Quantum Chemical Study on Conformational Properties of Bipyridine Cardiotonics

Akihiro NOGUCHI,* Shin-ichi KONDO, and Masayuki KUZUYA

Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University, 5–6–1, Mitahora-higashi, Gifu 502, Japan. Received October 6, 1992

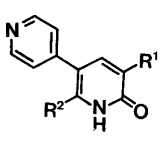
The conformational properties of bipyridine cardiotonics were investigated by means of quantum chemical (AM1 (Austin Model 1)) calculations. The calculations for the tautomeric and ionic structures of 3,4′-bipyridin-6(1*H*)-one (1), the basic structure for bipyridine cardiotonics, showed that the equilibrium conformations in the ionic structures are more planar than those in the neutral structures and that the rotational barrier of the cationic pyridone structure is characteristically higher compared to those of the pyridinol tautomer and 1′-hydro-3,4′-bipyridinium cation. The difference in conformation between the well known cardiotonics, amrinone and milrinone, is more distinctive in the cationic structure, which is considered to be the usual structure in biological environments, than in the neutral structures.

Keywords bipyridine cardiotonic; conformation; molecular orbital; Austin Model 1; amrinone; milrinone

Amrinone (5-amino-(3,4′-bipyridin)-6(1*H*)-one) and milrinone (5-cyano-2-methyl-(3,4′-bipyridin)-6(1*H*)-one) are important synthetic cardiotonic drugs.[1,2] Milrinone is from 20 to 50 times more potent than amrinone,[2,3] and the marked difference in activity may provide a clue in the search for more potent and safer drugs for the treatment of congestive heart failure. The structure–activity relationships[3] and computer-assisted pharmacophore search[4] have been exhaustively studied, the high activity of milrinone has been attributed to the twisted conformation caused by the steric effect of the 2-methyl substituent.

The difference in conformation between amrinone and milrinone has been studied by X-ray crystal structure analyses[3,5] and molecular orbital calculations.[6] A remarkable difference in conformation between amrinone ($\theta = 1.3°$, where θ is the angle between the planes of the two rings) and milrinone ($\theta = 52.2°$) has been shown in crystal structure analyses of the hydrochloride salts by Robertson *et al.*[3] Crystal structure analyses of the neutral structures have been reported by Cody[5b] and the torsional angles were 8.7—21.7° for amrinone and 42.4° for milrinone. Also, the torsional angles of 9.0—24.3° and 10.0—37.4° have been reported for the α- and β-crystal modifications of amrinone, respectively, by Reck *et al.*[5a]

Quantum chemical studies on the conformations of amrinone and milrinone have been made using the *ab initio* STO-3G[5a] and the NDDO methods,[6b] by Hofmann *et al.* The calculated equilibrium conformations for amrinone and milrinone were $\theta = 37.1°$ and $\theta = 67.1°$, respectively, in the *ab initio* STO-3G results, and $\theta = 34°$ and $\theta = 62°$, respectively, in the NDDO results. Those calculated conformations are distinctly twisted compared to the crystal data.



amrinone: $R^1 = NH_2$, $R^2 = H$
mirlinone: $R^1 = CN$, $R^2 = CH_3$
1: $R^1 = R^2 = H$

Chart 1

We have previously reported on the substituent effects in the tautomeric equilibria of 2-pyridones.[7] Bipyridine cardiotonics are pyridyl derivatives of 2-pyridone and the tautomeric and ionic equilibria are considered to be important in relation to the conformational properties. Thus, it is of interest to study the conformational behavior in the tautomeric and ionic structures of bipyridine cardiotonics.

In this study, the conformations of the ionic and tautomeric structures of 3,4′-bipyridin-6(1*H*)-one (**1**), the basic structure for bipyridine cardiotonics, were investigated by means of AM1 (Austin Model 1) calculation,[8] and the UV spectra were measured in various solutions. Based on the results, the difference in conformational properties between amrinone and milrinone is discussed.

