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Structural Studies on McN-5652-X, a High-Affinity Ligand for the Serotonin Transporter in Mammalian Brain

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Abstract—McN-5652-X, (+)-**1**, is a potent, selective inhibitor of serotonin reuptake in mammalian brain. When radiolabeled with ^{11}C, it has served as a positron-emission tomography (PET) radiotracer for in vivo imaging of central serotonin transporters. We have determined the solid-state structures of (+)-**1**·$HClO_4$ and (+)-**1**·(+)-(2*R*,3*R*)-tartrate by single-crystal X-ray diffraction, thereby confirming the *trans* relative configuration (Chemical Abstracts Service rules of nomenclature) and the 6*S*,10b*R* absolute configuration for (+)-**1**. Results from a vibrational circular dichroism (VCD) study on (+)-**1** in $CDCl_3$ are consistent with the 6*S*,10b*R* absolute configuration.
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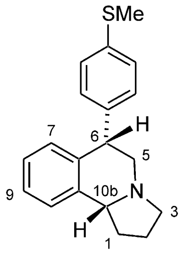
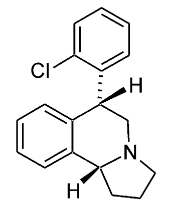
Reuptake sites for biogenic amine neurotransmitters on presynaptic neurons play a crucial role in removing norepinephrine (NE), dopamine (DA), and serotonin (5-HT) from the synaptic cleft.[1] By reducing the neurotransmitter levels in areas of the central nervous system (CNS), these monoamine transporters can significantly attenuate physiological stimuli. Various antidepressant drugs interfere with the transporters for NE and 5-HT, either selectively or with dual action.[1,2] Indeed, the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, citalopram, and paroxetine, have revolutionized the pharmacotherapy of affective disorders in the past two decades.[3]

We discovered a novel series of pyrrolo[2,1-*a*]isoquinolines with potential as antidepressant agents, and investigated their chemical and biological properties.[4–12] Certain compounds from this series, such as McN-5652-X, (+)-**1**, selectively inhibit the reuptake of 5-HT and strongly potentiate the effects of 5-HT in vivo.[8,10] This prototype SSRI, with ^{11}C radiolabeling on the *S*-methyl group, has received considerable attention for the mapping of 5-HT transporters in brain tissue of various animal species via positron-emission tomography (PET) imaging.[13]

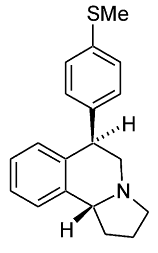
Potent activity for compounds of this structure type is exclusively associated with the *trans* diastereomers,[14] which also exhibit high enantioselectivity.[4,10] Thus, for the racemate McN-5652-Z, (±)-**1**, virtually all of the biological activity resides in the (+)-enantiomer,[15] that is, (+)-**1**.[4,10–12] We established the relative configuration of (±)-**1**, and its congeners, as *trans*[14] by the use of NMR spectroscopy and X-ray crystallography, as well as by chemical correlations.[4,9,11,16] The 6*S*,10b*R* absolute configuration for (+)-**1** (as shown) was assigned on the basis of enantiospecific synthesis[11] and stereochemical correlation with close analogues, such as McN-5707-X, (+)-**2**.[4,5,10,12,17]



(+)-**1** (McN-5652-X)
trans-(6*S*,10b*R*)



(+)-**2** (McN-5707-X)
trans-(6*R*,10b*R*)



(±)-**3** (McN-5655-Z)
cis-(6*R**,10b*R**)

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Given our extensive structural studies with this pyrroloisoquinoline series,[4,5,9,11,12,16] we were surprised to see a recent paper that expressed confusion about the stereochemical assignment for McN-5652 and its close analogues.[18,19] However, this issue has been settled and the scientific literature has been amended.[20] In their paper, Schulze et al.[18] reported an X-ray structure for (±)-**3**, McN-5655-Z, the racemate of the inactive *cis* isomer.[19] We have now determined the solid-state structures of (+)-**1**·$HClO_4$ and (+)-**1**·(+)-(2*R*,3*R*)-tartrate, which represent the bioactive isomer, by single-crystal X-ray diffraction. These results serve to confirm the *trans* relative configuration between C_6 and C_{10b} of (+)-**1**, as well as the 6*S*,10b*R* absolute configuration. In addition, we conducted a vibrational circular dichroism (VCD)[21] study on (+)-**1** in $CDCl_3$, which assigns the 6*S*,10b*R* absolute configuration and indicates the most abundant conformers of the free base in solution.

Results and Discussion

As alluded to above, we had performed a variety of structural studies on pyrroloisoquinoline antidepressant compounds to assign relative and absolute configuration within the chemical series, as well as to understand the favored conformations in solution.[4a,9] Our efforts have encompassed several X-ray crystal structures, including an anomalous dispersion study on (+)-**2**·HBr.[4a] However, we did not have the opportunity to carry out X-ray analyses on McN-5652-Z [(±)-**1**] or its close congeners McN-5652-X [(+)-**1**], McN-5652-W [(−)-**1**], or McN-5655-Z [(±)-**3**].[19] The X-ray structure of McN-5655-Z is the first one reported for this set of stereoisomers;[18] however, this *cis* isomer is essentially biologically inactive. Consequently, we thought that it would be worthwhile to obtain an X-ray structure for the bioactive *trans* isomer, McN-5652-X, including a determination of its absolute configuration.

