" Cipso and Cpara (see Table 1)].

Scopolamine methobromide (methscopolamine bromide, **8**) is also an anticholinergic drug.[27] We have recently reported its solid-state structure determination by X-ray crystallography.[21] The methobromide **8** has a *compact* conformation similar to that of the analogous methiodide[17] (**9**), HBr sesquihydrate **4**, and (−)-hyoscyamine HBr[14] (**10**, the *levo*-enantiomer of racemic atropine). The rms difference in the superimposition of all heavy atoms (with the exception of the oxiranyl-O and the *N*-methyls) of **8**, **9**, and **10** on corresponding atoms in **4** was, respectively, 0.167, 0.240, and 0.299 Å. If ortho, meta, and para aromatic carbons are removed from the superimposition, the rms difference of **8**, **9**, and **10** compared to **4** improves to 0.153, 0.206, and 0.200 Å., respectively. Figure 3 shows that neighboring H(1′) and H(7) protons are, respectively, 2.49 Å above and 2.91 Å below the phenyl-ring-best plane of **8**. CPMAS ^{13}C NMR spectroscopy shows an immobile phenyl ring in both **8** and **10** since all six aromatic carbons are clearly observed as sharp signals (see Table 1). Therefore, the presence and absence of a π-flip appears to be correlated to the void-space above and below the phenyl-ring in both tertiary-ammonium and quaternary-ammonium salts of

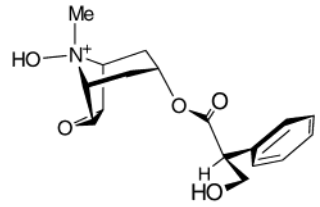
(26) Reference 1, p 261 and references therein.

(27) Reference 1, p 1028 and references therein.

scopolamine. The limited number of three *extended* and three *compact* conformational examples investigated strongly suggests that lattice deformations enable a π-flip to be observed when the nearest neighbor to both sides of the phenyl-ring is ca. 3.0 Å to the best-plane, while the ring is immobile when this minimum distance decreases to ca. 2.5 Å.

Inspection of Table 1 shows that with the exception of the above-mentioned severely reduced anisochronicity from internally diastereotopic pairs of carbon nuclei, the chemical shift values for carbons in the rigid scopine moiety of **3** are very similar to values for corresponding carbons in sesquihydrate **4**. However, there is a third feature of note in the anhydrate **3** CPMAS spectrum. The methylol carbon, C(11), now affords the lowest field aliphatic chemical shift (unequivocally assignable from the CPPI "methylene-only" spectrum). This δ 64.6 value in *extended* conformation **3** is significantly downfield compared to the δ 60.5 value for the corresponding nucleus in the *compact* conformation of sesquihydrate **4**. The chemical shift of this nucleus appears to be dependent upon the tropate ester conformation about the sp^2-sp^3 C(9)−C(10) bond. To a smaller extent, we have found that the chemical shift of the carbonyl nucleus, C(9), is also conformationally linked. Using the X-ray crystallographically determined structures of scopolamine salts **3**−**5** and other structurally related analogues (**7**, **8**, **10**, and **11**) it appears that there is a correlationship between the O(3)−C(9)−C(10)−C(11) torsion angle and the methylol C(11) [$\rho^2 = 0.902$ for the seven compounds in the study] and carbonyl, C(9), chemical shift values. As the tropate ester conformation changes from *extended* to *compact*, the (+)-*synclinal* [(+)-*gauche*, ca.60°] O(3)···C(11) *staggered* arrangement becomes more *eclipsed*, i.e., approaches a *synperiplanar* (ca. 0°) O(3)−C(9)−C(10)−C(11) torsion angle, and the methylol, C(11) chemical shift value moves upfield closer to TMS: δ 65.5 [61° O(3)−C(9)−C(10)−C(11) angle,[15] for **7**], 64.6 (56°,[18] for **3**), 64.3 (53°,[21] for **5**), 63.4 [25°,[28] for scopolamine *N*-oxide HBr (**11**)], 61.5 (18°,[14] for **10**), 60.5 (16°,[19] for **4**), and 59.7 (5°,[21] for **8**). Newman projections (see structures **12**−**14**) about the C(9)−C(10) bond are illustrated for the respective *extended*, *N*-oxide, and *compact* conformations (structures are actual iconic projections[29] of the X-ray crystallographically determined 3D structures of **3**, **11**, and **4**, respectively). The carbonyl chemical shift value (with the exception of that for **11**) varies in a similar manner: δ 175.6 [61° O(3)−C(9)−C(10)−C(11) angle,[15] for **7**], 173.2 (56°,[18] for **3**), 173.2 (53°,[21] for **5**), 171.0 [25°,[28] for scopolamine *N*-oxide HBr (**11**)], 172.8 (18°,[14] for **10**), 171.4 (16°,[19] for **4**), and 171.4 (5°,[21] for **8**).

