Polish J. Chem., **75**, 1483–1491 (2001) **PHYSICAL CHEMISTRY**

Conformational Preference in Isolated Neutral Cytisine

by E. Górnicka[1], M. Makowski[2], M. Darowska[3] and E.D. Raczyńska*[3]

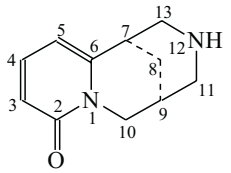
[1]*Interdisciplinary Department of Biotechnology, Warsaw Agricultural University (SGGW), 02-528 Warszawa, Poland*
[2]*Faculty of Chemistry, University of Gdańsk, 80-952 Gdańsk, Poland*
[3]*Department of Chemistry, Warsaw Agricultural University (SGGW), 02-528 Warszawa, Poland*

(Received April 6th, 2001)

Two isomers (**1a** and **1b**) of almost equal total energies were found for isolated cytisine by the semiempirical (AM1 and PM3) as well as *ab initio* methods (HF/6-31G*//HF/6-31G* and MP2/6-31G*//HF/6-31G*). They differ only by orientation of the hydrogen on the piperidine nitrogen. Geometrical parameters calculated at the AM1, PM3 and 6-31G* levels are close to those reported for crystal cytisine. Aromatic character of the pyridone moiety in the calculated molecules is slightly smaller than that in the experimental crystal cytisine.

Key words: cytisine, conformational preference, semiempirical and *ab initio* calculations, aromatic character of pyridone moiety

Cytisine (**1**), a quinolizidine alkaloid synthesized by various plants (e.g. *Cytisus laburnum*, *Thermopsis rhombifolia*, *Anagyris foetida*, *Baptisia australis*, *Sarothamnus scoparius*) belongs to the same pharmacological group as nicotine [1]. Its binds with high affinity to nicotinic acetylcholine receptors, however its complex behavioural and physiological effects are slightly different from those of nicotine [2]. To better understand these differences, it is very important to know structure of cytisine and its physicochemical properties in different environments.



1

Crystal structure of neutral cytisine has been determined by X-ray crystallography [3–5]. Two independent molecules of identical conformation – linked together by the intermolecular hydrogen bond between the NH group and the carbonyl oxygen atom – have been identified in the unit cell. Such kind of hydrogen bond has not been detected in $CDCl_3$ solutions [3,6–8]. Only conformational isomers have been identified. Gas phase structure has not yet been reported.

In this paper semiempirical (AM1 [9] and PM3 [10]) calculations were performed for all possible conformations of isolated **1** and its model compounds: N-methyl-2-pyridone (**2**) and piperidine (**3**). For the most stable structures of **1**, *ab initio* calcula-

tions (HF/6-31G*//HF/6-31G* and MP2/6-31G*//HF/6-31G* [11–13]) were also realized. Geometrical parameters calculated at the AM1, PM3 and HF/6-31G* levels were compared with those obtained on the basis of X-ray measurements [3,4]. Aromatic character of the pyridone moiety was quantitatively measured by the HOMA (Harmonic Oscillator Model of Aromaticity) index [14,15].

COMPUTATIONAL DETAILS

Semiempirical calculations: Geometries of eight isomers of cytisine (structures **1a**–**1h)** given in Figure 1, two isomers of 1-methyl-2-pyridone (**2a** and **2b**) and two isomers of piperidine (chair structures **3a** and **3b**) given in Figure 2 were optimized at the semiempirical AM1 [9] and PM3 levels [10] using the HYPERCHEM program [16]. Total energies and dipole moments were calculated for all structure considered here. Geometrical parameters were collected only for the most stable structures of cytisine (**1a** and **1b**).