Experimental

3,4′-Bipyridin-6(1*H*)-one (**1**) was prepared according to the literature.[9] 1-Methyl-3,4′-bipyridin-6(1*H*)-one[10] was prepared by treatment of **1** with methyl iodide and potassium carbonate in acetone. The UV spectra of **1** were measured at the concentration of 5×10^{-5} mol/dm^3 in water, 0.001 N H_2SO_4 aqueous solution, ethanol, and acetonitrile on a Shimadzu UV-3101PC spectrometer. The pK_a value of **1** in an aqueous solution was determined by the spectrometric method at 24 °C.

Calculations The AM1 method[8] is one of the most advanced semi-empirical molecular orbital methods and well reproduces the conformational properties of biphenyls and bipyridines which are free from hydrogen-nitrogen lone pair interactions between the *ortho* positions of the two rings, although the method underestimates rotational barriers.[11] Thus, the torsional potentials around the inter-ring CC bond for the tautomeric and ionic structures of 3,4′-bipyridin-6(1*H*)-ones were calculated by the AM1 method. In the calculations, the torsional angle θ was spanned in steps of 15° over the range from 0° to 90° and the geometry at each torsional angle was optimized on assumption of planar structure for the rings.

Calculations were carried out on a FACOM M-780/20 computer at the Computation Center of Nagoya University.

Results and Discussion

UV Spectra of 1 The structures of **1** in various solutions were investigated by UV spectral measurements. The UV spectra of **1** are shown in Fig. 1. The spectrum in an aqueous solution is similar to those in ethanol and acetonitrile except for the apparent shoulder at around

320 nm. The band around 320 nm is attributed to the cationic structure of **1**, based on the spectral changes associated with lowering of the pH of the solution.

We also measured the UV spectra of the 1-methyl compound of **1**, a model compound for the pyridone tautomer of **1**, in order to investigate the tautomeric structures. The spectra of the 1-methyl compound measured in the same way as described for **1** are almost the same as those of **1**. Thus, **1** exists as the pyridone tautomers in both the neutral and cationic structures. The estimated pK_a value (5.33) for the cation of **1** is nearly the same as the known value (5.25) for the monocation of amrinone.[12]

From these results, it is clear that the cationic structure of bipyridine cardiotonics is a major form in slightly acidic solutions and also is important for the activity. Thus, the conformational behavior in the cationic structure of bipyridine cardiotonics seems to be of importance for understanding the relationship between the conformation and the pharmacological activity, together with that in the neutral structure.

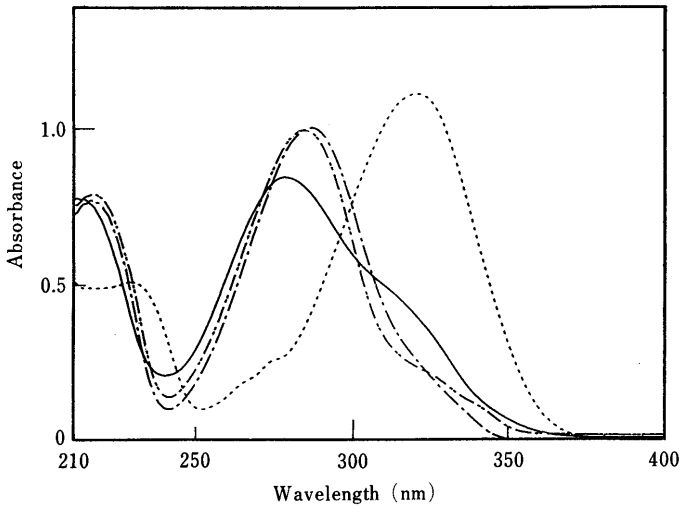


Fig. 1. UV Spectra of **1**

Solvent: ——, H_2O; ------, 0.001 N H_2SO_4; ——·——, C_2H_5OH; ——··——, CH_3CN.