These γ-gauche effect results have experimental precedent in the ca. 2.8 and 5.2 ppm closer-to-TMS respective $\delta(CH_3)$ and $\delta(C{=}O)$ values estimated by Stothers and Tan for *equatorial* 2-methylcyclohexanone [*synperiplanar* O=C−C(α)−CH_3 dihedral angle] vis-à-vis those for the *axial* 2-methylcyclohexanone conformer [*orthogonal* O=C−C(α)−CH_3].[30] RHF GIAO isotropic magnetic shielding tensors (σ_{calcd}) using a 6-311+G(2d,p) basis set were calculated[31,32] for B3LYP density functional theory [6-31G-(d) basis set] optimized geometries of *equatorial* and *axial* 2-methylcyclohexanone models. Scaled δ_{calcd} chemical shifts for the σ_{calcd} values were consistent with experimental trends: 1.1 and 1.4 ppm closer-to-TMS respective $\delta(CH_3)$ and $\delta(C{=}O)$ values for *equatorial* versus *axial* 2-methylcyclohexanone models exhibiting 2.0° and 99.4° O=C−C(α)−CH_3 dihedral angles, respectively. Analogous calculations for methyl (*S*)-tropate models afforded 2.1 and 1.0 ppm closer-to-TMS respective $\delta_{calcd}(CH_2OH)$ and $\delta_{calcd}(C{=}O)$ chemical shifts for the +10.0° O=C−C(α)−CH_2OH geometry-optimized torsion angle conformation (similar to the *compact* conformation for **4**) vis-à-vis those found when the angle was opened up to +55.6° (similar to the *extended* conformation for **3**). The co-relationships between methylol/carbonyl chemical shift values and the O(3)−C(9)−C(10)−C(11) torsion angle strongly suggest that these δ values can be utilized as diagnostic markers for the tropate ester conformation,and that they are not artifacts of solid-state crystal packing. In the *compact* conformational family (**4**, **8**, and **10**) with *synperiplanar*-like O(3)−C(9)−C(10)−C(11) torsion angle values, methylol C(11) is upfield of the scopine C(3) alkoxy carbon, while the relative order is reversed for the *extended* conformational family (**3**, **5**, and **7**) with (+)-*synclinal* values [C(11) is now downfield from the C(3) value].



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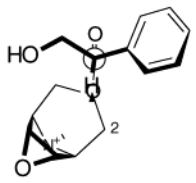

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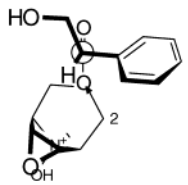

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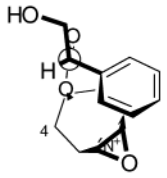

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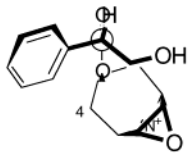

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Since it is well-known that esters typically prefer the trans conformation,[33] i.e., *antiperiplanar* C(3)−O(2)−C(9)−C(10) torsion angles, the conformation about the C(3)−O(2) and C(9)−C(10) bonds primarily determines the disposition of the tropate ester vis-à-vis the piperidine ring. The *extended* and *compact* conformations differ by the tropate ester tilting toward one diastereotopic side of the piperidine ring or the other *and* by rotation about the C(9)−C(10) bond. The *extended* conformation may be defined by its two (+)-*synclinal* H(3)−C(3)−O(2)−C(9) and O(3)−C(9)−C(10)−C(11) angles, while the *compact*

(28) Huber, C. S.; Fodor, G.; Mandava, N. *Can. J. Chem.* **1971**, *49*, 3258.
(29) *CSChemDraw Ultra 5.0* and *CSChem3D Pro 4.0*; CambridgeSoft: Cambridge, MA, 1998.
(30) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308.
(31) *Gaussian-98W revision A-6*; Gaussian Inc.: Pittsburgh, 1998.
(32) Cheeseman, J. R.; Trucks, G. W.; Keigh, T. A.; Frisch, M. J. *J. Chem. Phys.* **1996**, *104*, 5497.
(33) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 618.

