

For Supporting Info:

A. B3LYP Coordinates of the two conformers.

Major Conformer				Minor Conformer			
C	3.671100	0.881300	-0.004900	C	3.582500	0.997800	0.063200
C	4.636300	-0.069200	-0.352900	C	4.584600	0.121800	-0.368100
C	4.306900	-1.417400	-0.511300	C	4.312800	-1.223600	-0.627100
C	2.988500	-1.844800	-0.315500	C	3.018000	-1.727000	-0.450200
C	2.012800	-0.913100	0.023100	C	2.005900	-0.870900	-0.030700
C	2.359100	0.438500	0.171900	C	2.295800	0.482600	0.218100
N	1.209000	1.197700	0.487800	N	1.114300	1.164200	0.597700
C	0.001200	0.336000	0.414900	C	-0.043600	0.265300	0.389800
C	0.553200	-1.128300	0.365000	C	0.563200	-1.169300	0.328600
C	0.365500	-1.839100	1.730200	C	0.446200	-1.888900	1.697800
C	-1.099800	-2.280300	1.702800	C	-1.001300	-2.395800	1.722600
N	-1.368700	-2.618300	0.292800	N	-1.348700	-2.673900	0.316000
C	-0.269400	-2.078800	-0.557900	C	-0.264200	-2.149800	-0.562800
C	-0.820300	-1.405200	-1.817500	C	-0.860200	-1.528200	-1.828000
C	-1.739700	-0.243100	-1.393200	C	-1.723200	-0.315700	-1.421000
C	-0.813700	0.836100	-0.793000	C	-0.738100	0.739800	-0.899700
C	1.082100	2.562700	0.314100	C	0.902800	2.531300	0.526600
O	2.038700	3.317100	0.193800	O	1.804400	3.357200	0.511300
C	-0.358700	3.075500	0.317000	C	-0.581700	2.900600	0.453100
C	-1.419800	2.203500	-0.412300	C	-1.302400	2.173700	-0.719400
O	-2.522900	2.141700	0.488100	O	-2.725500	2.247900	-0.661500
C	-3.713800	1.536400	-0.021900	C	-3.420100	1.619100	0.402900
C	-3.717000	0.035000	0.139100	C	-3.426300	0.111200	0.420100
C	-2.821300	-0.767400	-0.447800	C	-2.727500	-0.739100	-0.342600
C	-2.721600	-2.250600	-0.154800	C	-2.706900	-2.229000	-0.059000
H	2.733600	-2.896100	-0.425600	H	2.810200	-2.777500	-0.638800
H	5.074700	-2.137300	-0.780300	H	5.108200	-1.884200	-0.960400
H	5.663000	0.254700	-0.501500	H	5.593700	0.502100	-0.503100
H	3.914400	1.928000	0.113700	H	3.779800	2.043000	0.261000
H	1.031800	-2.708300	1.774200	H	1.153200	-2.726200	1.718600
H	0.605900	-1.192100	2.579900	H	0.686700	-1.233100	2.540900
H	-1.287400	-3.143200	2.354400	H	-1.111100	-3.296900	2.339700
H	-1.751000	-1.461000	2.050000	H	-1.666800	-1.629000	2.149700
H	-0.686300	3.149200	1.361600	H	-1.053100	2.623700	1.404400
H	-0.326200	4.092600	-0.078100	H	-0.655400	3.984300	0.350300
H	-0.600400	0.478900	1.318500	H	-0.727400	0.349100	1.237900
H	-0.086100	1.061100	-1.587100	H	0.062200	0.825200	-1.648300
H	0.388600	-2.908800	-0.853700	H	0.396500	-2.983600	-0.841900
H	-3.433000	-2.545700	0.622800	H	-3.385600	-2.487100	0.759400
H	-2.973800	-2.843000	-1.044800	H	-3.040500	-2.805200	-0.931600
H	0.009900	-1.034500	-2.429600	H	-0.057700	-1.212200	-2.503800
H	-1.358000	-2.137300	-2.429700	H	-1.444400	-2.281300	-2.367700
H	-4.459700	-0.392800	0.811500	H	-4.082400	-0.301900	1.189200
H	-2.223400	0.186900	-2.283500	H	-2.254500	0.081700	-2.294600
H	-4.533300	1.981800	0.549800	H	-3.061900	1.983700	1.382200
H	-3.853200	1.827800	-1.076800	H	-4.451100	1.985700	0.312300
H	-1.748900	2.706800	-1.336000	H	-1.086300	2.732700	-1.634500