X-ray crystallographic studies

At first, we investigated the crystal structure of the perchlorate salt of McN-5652-X [(+)-**1**·$HClO_4$], which was obtained from absolute ethanol as colorless rhombic crystals, mp 189–191 °C (corr.), $[\alpha]_D^{23}$ 52.9° (*c* 0.238, MeOH).[22] There were two crystallographically independent ammonium cations in the asymmetric unit cell. In Cation 1, the 4-(methylthio)phenyl substituent is disordered between two preferred orientations in the crystal lattice, principally involving ca. 180° rotation of the SMe group (Fig. 1). The major (specified by S_1, H_6, C_{11}–C_{17}) and minor ($C_{1'}$, $H_{6'}$, $C_{11'}$–$C_{17'}$) orientations are occupied 62.2 and 37.8% of the time, respectively. Both orientations of this phenyl substituent gave the same stereochemistry at chiral carbon C_6, even though this feature was not imposed on the structure. Cation 2 (not shown) is ordered and has no ambiguities. This crystallographic result for (+)-**1**·$HClO_4$ provides unambiguous proof of the *trans* relative configuration at C_6 and C_{10b}, and is indicative of the 6*S*,10b*R* absolute configuration.

We were interested in determining absolute configuration from the crystal structure of (+)-**1**·$HClO_4$ by using the anomalous dispersion technique. However, given the disorder in a key region of ammonium ion that contains the C_6 stereogenic atom center (Fig. 1), we deemed this structure unsuitable for that purpose, and thus pursued an alternative X-ray study. We obtained single crystals of the (+)-(2*R*,3*R*)-tartrate of (+)-**1** from MeOH/*i*-PrOH as pale yellow plates, mp 167–169 °C (corr.), $[\alpha]_D^{23}$ 62.3° (*c* 0.565, MeOH). The absolute configuration of the ammonium cation was established by relating it to that of the tartrate anion. (The known absolute configuration of the tartrate anion was also experimentally confirmed by anomalous dispersion.) Therefore, the ammonium cation possesses the *trans* relative configuration between C_6 and C_{10b}, and the 6*S*,10b*R* absolute configuration (Fig. 2). The structural disposition of this cation resembles that of Cation 1 from the X-ray study of (+)-**1**·$HClO_4$ (Fig. 1).

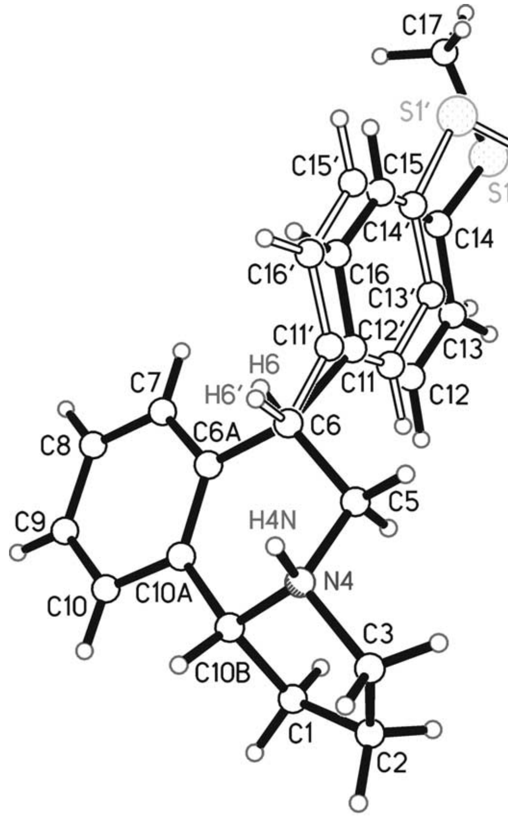
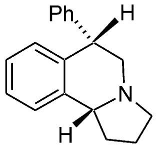
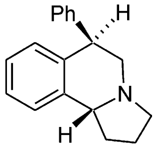


Figure 1. Perspective drawing of the solid-state structure of the first two crystallographically independent molecules of (+)-**1**·$HClO_4$ in the asymmetric unit (Cation 1), with the atom-numbering scheme. The perchlorate anion is not displayed. The 4-(methylthio)phenyl group in Cation 1 is disordered between two preferred orientations in the lattice, as shown. The major form, occupied 62.2% of the time, represented with filled bonds, is specified with S_1, H_6, C_{11}–C_{17} and their hydrogens; the minor form, occupied 37.8% of the time, represented with open bonds, is specified with $S_{1'}$, $H_{6'}$, $C_{11'}$–$C_{17'}$ and their hydrogens.