conformation exhibits (−)-*synclinal* and *synperiplanar* magnitudes for these respective angles. Inspection of the *N*-oxide conformation (Newman projection **13**) shows it to be a variant of the *extended* conformation (Newman projection **12**). Both share a common (+)-*synclinal* H(3)−C(3)−O(2)−C(9) torsion angle, but they differ in their O(3)−C(9)−C(10)−C(11) torsion angle: the 25° value in the crystalline *N*-oxide **11** is almost intermediate between those of the more typical ca. 0° *compact* and ca. 60° *extended* examples. Table 1 shows that the C(3) and C(11) chemical shifts are almost the same for this *N*-oxide **11** intermediate solid-state conformation. Crystalline scopolamine *equatorial N*-cyclopropylmethyl bromide quaternary ammonium salt[16] shows a fourth crystallographically determined conformation for the tropate ester. This conformation (Newman projection **15**) shares a common (−)-*synclinal* H(3)−C(3)−O(2)−C(9) torsion angle with the *compact* conformation (Newman projection **14**) but differs in the O(3)−C(9)−C(10)−C(11) torsion angle: a −124° (−)-*anticlinal* (ca. 120°) value in **15** versus 16° in **14**. As a result, the carbonyl eclipses the H(10) α-proton in **15** rather than the methylol C(11) in **14**.

Using the *extended* and *compact* conformations as input structures for MMX/GMMX[34] molecular mechanics conformational searches, the O(3)−C(9)−C(10)−C(11) torsion angle in each case was varied to stochastically sample conformational space around the central bond. In the case of the (+)-*synclinal* H(3)−C(3)−O(2)−C(9) set of C(9)−C(10) rotamer models, the lowest energy in the series is for the (+)-*synclinal* arrangement of C(11) vis-à-vis O(3) found for the *extended* conformation [followed by the 0.3 kcal mol^{-1} higher *N*-oxide type (**11**), the 0.6 kcal mol^{-1} higher s*ynperiplanar*, and the 0.7 kcal mol^{-1} higher (−)-*anticlinal* conformations]. In the case of the analogous (−)-*synclinal* H(3)−C(3)−O(2)−C(9) angle set of C(9)−C(10) rotamers, the lowest energy in the series is for the *synperiplanar* arrangement of C(11) vis-à-vis O(3) found for the *compact* conformation [followed by 1.4 kcal mol^{-1} higher (−)-*anticlinal* (**15** type) and the 1.6 kcal mol^{-1} higher (+)-*orthogonal* and *antiperiplanar* conformations]. In these molecular mechanics studies, the *extended* and *compact* conformations were the lowest in calculated energies (the *compact* being 0.4 kcal mol^{-1} slightly lower in energy compared to that for the *extended* conformation).

Ab initio geometry optimizations,[35] performed at the RHF/3-21G* basis set level (using crystal-state geometries as the input), were then followed by RHF/6-31G* single-point energy calculations and showed that the *extended* conformation was now slightly more stable than the *compact* conformation by 0.8 kcal mol^{-1}. During the ab initio geometry optimization, the *N*-oxide **11** conformation was interconverted into that of the *extended* conformation. The (−)-*anticlinal* O(3)−C(9)−C(10)−C(11) conformation in **15** afforded the highest calculated energy in the series of three stable ab initio geometry optimized structures: 1.7 kcal mol^{-1} higher energy relative to that of the *extended* conformation. Inspection of Newman projections **12**−**14** suggests that from the perspective of these drawings the least movement interconversion pathway from the *extended* to the *N*-oxide type (**13**) toward the *compact* conformation proceeds via a clockwise movement involving a (+)-*synclinal* to *synperiplanar* change in the O(3)−C(9)−C(10)−C(11) angle and a (+)- to (−)-*synclinal* change in the H(3)−C(3)−O(2)−C(9) angle. Since the calculated energy differences between the *extended* and *compact* conformations are relatively small, it is reasonable to expect that differential solvation efficiencies in various solvents might result in a bias of one over the other.