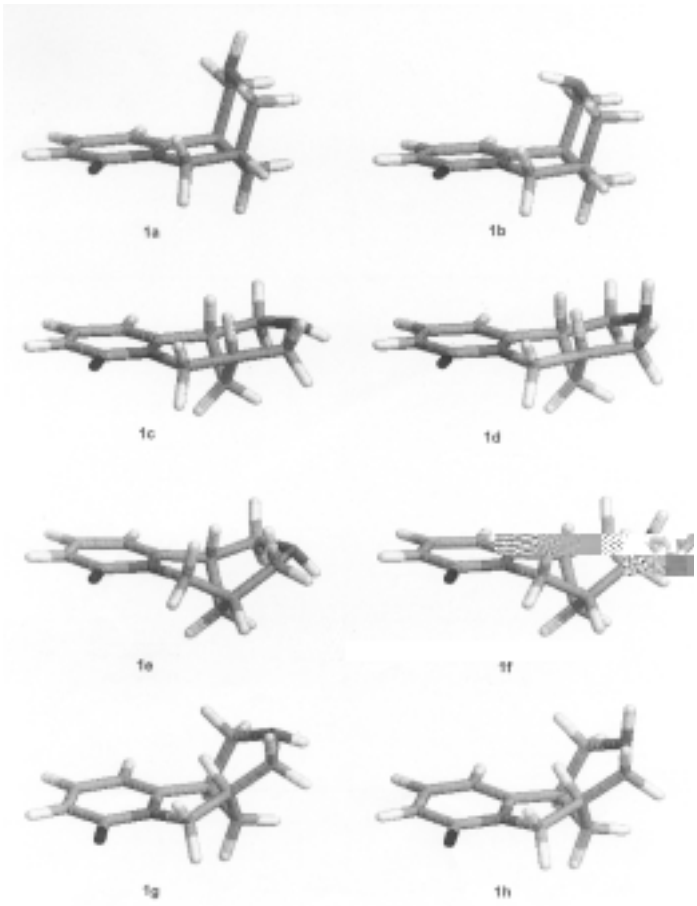


Figure 1. Possible structures for cytisine (**1a**–**1h**).

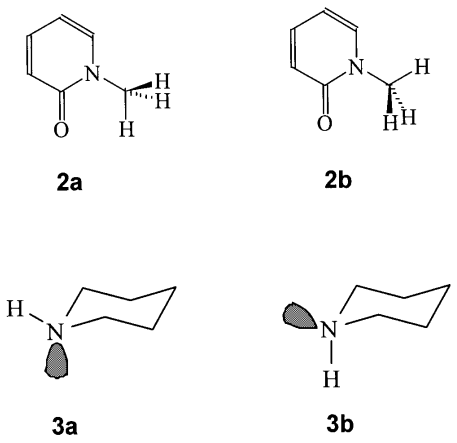


Figure 2. Possible structures for N-methyl-2-pyridone (**2a** and **2b**) and piperidine (**3a** and **3b**).

***Ab initio* calculations**: For the most stable structures of cytisine (**1a** and **1b**), calculations were performed at the *ab initio* level using the 6-31G* basis set (split valence basis with polarization functions on the heavy atoms) [11]. The geometries were fully optimized without symmetry constraint and the stationary point on the potential energy surface found. RHF [11] and MP2 calculations [12,13] were realized with the GAMESS 98 program [17].

RESULTS AND DISCUSSION

Possible and prefered structures: Cytisine (**1**) contains two asymmetric carbon atoms (C^7 and C^9) for which four configurations are possible (RS, SR, SS and RR) and one amino nitrogen atom, included in the aliphatic six-membered ring (piperidine moiety), for which two orientations of the lone pair of electrons (*axial* and *equatorial*) can be considered. Eight structures (**1a**–**1h**) are thus possible (Figure 1). Semiempirical (AM1 [9] and PM3 [10]) calculations were realized for all of them, and the total energies (E in kcal mol^{-1}, 1cal = 4.184 J) and dipole moments (μ in Debayes) calculated (Table 1). Calculations were also performed for model compounds: 1-methyl-2-pyridone (**2**) and piperidine (**3**). For models, two rotational isomers of the methyl group (**2a** and **2b**), and two conformations (**3a** and **3b**) with the *axial* and *equatorial* orientation of the nitrogen lone pair of electrons were considered (Figure 2).