(±)-**4** (McN-4612-Z)
trans-(6*R**,10b*S**)



(±)-**5** (McN-4111)
cis-(6*R**,10b*R**)

In the ammonium cation of both salts, the tetrahydroisoquinoline ring adopts a standard half-chair conformation with the 4-methylthiophenyl ring equatorially disposed on the six-membered ring and twisted out of the molecular plane by ca. 60–70°.[4a,9,23] It is interesting to note that the *cis* relative configuration exists between the N_4 and C_{10b} stereocenters, as observed in the solid-state structures of several related compounds.[9] This is the '*cis*-B' ring-fused geometry, in which the proton on N_4 is axial and the proton on C_{10b} is equatorial on the six-membered ring (Fig. 3). These structural characteristics correspond to those found for the HBr salt of the parent *trans* compound, (±)-**4**·HBr, which lacks the SMe group, as determined by ^{1}H NMR.[9] Thus, *trans* diastereomer (±)-**4**·HBr adopts a *cis*-B conformation with an equatorial phenyl substituent in $CDCl_3$ solution to the extent of at least 90%.[9] By contrast, *cis* diastereomer (±)-**5**·HBr exists initially as a 75:25 mixture of *trans*- and *cis*-A ring-fused species (Fig. 3), and then converts to a 10:90 mixture of these forms on standing for 2–3 h.[9] The body of evidence indicates that (±)-**5**·HBr possesses mainly a *trans* ring fusion in the solid state, which is reflected just after dissolution in $CDCl_3$.[9] For (+)-**1**·$HClO_4$ and (±)-**4**·HBr, one might surmise that the *cis*-B ring fusion predominates to avoid an adverse 1,3 *syn*-axial interaction between an axial 6-aryl group and an axial N_4 proton in the alternative *trans*-fused form or an adverse 1,3 *syn*-axial interaction between axial 6-aryl and C_3 methylene groups in the alternative *cis*-A form (Fig. 3).

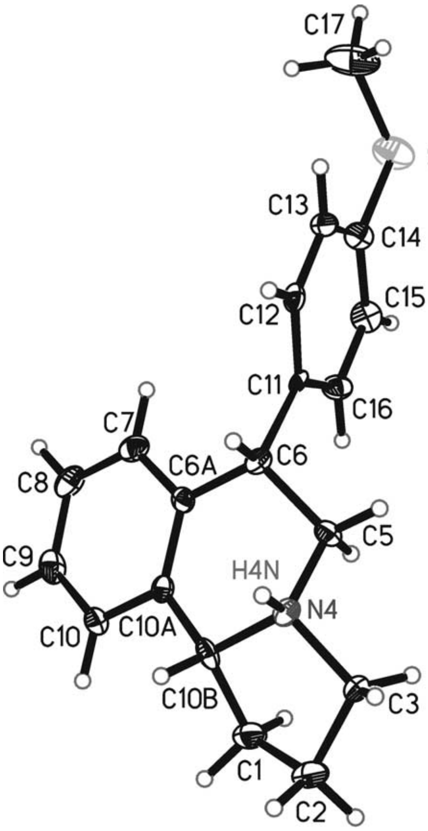
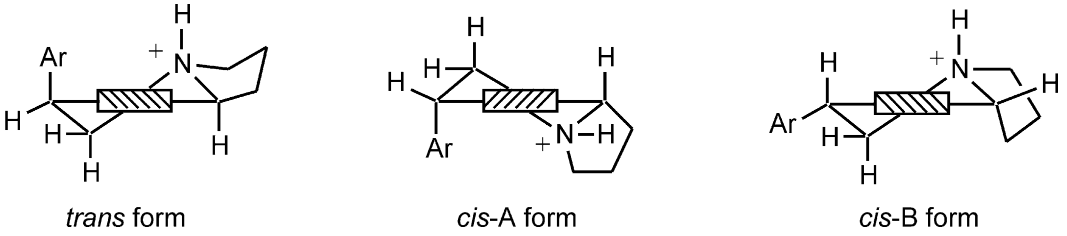


Figure 2. Perspective drawing of the asymmetric unit for the solid-state structure of (+)-**1**·(+)-(2*R*,3*R*)-tartrate, with the atom-numbering scheme. The tartrate monoanion is not displayed. Nonhydrogen atoms are represented by 50% probability thermal vibration ellipsoids and hydrogen atoms are represented by small spheres of arbitrary size. This structure is substantially similar to that of Cation 1 of (+)-**1**·$HClO_4$ (Fig. 1).

VCD studies

Vibrational circular dichroism (VCD) has been used to determine the absolute configuration of chiral molecules of medium size. Two key developments for the practicality of the method are: (1) the widespread availability of instrumentation for the measurement of high-quality VCD spectra[21e,24] and (2) the availability of software for the calculation of VCD intensities by using ab initio quantum chemistry.[21e,25,26] The VCD spectra derive from the difference in the absorbance of left versus right circularly polarized infrared radiation for a chiral molecule undergoing a vibrational transition.[21f] A pair of enantiomers will produce spectra that are equal and opposite in sign, while a racemic mixture will give a null spectrum. VCD spectra can be measured for all kinds of enantiomerically enriched, chiral molecules, irrespective of their size. Instrumentation is based on a Fourier transform infrared (FT-IR) spectrometer, which offers frequency precision, high throughput, and multiplexing.[27] The light coming from the FT-IR is directed to a polarizer to create linearly polarized light and then to a photoelastic modulator (PEM) that modulates the polarization between left and right circularly polarized. The chiral sample is located between the PEM and the detector.