NMR Spectroscopic Studies on the Tropate Ester Conformational Preference in Solution. Distortionless enhancement by polarization transfer (DEPT) provides carbon multiplicities, and 2D-HMQC hetereonuclear $^{1}H/^{13}C$ correlation can now be utilized for carbon assignments in solution-state spectra. The γ-gauche effect from the *synclinal* C(8)−N−C(1)−C(2)/C(8)−N−C(5)−C(4) torsion angles is nicely exemplified by the δ ca. 32 solid-state CPMAS determined ^{13}C NMR chemical shifts of the *axial N*-methyl groups in crystalline **3**−**5** versus the δ 40.8 value measured for the *equatorial N*-methyl in solid **10** (where the above-mentioned angles are now *antiperiplanar*). These solid-state values enable a facile assignment of *axial* and *equatorial* descriptors to the respective δCH_3 31.95 (minor) and 39.27 (major) *N*-methyl diastereomers of atropine mesylate in CD_2Cl_2 solution.[3] Similarly, assignment of *axial* and *equatorial* descriptors to the δCH_3 32.12 (minor) and 45.06 (major) *N*-methyl scopolamine HBr diastereomers in CD_2Cl_2 solution is also clearly forthcoming from the solid-state crystallographic-stereochemistry/CPMAS correlation (note the deshielding of the *equatorial N*-methyl carbon due to the presence of a nearby transannular oxiranyl oxygen).[3] In all the **3**−**11** crystal structures, the methylol oxygen is *antiperiplanar* to the phenyl ring and the ring eclipses the Cα−H bond. Vicinal coupling constants show that this same orientation about the C(10)−C(11) bond is preferred for the atropine and scopolamine cations in D_2O[36] and the major species of atropine mesylate[3] in CD_2Cl_2 solution.

The disposition of the phenyl ring vis-à-vis the scopine moiety can now be ascertained using the solid-state determined C(11) and C(3) chemical shifts to deconvolute the weighted time-averaged values found for these nuclei in various solvents. For example, the δ 64.22 C(11) and 62.65 C(3) values for the N-protonated *axial N*-methyl scopolammonium cation in CD_2Cl_2 clearly suggest a preference for the *extended* conformation in which both faces of the phenyl ring are exposed to the organic solvent. On the other hand, these values change to δ 64.64 and 66.26 for the same respective nuclei when the solvent is now D_2O. This change now strongly points to a conformational bias in favor of the *compact* conformation in which only one of the phenyl-ring faces is exposed to the polar aqueous medium. One referee has referred to this as a "hydrophobic collapse" of less polar groups when the molecule resides in the polar aqueous medium. Similarly, the δ 63.96 C(11) and δ 61.42 C(3) chemical shifts for *axial N*-*n*-butyl scopolammonium bromide (pseudobuscopan, **16**) quaternary ammonium salt in $CDCl_3$ point to an *extended* conformation preference, while the corresponding δ 64.54 and 65.19 values suggest a bias for the *compact* conformation in D_2O. While scopolamine methobromide (**8**) quaternary ammonium salt is insoluble in $CDCl_3$, the δ 64.58 C(11) and δ 65.07

(34) PCModel/MMX 5.0 and GMMX (Global-MMX) Macintosh versions; Serena Software: Bloomington, IN, 1996.

(35) *MacSpartan Plus 1.1.7*; Wavefunction: Irvine, CA, 1997.

(36) Dimitrov, V. S.; Spassov, R. S.; Radeva, T. Z.; Ladd, J. A. *J. Mol. Struct.* **1975**, *27*, 167.

C(3) chemical shifts also suggest a *compact* conformational preference in D_2O.

In the above examples, it is apparent that the quantity of *compact* conformation in the interconverting mixture was reduced upon a change from an aqueous medium to a chlorinated organic solvent. In those instances, this reduction was significant enough to favor the *extended* conformation in the organic solvent. However, in some cases, the *compact* conformation still remained the dominant contributor to the conformational equilibrium even in CD_2Cl_2 or $CDCl_3$, although the extent of its bias relative to the *extended* form appeared to be decreased compared to that found in D_2O. This is seen in the smaller $\Delta\delta$ value measured for atropine protonated *N*-H *equatorial N*-methyl diastereomer in CD_2Cl_2 versus D_2O [$\delta C(3) - \delta C(11) = 1.10$ (CD_2Cl_2) versus 3.39 (D_2O)]. However, the $\Delta\delta$ value measured for *equatorial N*-*n*-butyl scopolammonium bromide (Buscopan) quaternary salt in $CDCl_3$ versus D_2O is only very slightly reduced [$\delta C(3) - \delta C(11) = 1.34$ ($CDCl_3$) versus 1.50 (D_2O)].

Conclusion

In conclusion, solution-state NOE intensity enhancements in spectra of rapidly interconverting mixtures of flexible conformers are usually not readily interpretable in terms of a conformational bias of one particular conformation or another. However, X-ray crystallographically determined conformational poly- or pseudopolymorphism in conjunction with solid-state cpmas NMR spectroscopy can be a powerful tool for unraveling the contributors to weighted time-averaged structures resulting from rapid conformational interchange in solution.