First perusal of the E values shows that both semiempirical methods give similar behaviour between the considered structures. The orders of the relative energies for cytisine isomers are the same: **1b**>**1a**>**1g**>**1e**>**1h**>**1f**>**1d**>**1c**. Two structures (**1a** and **1b**) have the lowest total energies. Structure **1b** is more stable than **1a** by only 3.7 at the AM1 and 2.0 kcal mol^{-1} at the PM3 level. Both structures have the same configurations on the asymmetric carbon atoms (Figure 1). They differ only by conformation on the nitrogen atom in the piperidine moiety similarly as model structures (**3a** and

3b) of piperidine (Figure 2). The same difference in conformation on the nitrogen atom is between **1c** and **1d**, **1e** and **1f**, and **1g** and **1h**. The total energies in these pairs of isomers differ by not more than 2 (AM1) or 1 kcal mol^{-1} (PM3). Difference in the total energies between two isomers of piperidine (**3a** and **3b**) is equal to 2.7 (AM1) or 2.2 kcal mol^{-1} (PM3) with preference of the structure **3b** containing the *equatorial* orientation of the lone pair of electrons on the nitrogen atom.

Table 1. Total energies (E in kcal mol^{-1}) and dipole moments (μ in Debayes) for cytisine (**1a**–**1h**), 1-methyl-2-pyridone (**2a** and **2b**) and piperidine (**3a** and **3b**) calculated at the AM1 and PM3 levels.

	AM1		PM3	
Structure	E	μ	E	μ
1a	–53855.7	5.32	–49292.0	5.18
1b	–53859.4	3.73	–49294.0	3.50
1c	–53688.7	4.24	–49147.7	3.69
1d	–53690.7	3.55	–49147.7	3.17
1e	–53780.4	3.76	–49226.8	3.48
1f	–53778.4	3.41	–49225.6	3.31
1g	–53780.6	4.17	–49227.5	3.77
1h	–53778.7	3.54	–49226.4	3.37
2a	–32082.2	3.72	–29386.0	3.54
2b	–32082.0	3.77	–29386.3	3.60
3a	–23049.1	1.17	–21333.7	1.18
3b	–23051.8	1.37	–21335.9	1.37

In the most stable semiempirical structure of isolated cytisine (**1b**), the lone pair of electrons on the nitrogen atom in the piperidine ring is also *equatorial*. Dipole moment of **1b** (3.5 D) is close to that of model compound **2** but lower than that of **1a** (5.2 D) indicating additionally that the first one (as less polar) should be prefered in the gas phase. Structure **1a** (more polar) with the *axial* lone pair of electrons on the piperidine nitrogen atom has been found as the most stable in the solid state [3–5]. In crystal cytisine, the *equatorial* hydrogen of the piperidine nitrogen of one molecule forms the intermolecular hydrogen bond with the pyridone oxygen of the other molecule and stabilizes additionally the crystal structure. The total energies of other structures of cytisine are larger than that of the most stable structure **1b** by *ca*. 80 (**1e**-**1h**) and 170 kcal mol^{-1} (**1c** and **1d**) at the AM1 level (or by *ca.* 70 and 150 kcal mol^{-1}, respectively at the PM3 level). For this reason, their presence in the gas phase is less probable, although all of them have the polarity (between 3.2 and 4.2 D) close to that of **1b**.

Ab initio calculations (using the 6-31G* basis set) were realized only for the most stable structures of cytisine (**1a** and **1b**). For calculations two models (RHF and MP2) were applied [11–13]. The total energy of structure **1a** (Table 2) computed by both *ab*

initio methods is almost the same as that of **1b** (ΔE 0.3 and 0.005 kcal mol^{-1} at the HF/6-31G*//HF/6-31G* and MP2/6-31G*//HF/6-31G* levels, respectively) confirming semiempirical results that cytisine exists as mixture of two conformers in the gas phase. These conformations have also been proposed for cytisine in solution ($CDCl_3$) on the basis of NMR experiments [3,6–8]. However, their mole fractions have not been determined.

Table 2. Total energies (E in kcal mol^{-1}) calculated for cytisine structures **1a** and **1b** using the RHF and MP2 models [11–13].