trans form *cis*-A form *cis*-B form

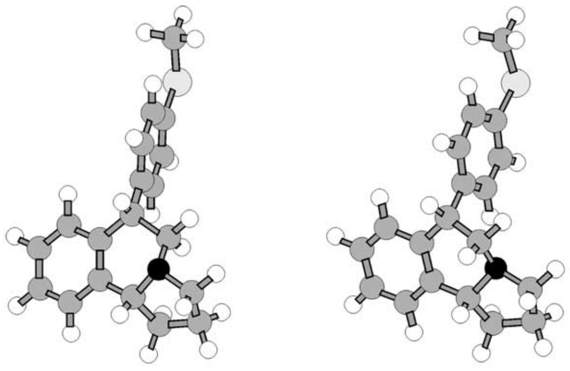
Figure 3. Depiction of the three structures associated with *cis* and *trans* ring fusions between rings C_5N and C_4N in the ammonium salt of (+)-**1**·HX.

For the determination of absolute configuration, VCD can provide a viable alternative to X-ray crystallographic analysis. Significantly, while the X-ray method requires suitable crystalline material and, possibly, the presence of a heavy atom, the VCD method is conducted on the native molecule in solution. The absolute stereochemistry is established by comparing the solution-phase VCD spectrum to the results of an ab initio quantum chemistry calculation. If the measured VCD spectrum for a specific enantiomer agrees with the theoretical spectrum in sign and relative intensity, then that enantiomer is assigned the calculated configuration. As a bonus, the VCD result also yields a perspective on the principal solution-phase conformations that are populated in the solvent used.

We conducted a VCD study on amine free base (+)-**1** in $CDCl_3$, using VCD spectra in the mid-infrared region.

From DFT calculations (see Experimental), two optimized conformations of (+)-**1** with the 6*S*,10b*R* configuration, differing in the C_5N ring by inversion of the nitrogen atom, were obtained (Fig. 4). Two conformers with the 6*S*,10b*S* configuration were also obtained. For the 'SR' set, conformer SRb (*trans*-fused) was calculated to have the lower relative energy, with conformer SRa (*cis*-fused) being 1.63 kcal/mol higher. For the 'SS' set, conformer SSb (*trans*-fused) was calculated to have the lower relative energy, with conformer SSa (*cis*-fused) being 2.08 kcal/mol higher.[28]

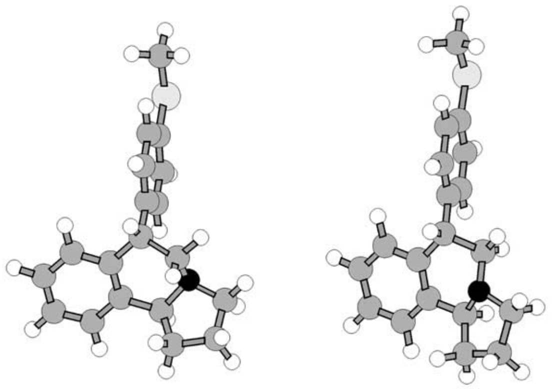
The calculated VCD and IR spectra of the two SR conformers are compared to experiment in Figure 5, and the spectra of the two SS conformers are compared to experiment in Figure 6. The positive VCD feature at ca. 1600 cm^{-1} for both conformers of the SS and SR configurations corresponds to a superposition of four in-phase and out-of-phase coupled ring deformation motions of the two phenyl rings. The net sign of the VCD for these four modes depends on the relative orientation of the two rings, and is thus a marker band for the chirality at position 6. The positive intensity of this band is associated with the 6*S* configuration. The CH_2 scissors motions contribute to the bands between 1450–1500 cm^{-1}, and reflect chirality and conformation of the saturated five- and six-membered rings. The modes between 1275 and 1450 cm^{-1} involve methine deformation at the two chiral centers, coupled with



Conformer SRa
+1.63 kcal/mol

Conformer SRb
0.0 kcal/mol

(6*S*,10b*R*)-configuration



Conformer SSa
+2.08 kcal/mol

Conformer SSb
0.0 kcal/mol

(6*S*,10b*S*)-configuration

Figure 4. Optimized structures of conformers SRa, SRb, SSa, and SSb, with relative energies and configuration designations.