Experimental Section

(−)-Hyoscyamine HBr and (−)-scopolamine HBr, HCl, *N*-oxide HBr, and methyl bromide were purchased from Sigma. (−)-Scopolamine *equatorial n*-butyl bromide (Buscopan), and pseudobuscopan (epimeric *axial n*-butyl bromide) were gifts of Boehringer Ingelheim KG.

Crystallography. Scopolamine methobromide (**8**), HBr (**3**), and HCl (**5**) anhydrates were recrystallized by vapor diffusion of acetone into an absolute ethanolic solution of the appropriate salt. Recrystallization of Buscopan from methanol afforded the methanol solvate adduct **7**. Scopolamine HBr·1.5H_2O (**4**) was obtained by dissolving the salt in water followed by slow evaporation to dryness.[21]

NMR Spectroscopy. ^{13}C and ^{15}N NMR spectra were recorded at 125.76 and 50.70 MHz, respectively, at ambient temperature on a Bruker DMX-500 digital FT NMR spectrometer. Solid-state CPMAS spectra were measured in a BL-4 cpmas probehead and a high-resolution/high-performance (HPHP) ^1H preamplifier for solids. All CPMAS spectra were calibrated with an external spectral reference (^{13}C NMR: glycine δcarbonyl = 176.03, ^{15}N NMR ($CH_3{}^{15}NO_2$ scale): $^{15}NH_4{}^{+15}NO_3{}^-$ $\delta^{15}NO_3{}^- = -5.25$, $\delta^{15}NH_4{}^+ = -358.40$). A VACPTPPM (variable amplitude cross-polarization/two pulse phase modulation decoupling) pulse program was used for CPMAS spectra. VACPTPPMNQS (nonquaternary and nonmethyl signal suppression) and CPPI[22] (cross-polarization/polarization inversion) pulse programs were utilized to afford spectral-editing giving "quaternary-/methyl-only" and "methylene-only" spectra, respectively. Samples were placed in 4 mm zirconia rotors and spun at a rate of 11.0 kHz (vacptppm and vacptppmnqs) or 5.0 kHz (cppi) unless noted otherwise in the text. Nqs spectra used a 50 μs T_2 dipolar dephasing delay period. T_1 values were determined by the fast inversion−recovery technique. Nonmethyl and reduced-intensity methylol edited spectra were obtained using a single T_1 delay period of 30 s.

Solution-state ^{13}C NMR {^1H} spectra were measured in D_2O, CD_2Cl_2, or $CDCl_3$ (as noted in the text and tables) using the appropriate deuterium solvent as an internal lock and tetramethylsilane (TMS) or 4,4-dimethyl-4-silapentanesulfonate sodium salt (DSS) as internal spectral references. DEPT (90° and 135° pulse angles) pulse programs were used to ascertain the hydrogen multiplicity of the ^{13}C signals. HMQC 2D-NMR spectroscopy was used to correlate the ^{13}C and ^1H chemical shifts.

Molecular Modeling. 2D-iconic projections (**11**−**15**) of the X-ray crystallographic or molecular modeling structures were generated using the combination of CS-Chem3D Pro 4.0 and CS-ChemDraw Ultra 5.0 programs.[30] Superimposition of molecular structures were performed with the MacMimic 3.0 program.[37] Molecular mechanics geometry optimization was performed using the MMX force field encoded within the PCModel 5.04 program.[34] MMX is an enhanced version of Allinger's MM-2 program[38] with MMP1 π-subroutines[39] incorporated for localized π-electron systems. GMMX[34] stochastic conformational searches calculated to produce a set of 1000 structures were performed on each of the *extended* and *compact* conformation input structures. Ab initio calculations (RHF/3-21G* basis set geometry optimization and 6-31G* basis set single-point energy) were performed with the MacSpartan Plus 1.1.7 program[35] running on a PowerMacintosh G3/300 computer. GIAO RHF/6-311+G(2d,p) calculations based upon B3LYP/6-31G(d) geometry optimizations were performed with Gaussian-98W revision A-6[31] running on a Hewlett-Packard Kayack PC-workstation. On the basis of experimentally determined ^{13}C chemical shifts for rigid molecules, a scaling factor for the GIAO isotropic magnetic shielding tensors (σ_{calcd}) was determined: $\delta_{expt}{}^{13}C = -0.88370 \cdot \sigma_{calcd}{}^{13}C + 178.38$ ($\rho^2 = 0.992$, $n = 16$).

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