Structure	HF/6-31G*//HF/6-31G*[a]	MP2/6-31G*//HF/6-31G*
1a	–381785.7760	–383017.5982
1b	–381785.4356	–383017.5933

[a] Thermal corrections included.

Geometrical parameters of the preferred structures: Geometrical parameters (bond length in Å and angles in degrees) were computed for **1a** and **1b** at the semiempirical (AM1 and PM3) and *ab initio* levels (RHF/6-31G*). Since configuration (RS) on the asymmetric carbon atoms in **1a** and **1b** is the same as in two independent molecules of cytisine (**1a** and **1a′**) in the solid state [3,4], the results obtained here are compared with the literature X-ray data (Table 3).

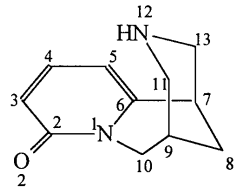
The comparison indicates that the larger differences are present for the following parameters: the bond lengths in the pyridone moiety, the CN bond lengths in piperidine moiety, and the angles containing the nitrogen atom. However, these differences do not exceed 0.05 Å in distance and 6° in angle. Other computed bond lengths do not differ from crystal ones by more than 0.02 Å. For other angles, the differences are not larger than 2°.

Generally, the pyridone moiety is planar. Sum of the angles around the N^1 atom (C^2–N^1–C^6, C^2–N^1–C^{10} and C^6–N^1–C^{10}) is equal to 360° similarly as that in crystal structure. The same is found for the sum of the angles around the C^2 as well as the C^6 atom (360°). Single angles in the pyridone moiety are close to 120°. The cyclic moiety linked to the pyridone one has half-chair conformation. The angles around the C^6 and N^1 atoms in the ring are close to 119–124°, and those at the C^7, C^8, C^9 and C^{10} atoms are close to 107–116°. Full-chair conformation has only the piperidine moiety in which all angles are close to 107–116°.

Aromatic character of the pyridone moiety: Although the binding sites in the nicotinic receptors and their geometry are not yet well known [2,5], there is an indication common for all agonists that π electrons in aromatic (or unsaturated) systems play an important role in activity of drug. For this reason, it is interesting to determine properties of the π electrons in cytisine.

Aromatic character of the pyridone moiety can quantitatively be measured by the HOMA index (close to 1 for benzene) [14,15]. HOMA indices calculated for theoretical (AM1, PM3 and 6-31G*) and experimental (crystal) bond lengths using eq. 8 from

Table 3. Comparison of calculated (AM1, PM3 and 6-31G*) geomertical parameters of the most stable structures (**1a** and **1b**) with those reported for two independent molecules in the unit cell of the crystal cytisine (**1a** and **1a′**).



Bond length	AM1		PM3		6-31G*		Crystal [3]		Crystal [4]	
or angle	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1a′**	**1a**	**1a′**
N^1–C^2	1.421	1.421	1.439	1.440	1.395	1.394	1.428	1.408	1.405	1.406
C^2–C^3	1.460	1.460	1.456	1.458	1.444	1.448	1.408	1.432	1.424	1.424
C^3–C^4	1.358	1.358	1.354	1.353	1.342	1.342	1.394	1.332	1.381	1.344
C^4–C^5	1.422	1.424	1.423	1.425	1.428	1.429	1.402	1.410	1.398	1.402
C^5–C^6	1.382	1.380	1.370	1.368	1.350	1.350	1.356	1.379	1.358	1.346
N^1–C^6	1.382	1.386	1.403	1.407	1.363	1.369	1.371	1.369	1.388	1.385
C^2–O^2	1.249	1.248	1.229	1.228	1.209	1.205	1.239	1.245	1.236	1.241
C^6–C^7	1.510	1.509	1.507	1.506	1.512	1.512	1.516	1.528	1.501	1.514
C^7–C^8	1.521	1.522	1.524	1.525	1.528	1.525	1.538	1.532	1.528	1.525
C^8–C^9	1.519	1.520	1.523	1.523	1.524	1.523	1.517	1.501	1.538	1.533
C^9–C^{10}	1.530	1.529	1.529	1.528	1.529	1.529	1.542	1.516	1.530	1.511
N^1–C^{10}	1.453	1.454	1.491	1.492	1.472	1.476	1.495	1.478	1.486	1.478
C^7–C^{13}	1.540	1.545	1.536	1.539	1.533	1.545	1.536	1.550	1.543	1.530
C^9–C^{11}	1.536	1.538	1.534	1.536	1.528	1.535	1.527	1.532	1.533	1.522
N^{12}–C^{11}	1.448	1.448	1.484	1.481	1.447	1.448	1.466	1.470	1.469	1.462
N^{12}–C^{13}	1.448	1.447	1.484	1.480	1.443	1.450	1.488	1.447	1.463	1.474