B. Computational details for the correlated calculations

The correlated electronic structure calculations use the MOLPRO 2008 program package,¹ and are single points at the B3LYP/6-31G(d) structures. All these calculations were performed in vacuum, and used the standard cc-pVTZ correlation consistent polarized basis sets of Dunning et al.² on all atoms. Hartree-Fock

calculations in MOLPRO used the density fitting procedure (DF-HF³) for greater efficiency, with density fitting basis functions developed for use with the corresponding cc-pVTZ basis. Canonical second-order perturbation theory calculations and local correlated calculations were also carried out using density fitting (DF-MP2, DF-LMP2-F12⁴ and DF-LMP2,⁵ and DF-LCCSD(T0)⁶ methods), again with the appropriate VTZ fitting basis. Comparative studies have shown that the density fitting approximation delivers remarkable increases in efficiency, especially with large basis sets, and causes only minute errors.⁷

Local correlation methods were used, in which the occupied HF orbitals are localized using the Pipek-Mezey criterion. Excitations from the localized orbitals needed to describe correlation are restricted based on locality criteria associated with virtual orbital domains situated close to the corresponding occupied orbitals. In all cases, orbital domains were generated using the automatic procedure of Boughton and Pulay,⁸ using the default threshold of 0.98. The orbital domains were inspected, and were found to be slightly different from one conformer to another. This leads to slight changes in correlation energy. Accordingly, for the key LCCSD(T0) calculations, the orbital domains determined for the HF wavefunction of the *major* conformer were used also for the LCCSD(T0) calculation of the minor conformer. The analogous procedure in which the minor species domains were used led to a difference in relative energy of only 0.3 kJ/mol. For the LMP2 and LMP2-F12 calculations, in contrast, the domains determined for each species were used, as the aim is to obtain a correction term $E(\text{LMP2-F12}) - E(\text{LMP2})$ that approximately describes removal of the orbital domain error and of the basis set incompleteness effect, through inclusion of explicit correlation.

The local coupled-cluster calculations used the approximate T0 scheme for computation of the perturbative triples correction; this has been shown to give results very close to those obtained with the usual perturbative triples ansatz at a reduced computational expense.⁶

In brief, the 'Best' electronic energies are obtained as:

$$E_{\text{best}}(\text{major}) = E(\text{LCCSD(T0)}_{\text{majdom}}) + E(\text{LMP2-F12}_{\text{majdom}}) - E(\text{LMP2}_{\text{majdom}})$$

$$E_{\text{best}}(\text{minor}) = E(\text{LCCSD(T0)}_{\text{majdom}}) + E(\text{LMP2-F12}_{\text{mindom}}) - E(\text{LMP2}_{\text{mindom}})$$

This was corrected by including the zero-point energy, thermal energy, and entropic terms from the B3LYP/6-31G(d) frequency calculation, and the solvation free energy derived from the B3LYP PCM computation.

Table S1. Comparison of interproton distances for strychnine determined by NOE, computationally for each conformer, and by Boltzmann averaging of both conformers.