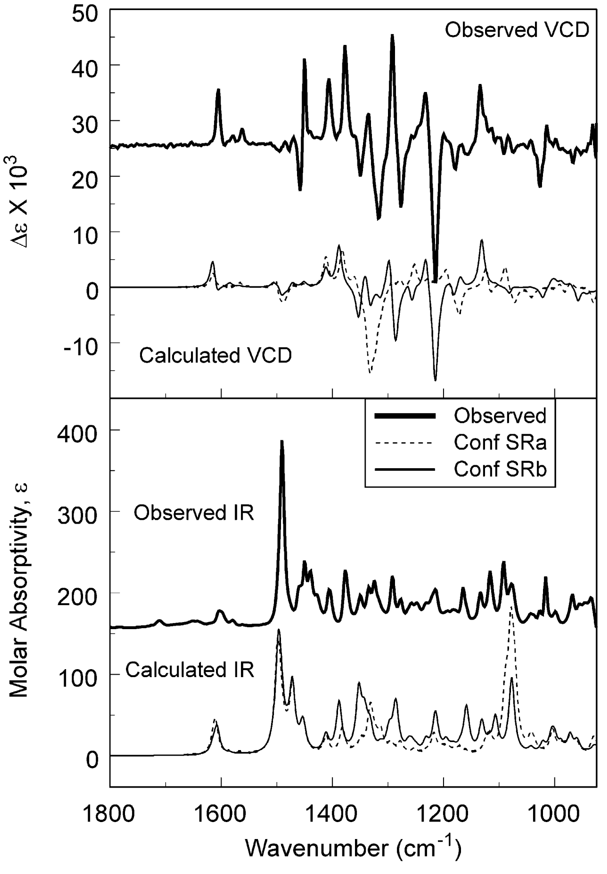


Figure 5. Comparison of observed IR (lower frame) and VCD (upper frame) spectra for (+)-**1** with calculated spectra for conformer SRa and conformer SRb. Observed spectra offset for clarity.

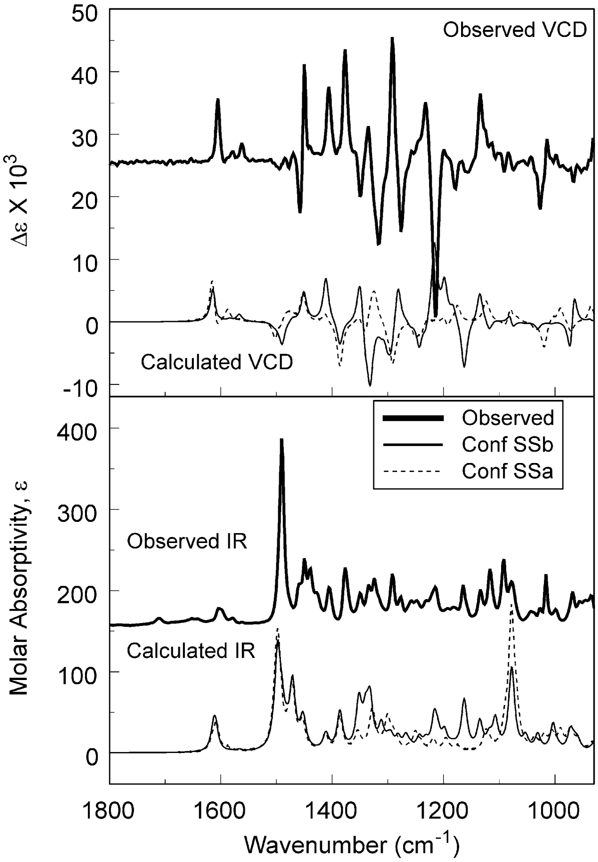


Figure 6. Comparison of observed IR (lower frame) and VCD (upper frame) spectra for (+)-**1** with calculated spectra for conformer SSa and conformer SSb. Observed spectra offset for clarity.

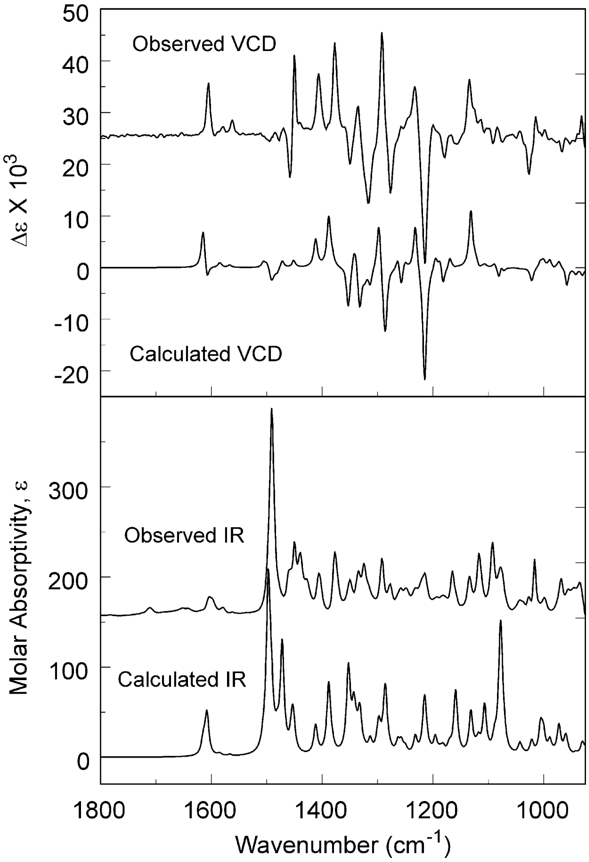


Figure 7. Comparison of observed IR and VCD spectra for (+)-**1** with calculated spectra for 85% conformer SRb and 15% conformer SRa, in molar absorptivity units. Half-width for calculated spectra is 4 cm^{-1}. Observed spectra offset for clarity.

other ring and methylene deformation motions in the molecule. These modes depend on both the configuration and ring conformation. The intense negative VCD band at 1215 cm^{-1} in conformer SRb corresponds to motion of the nitrogen, the methine at position 10b, and the methylene groups in the five-membered ring. This band is a marker for the chirality at position 10b, since the corresponding mode in conformer SSb is calculated to have a large positive intensity. Distinct VCD features in this region are not calculated for either SSa or SRa, the higher energy conformer for each diastereomer.