Table 3 (continuation)

N^1–C^2–C^3	117.2	117.3	117.4	117.4	116.0	116.0	116.2	115.3	116.2	115.9
C^2–C^3–C^4	121.0	121.0	120.7	120.7	120.8	120.7	121.3	122.1	121.2	121.2
C^3–C^4–C^5	120.0	120.0	120.5	120.5	120.5	120.6	119.8	121.1	119.5	120.7
C^4–C^5–C^6	120.0	120.1	120.9	121.0	119.3	119.3	119.9	118.8	121.5	120.5
C^5–C^6–N^1	121.3	121.2	120.5	120.4	120.7	120.5	121.1	120.1	119.0	119.4
C^5–C^6–C^7	119.0	119.1	119.6	119.8	120.6	120.8	119.8	120.1	122.5	122.0
C^6–N^1–C^2	120.5	120.4	120.1	120.0	122.7	122.8	121.6	122.6	122.7	122.3
O^2–C^2–N^1	118.4	118.4	117.3	117.2	119.9	120.1	118.0	118.5	119.2	119.1
O^2–C^2–C^3	124.3	124.3	125.3	125.4	124.1	123.9	125.8	126.2	124.6	124.9
N^1–C^6–C^7	119.7	119.6	119.9	119.8	118.7	118.6	119.0	119.8	118.5	118.5
C^6–C^7–C^8	110.7	110.6	110.8	110.7	110.1	110.6	108.6	109.6	110.3	110.7
C^7–C^8–C^9	107.4	107.6	107.8	107.8	106.5	106.7	108.2	107.5	106.5	106.1
C^8–C^9–C^{10}	110.1	109.9	110.0	109.9	109.6	109.4	109.9	109.3	110.4	109.0
C^9–C^{10}–N^1	116.0	115.9	115.4	115.3	115.0	114.6	114.5	115.6	115.6	115.8
C^{10}–N^1–C^6	122.6	122.5	121.9	121.8	124.0	123.6	124.3	122.4	123.2	122.7
C^{10}–N^1–C^2	116.9	116.8	118.0	118.0	113.3	113.3	114.0	115.0	114.1	114.9
C^{11}–N^{12}–C^{13}	114.6	113.3	113.7	113.2	113.1	112.6	111.2	111.8	111.7	110.9
N^{12}–C^{13}–C^7	112.6	114.9	110.9	113.8	109.5	113.8	110.3	110.8	110.2	109.0
N^{12}–C^{11}–C^9	113.3	115.5	111.8	114.7	109.8	114.6	109.8	109.6	109.6	110.6
C^6–C^7–C^{13}	109.5	109.4	110.2	110.5	111.1	110.6	111.7	109.8	112.2	110.7
C^8–C^7–C^{13}	109.1	108.8	109.5	109.4	109.6	109.2	109.4	108.7	109.7	110.0
C^{10}–C^9–C^{11}	111.8	111.8	113.0	113.2	113.0	113.4	112.4	113.4	112.3	113.7
C^8–C^9–C^{11}	109.5	109.3	109.8	109.7	109.6	109.6	109.4	110.9	109.0	109.9

ref. 14 and the new parameters for the CC bond are given in Table 4. The estimation confirms differences between the computed (isolated) and crystal structures in the pyridone moiety. Both semiempirical (AM1 and PM3) and *ab initio* methods (6-31G*) predict smaller aromatic character of the pyridone moiety for isolated molecules than experiment for crystal structures. To our surprise, HOMA indices calculated for AM1 structures are close to those for *ab initio* ones indicating some kind of similarity in these computational methods. This observation is very important for our more complicated investigations on interactions of cytisine with representative model compounds corresponding to sites in the receptor.