Proton pair	Distances (Å)				Conformer 1 – average (Å) (%)	
	NOE-determined distance ⁹	Conformer 1	Conformer 2	Boltzmann (r^{-6}) average of 1 and 2.		
H11b-H23b	3.49	4.1	2.11	3.60	0.50	12.2
H22-H23a	2.97	2.98	2.48	2.96	0.02	0.7
H8-H22	3.63	3.99	3.42	3.97	0.02	0.6
H11b-H8	2.53	2.67	2.3	2.66	0.01	0.5
H18b-H22	3.01	3.16	2.92	3.15	0.01	0.2
H13-H11a	3.25	3.39	3.81	3.40	-0.01	-0.2
H13-H12	2.25	2.35	2.23	2.35	0.00	0.1
H18a-H16	3.67	3.63	3.53	3.63	0.00	0.1
H15a-H1	4.03	3.86	3.76	3.86	0.00	0.1
H14-H8	3.75	3.96	3.86	3.96	0.00	0.1
H18b-H20b	2.41	2.46	2.37	2.46	0.00	0.1
H22-H23b	2.37	2.39	2.51	2.39	0.00	-0.1
H11b-H12	2.79	2.93	3.04	2.93	0.00	-0.1
H14-H13	2.30	2.41	2.52	2.41	0.00	-0.1
H14-H22	3.70	3.86	3.95	3.86	0.00	0.0
H17a-H1	2.75	2.79	2.88	2.79	0.00	-0.1
H22-H20b	2.34	2.39	2.33	2.39	0.00	0.1
H18a-H20b	2.78	2.82	2.89	2.82	0.00	-0.1
H8-H17b	2.35	2.42	2.49	2.42	0.00	-0.1
H15a-H13	2.22	2.26	2.21	2.26	0.00	0.1
H13-H11b	3.66	3.66	3.71	3.66	0.00	0.0
H11a-H12	2.32	2.35	2.39	2.35	0.00	0.0
H15b-H20a	2.15	2.24	2.21	2.24	0.00	0.0
H17a-H16	2.64	2.71	2.68	2.71	0.00	0.0
H17b-H16	3.71	3.85	3.82	3.85	0.00	0.0
H8-H17a	3.54	3.61	3.64	3.61	0.00	0.0
H15a-H8	4.08	4.09	4.11	4.09	0.00	0.0
H13-H8	2.87	3.01	3.03	3.01	0.00	0.0
H15b-H14	2.52	2.48	2.5	2.48	0.00	0.0
H18b-H17b	2.44	2.43	2.42	2.43	0.00	0.0
H17a-H18a	2.41	2.43	2.42	2.43	0.00	0.0
H15a-H16	2.42	2.48	2.47	2.48	0.00	0.0
H18b-H16	3.70	3.89	3.88	3.89	0.00	0.0
H17b-H18a	2.79	2.73	2.74	2.73	0.00	0.0
H15a-H14	2.50	2.55	2.56	2.55	0.00	0.0
H15b-H16	2.41	2.48	2.49	2.48	0.00	0.0
H11b-H11a	1.74	1.76	1.77	1.76	0.00	0.0
H15a-H15b(ref)	1.76	1.76	1.76	1.76	0.00	0.0
H8-H18b	2.20	2.37	2.37	2.37	0.00	0.0
H18b-H18a	1.81	1.77	1.77	1.77	0.00	0.0
H20b-H20a	1.75	1.75	1.75	1.75	0.00	0.0

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- ¹ MOLPRO, version 2008.1, a package of *ab initio* programs, H.-J. Werner, P. J. Knowles, R. Lindh, F. R. Manby, M. Schütz, and others, see <http://www.molpro.net>.
- ² T. H. Dunning Jr., *J. Chem. Phys.* 1989, **90**, 1007-1023; R. A. Kendall, T. H. Dunning, Jr. and R. J. Harrison, *J. Chem. Phys.* 1992, **96**, 6796-6806.
- ³ R. Polly, H.-J. Werner, F. R. Manby, and P. J. Knowles, *Molec. Phys.* 2004, **102**, 2311-2321.
- ⁴ H.-J. Werner, *J. Chem. Phys.* 2008, **129**, 101103.
- ⁵ H.-J. Werner, F. R. Manby and P. J. Knowles, *J. Chem. Phys.* 2003, **118**, 8149-8160.
- ⁶ M. Schütz, *J. Chem. Phys.* 2000, **113**, 9986-10001; M. Schütz and F. R. Manby, *Phys. Chem., Chem. Phys.* 2003, **5**, 3349-3358.
- ⁷ J. Kaminsky, R. A. Mata, H.-J. Werner and F. Jensen, *Molec. Phys.* 2008, **106**, 1899-1906.
- ⁸ J. W. Boughton and P. Pulay, *J. Comput. Chem.* 1993, **14**, 736-740.
- ⁹ C. P. Butts, C. R. Jones, E. C. Towers, J. L. Flynn, L. Appleby and N. Barron, *Org. Biomol. Chem.*, DOI:10.1039/C0OB00479K.