The best overall fit between experiment and calculation over the entire region of measurement is for conformer SRb, the lower energy species of the 6*S*,10b*R* configuration. The calculations for the lower energy conformer with the 6*S*,10b*S* configuration show some agreement above 1250 cm^{-1}, but the disagreement in sign for the intense feature at 1215 cm^{-1}, in conjunction with the agreement in sign for this feature for conformer SRb, provides strong evidence that (+)-**1** possesses the 6*S*,10b*R* configuration. Ultimately, for completeness of this analysis, we employed a composite spectrum involving 15% conformer SRa and 85% conformer SRb to achieve an improved agreement with experiment (Fig. 7). This situation is consistent with the gas-phase calculation in which SRa is 1.6 kcal/mol higher in energy than conformer SRb. The spectral data suggest that both conformers are significantly populated in $CDCl_3$ solution with a preference for the *trans*-fused species by a factor of ca. 6. ^{1}H NMR spectral data for analogous amine compounds indicate populations of at least 90% in the *trans*-fused form.[9]

The other four possible amine structures, with RS and RR configurations, would generate VCD spectra of opposite sign to those for the above SR and SS species, depicted in Figures 5 and 6. The agreement with experiment would be poor for all RS or RR species.

There are two possible orientations of the SMe group that differ by 180° rotation for each pair of conformers. The optimized structure for the SMe rotamer of conformer SSb, that is, conformer SSb2, has a ring conformation identical to SSb and, lies just 0.02 kcal/mol higher in energy (Fig. 8). The IR and VCD spectra for SSb and SSb2 are nearly identical (not shown). Although corresponding SMe rotamers were not calculated for the other three structures (SRa, SRb and SSa), similar results would be expected. The low energy structure RRb2 (mirror image of SSb2 in Fig. 8) corresponds to the structure determined by X-ray diffraction of the racemic (RR + SS) compound by Schulze et al.[18]

In summary, the VCD measurements and calculations are most consistent with the 6*S*,10b*R* configuration for (+)-**1**, with a dominant conformation in which the nitrogen configuration is *R*, and a less populated con-

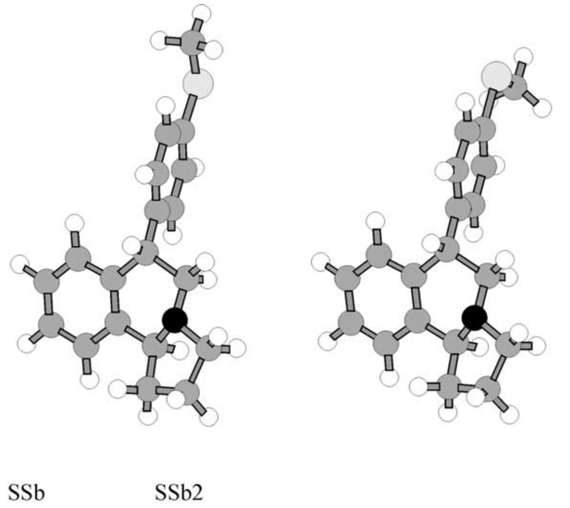


Figure 8. Optimized structures of conformer SSb and conformer SSb2.

formation in which the nitrogen configuration is *S* (conformations SRb and SRa). An excellent agreement between experiment and calculation is obtained for a composite of 85% SRb and 15% SRa species. There are two 180° rotamers of the SMe group that should be equally populated in solution.

Conclusion

Single-crystal X-ray diffraction results for (+)-**1**·$HClO_4$ and (+)-**1**·(+)-(2*R*,3*R*)-tartrate provide unambiguous proof for the *trans* relative configuration between C_6 and C_{10b} of (+)-**1**, as well as the 6*S*,10b*R* absolute configuration. A VCD study on (+)-**1** in $CDCl_3$ was consistent with the 6*S*,10b*R* absolute configuration and indicated that the most prevalent solution conformation has a *trans*-fused 5–6-ring junction (*R* configuration at the amine nitrogen). Consequently, the stereochemical assignment for the bioactive pyrroloisoquinoline McN-5652-X, (+)-**1**, is thoroughly established.