Table 4. HOMA indices[a] for the computed and crystal structures of cytisine[b].

Method	HOMA (**1a**)	HOMA (**1b**)
AM1	0.534	0.520
PM3	0.439	0.403
6-31G*	0.573	0.545
X-ray [3]	0.770	
	0.653	
X-ray [4]	0.775	
	0.656	

[a] Calculated according to eq. 8 taken from ref. [14] using the new parameters for the CC bond.
[b] Bond lengths taken from Table 3.

CONCLUSIONS

Two cytisine isomers (**1a** and **1b**), which differ by conformation on the piperidine nitrogen, can be observed in the gas phase in almost equal quantities, whereas in the solid state only one conformation (**1a**) is dominant. This conformation is stabilized by an intermolecular hydrogen bond between the NH group of one molecule and the CO group of the other one. This indicates that an interaction of the carbonyl group in the pyridone moiety with a hydrogen bond donor group in the receptor can favour structure **1a**, whereas an interaction between hydrophobic flat areas in cytisine and receptor cannot influence the conformational preference of cytisine.

Acknowledgment

Ab initio calculations were carried out with use of the resources and software at the Interdisciplinary Center for Molecular Modelling (ICM-Warsaw) and the Informatics Center of the Metropolitan Academic Network (IC MAN-Gdańsk) at the Technical University of Gdańsk.

REFERENCES

1. Cordell G.A., *An Introduction to Alkaloids: a Biogenic Approach*, Wiley, NY, 1981.
2. Chandler C.J. and Stolerman I.P., *Psychpharm.*, **129**, 257 (1997).
3. Mascagni P., Christodoulou M., Gibbons W. A., Asres K., Phillipson J.D., Niccolai N. and Mangani S., *J. Chem. Soc*., *Perkin Trans. II*, 1159 (1987).
4. Freer A.A., Robins D.J. and Sheldrake G.N., *Acta Cryst. Sect. C: Cryst. Struct. Commun.*, **C43**, 1119 (1987).
5. Barlow R.B. and Johnson O., *Br. J. Pharmacol.*, **98**, 799 (1989).
6. Liu Z., Yang L., Jia Z. and Chen J., *Magn. Reson. Chem.*, **30**, 511 (1992).
7. Wysocka W. and Brukwicki T., *J. Mol. Struct.*, **385**, 23 (1996).
8. Brukwicki T. and Wysocka W., *J. Mol. Struct.*, **474**, 215 (1999).
9. Dewar M.J.S., Zoebisch E.G., Healy E.F. and Stewart J.J.P., *J. Am. Chem. Soc.*, **107**, 3902 (1985).
10. Stewart J.J.P., *J. Comput. Chem.*, **10**, 221 (1989).
11. Hehre W.J., Radom L., Schleyer P. v. R. and Pople J.A., *Ab Initio Molecular Orbital Theory*, Wiley, NY, 1986.
12. Möller C. and Plesset M.S., *Phys. Rev.*, **46**, 618 (1934).
13. Pople J.A., Brinkley J.S. and Seeger R., *Int. Quantum Chem. Symp.*, **10**, 1 (1976).
14. Krygowski T.M., *J. Chem. Inf. Comput. Sci.*, **33**, 70 (1993).
15. Krygowski T.M. and Cyrański M.K., *Chem. Rev.*, in press (2001).
16. *HyperChem* (1995), Hypercube, Inc., Waterloo, ON, Canada.
17. Schmidt M.W., Baldridge K.K., Boatz J.A., Elbert S.T., Gordon M.S., Jensen J.H., Koseki S., Matsunaga N., Nguyen K.A., Su S.J., Windus T. L., Dupuis M. and Montgomery J.A., *J. Comput. Chem*., **14**, 1347 (1993).