Experimental

X-ray crystallography of (+)-1·$HClO_4$[29]

Single crystals of (+)-**1**·$HClO_4$, $[C_{19}H_{22}NS][ClO_4]$ (M_w 395.89 Da, colorless rhombic prisms from ethanol) are, at −90±2 °C, monoclinic [space group $P2_1$–C_2^2 (No. 4)] with $a = 8.777(4)$ Å, $b = 9.557(4)$ Å, $c = 22.618(9)$ Å, $\beta = 100.938(7)°$, $V = 1863(1)$ Å^3, and $d_{calcd} = 1.412$ g cm^{-3} for $Z = 4$ formula units. A full hemisphere of diffracted intensities (ω-scan width = 0.30°) was measured on a single crystal (0.26 × 0.34 × 0.40 mm) by using graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å) on a Bruker SMART CCD Single Crystal Diffraction System. The lattice constants were determined with the Bruker SAINT software package by using peak centers for 829 reflections. A total of 11948 integrated intensities having $2\theta(\mathrm{Mo}K_\alpha) < 56.56°$ were produced by using SAINT, 7128 of which were independent and gave $R_{int} = 0.037$. The Bruker SHELXTL-PC software package (Version 5) was used to solve the structure via ‘direct methods’ techniques. All stages of weighted full-matrix least-squares refinement were conducted by using F_o^2 data with SHELXTL-PC. The final agreement factors at convergence are: R_1(unweighted, based on F) = 0.055 for 4596 independent reflections with $2\theta(\mathrm{Mo}K_\alpha) < 56.56°$ and $I > 2\sigma(I)$; R_1 (unweighted, based on F) = 0.099 and wR_2 (weighted, based on F^2) = 0.143 for all 7128 independent reflections with $2\theta(\mathrm{Mo}K_\alpha) < 56.56°$. The absolute configuration was assigned experimentally as 6*S*,10b*R* by using the anomalous dispersion technique; the ‘Flack’ absolute structure parameter for this solution refined to a final value of 0.06(6).

The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. There are two crystallographically independent ammonium cations and perchlorate anions in the asymmetric unit. The 4-(methylthio)phenyl substituent of Cation 1 is disordered between two preferred orientations in the lattice. The major orientation, occupied 62.2% of the time, is specified by S_1, H_6, C_{11}–C_{17} and their hydrogens, and the minor orientation, occupied 37.8% of the time, is specified by $S_{1'}$, $H_{6'}$, $C_{11'}$–$C_{17'}$ and their hydrogens. Cation 2 is ordered and has no structural/conformational ambiguities. The phenyl rings of each orientation were included in the structural model as rigid hexagonal groups with fixed C–C bond lengths of 1.390 Å. Both amine hydrogen atoms (H_{4N} and H_{24N}) were located from a difference Fourier synthesis and refined as independent isotropic atoms. The three methyl groups (C_{17}, $C_{17'}$, C_{37}, and their hydrogens) were refined as rigid rotors, by using idealized sp^3-hybridized geometry and a C–H bond length of 0.98 Å, which were allowed to rotate about their C–C bonds in least-squares cycles. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms, on their respective carbon atoms, assuming sp^2- or sp^3-hybridized carbon atoms and C–H bond lengths of 0.95–1.00 Å. The isotropic thermal parameters for H_{4N} and H_{24N} refined to final U_{iso} values of 0.05(1) and 0.06(1) Å^2, respectively. The isotropic thermal parameters of the remaining hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. The molecular structure of (+)-**1**·$HClO_4$ is depicted in Figure 1.

X-ray crystallography of (+)-1·(+)-tartrate[29]

To form the tartrate salt of (+)-**1**, one mol-equiv of (+)-(2*R*,3*R*)-tartaric acid (confirmed by optical rotation) was added to a solution of the amine free base in MeOH, then 2-propanol was added to induce crystallization. Single crystals of (+)-**1**·(+)-(2*R*,3*R*)-tartrate, $[C_{19}H_{22}NS]$ $[C_4H_5O_6]$ (M_w 445.52 Da, pale yellow plates from MeOH/*i*-PrOH) are, at −80±2 °C, monoclinic [space group $P2_1$–C_2^2 (No. 4)] with $a = 7.975(1)$ Å, $b = 8.843(1)$ Å, $c = 15.135(2)$ Å, $\beta = 99.747(3)°$, $V = 1051.9(3)$ Å^3, and $d_{calcd} = 1.407$ g cm^{-3} for $Z = 2$ formula units. A full hemisphere of diffracted intensities (ω-scan width = 0.29°) was measured on a single crystal (0.04 × 0.50 × 0.60 mm) by using graphite-monochromated Mo*K*α radiation on a Bruker SMART System. The lattice constants were determined with SAINT by using peak centers for 1797 reflections. A total of 5338 integrated intensities having $2\theta(\mathrm{Mo}K_\alpha) < 50.68°$ were produced by using SAINT, of which 3456 were independent ($R_{\mathrm{int}} = 0.048$). SHELXTL-PC was used to solve the structure via direct methods. Full-matrix least-squares refinement was effected with F_o^2 data and SHELXTL-PC. The final agreement factors at convergence are: R_1 (unweighted, based on F) = 0.056 for 2714 independent reflections with $2\theta(\mathrm{Mo}K_\alpha) < 50.68°$ and $I > 2\sigma(I)$; R_1 (unweighted, based on F) = 0.080 and wR_2 (weighted, based on F^2) = 0.102 for all 3456 independent reflections with $2\theta(\mathrm{Mo}K_\alpha) < 50.68°$. The known absolute configuration of the tartrate anion was confirmed experimentally as 2*R*,3*R* via the anomalous dispersion technique; the 'Flack' absolute structure parameter refined to a final value of 0.11(13).

The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The four amine, carboxyl and hydroxyl hydrogen atoms (H_{4N}, H_{1O}, H_{3O} and H_{4O}) were located from a difference Fourier synthesis and refined as independent isotropic atoms. The one methyl group (C_{17} with its hydrogens) was refined as a rigid rotor (by using idealized sp^3-hybridized geometry and a C–H bond length of 0.98 Å) which was allowed to rotate about the S–C_{17} bond in least-squares cycles. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms, assuming sp^2- or sp^3-hybridized carbon atoms and C–H bond lengths of 0.95–1.00 Å. The isotropic thermal parameters for H_{1O}, H_{3O} and H_{4O} refined to final U_{iso} values of 0.09(2), 0.02(1) and 0.02(1) Å^2, respectively. Since the isotropic thermal parameter for H_{4N} repeatedly refined to a slightly negative, physically unreasonable, U_{iso} value, it was fixed at a value 1.2 times the equivalent isotropic thermal parameter of N_4. The isotropic thermal parameters of the remaining hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. The molecular structure of (+)-**1**·(+)-(2*R*,3*R*)-tartrate is depicted in Figure 2.

VCD study of (+)-1

A sample of amine free base (+)-**1** was dissolved in $CDCl_3$ at a concentration of 0.35 M (10 mg/100 µL). IR and VCD spectra were recorded in a 94-µm cell with BaF_2 windows, on a modified Chiral*ir*™ VCD instrument[24] (ABB Bomem/BioTools) at 4-cm^{-1} resolution. The measurement time for the sample and solvent was 9 h. IR, VCD, and VCD-noise spectra are displayed in Figure 9. Theoretical calculations were performed as follows: (1) Models of the structures were initially built with HyperChem (Hypercube, Inc.), and (2) calculations of optimized geometries, vibrational frequencies, and IR and VCD intensities were carried out at the DFT B3LYP/6-31G* level with Gaussian 98.[25] We obtained two conformations of (+)-**1** with the 6*S*,10b*R* configuration and different conformations of the C_6N ring due to nitrogen inversion, as well as two conformers with the 6*S*,10b*S* configuration (Fig. 4). For the SR configuration, conformer SRb (*trans*-fused) was calculated to have a lower relative energy than conformer SRa (*cis*-fused) by 1.63 kcal/mol; for the SS configuration, conformer SSb (*trans*-fused) was calculated to have a lower relative energy than conformer SSa (*cis*-fused) by 2.08 kcal/mol (gas-phase molecules). The calculated VCD and IR spectra for the two pairs of conformers are compared to experiment in Figures 5 and 6. IR and VCD spectra with 85% conformer SRb and 15% conformer SRa are compared to experiment in Figure 7. The best overall fit between experiment and calculation over the entire region of measurement is for the 6*S*,10b*R* configuration, with a mixture of conformer SRb and conformer SRa in a ratio of ca. 85:15.

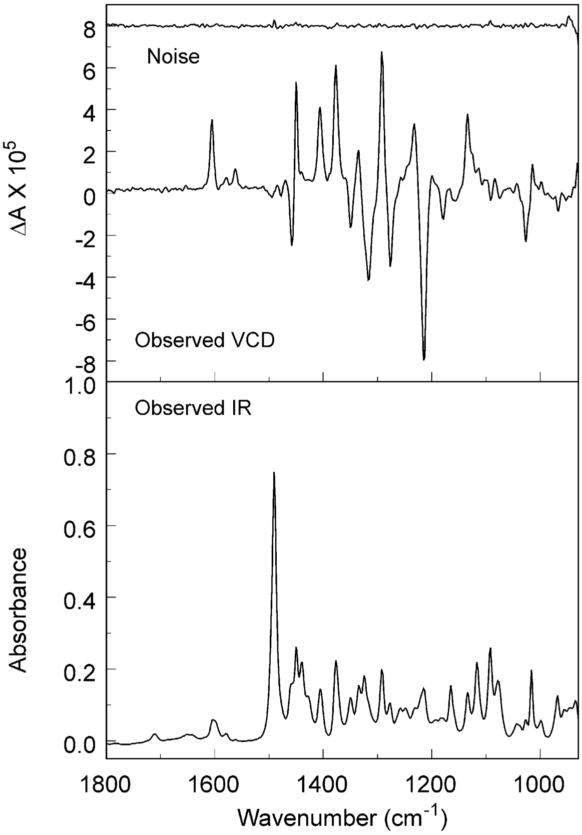


Figure 9. IR (lower frame) and VCD (upper frame) spectra of (+)-**1**. Uppermost trace is the VCD noise. Solvent spectra were subtracted from VCD and IR spectra.

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20. This issue is the subject of a recent Corrigendum (Schulze, O.; Schmidt, U.; Voss, J.; Nebeling, B.; Adiwidjaja, G.; Scharwächter, K. *Bioorg. Med. Chem.* **2002**, *10*, 3368) and Letter to the Editor (Maryanoff, B. E. *Bioorg. Med. Chem.* **2002**, *10*, 3367).

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