Stabilities of Tautomeric Structures In order to confirm the results of the above spectroscopic measurements, the stabilities of some typical tautomeric structures of **1** and its cation (**2**) were investigated by means of molecular orbital calculations (the AM1 method).[8] The calculated tautomeric and ionic structures of **1** are shown in Chart 2. For comparison, the calculations were also performed for 2-pyridone and its tautomer, 2-pyridinol. The calculated heats of formation and the torsional angles in the equilibrium conformation are given in Table I. The equilibrium conformations were determined by fitting conformational energies calculated in steps of 15° to a three-term Fourier expansion:

$$\Delta E = E(\theta) - E(0°)$$
$$= 1/2\{V_2(1-\cos 2\theta) + V_4(1-\cos 4\theta) + V_6(1-\cos 6\theta)\}$$

The calculations show that the pyridone (**a**) and pyridinol (**b**) tautomers are apparently more stable than the remaining tautomeric structures (**c**) in each of the neutral (**1**) and cationic (**2**) structures, and the calculated differences in stability between the pyridone (**a**) and pyridinol (**b**) tautomers are quite small in both the neutral (**1**)

Table I. Heats of Formation (ΔH_f) and Torsional Angles (θ) for Optimum Structures Calculated by the AM1 Method

Compound	ΔH_f (kcal/mol)[a]	θ (degree)
2-Pyridone	−11.304 (0.000)	—
2-Pyridinol	−11.763 (−0.459)	—
1a	24.223 (0.000)	38.3
1b	23.660 (−0.563)	38.1
1c	53.145 (28.922)	0.0
2a	172.728 (0.000)	21.5
2b	172.105 (−0.623)	25.4
2c	180.901 (8.173)	41.4
3	−10.707	18.4

a) The relative values to the pyridone form are given in parentheses.

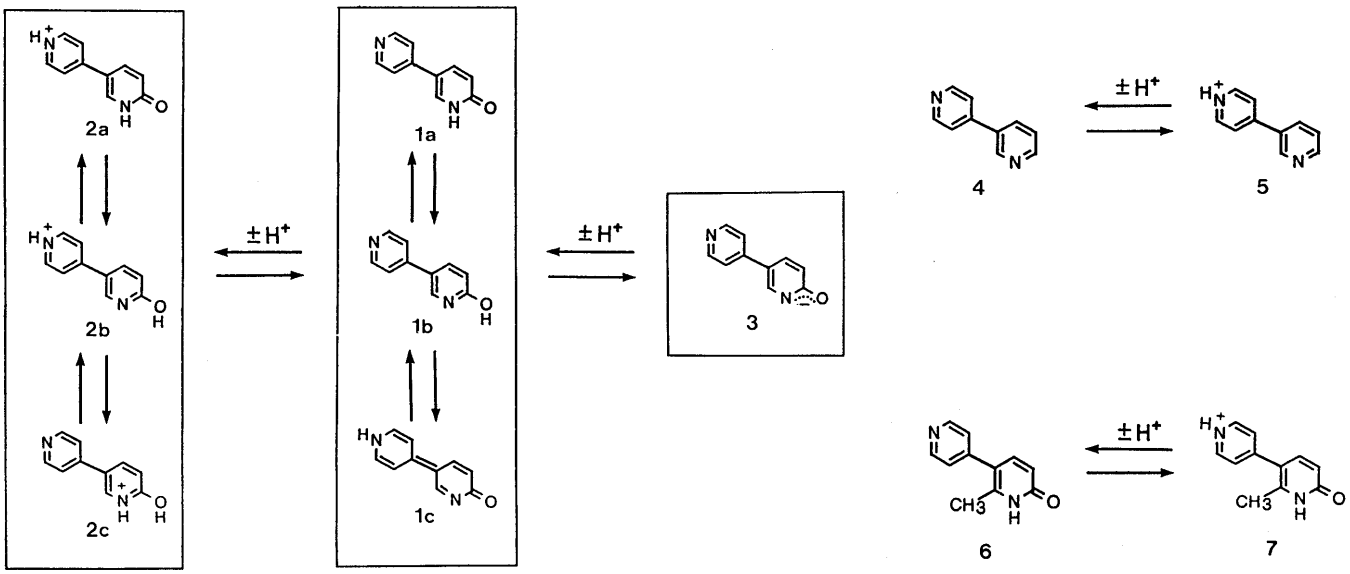


Chart 2

The cationic structure protonated at the NH group in **1c** was far less stable (by 50 kcal/mol in the calculated heats of formation) than **2c**.

and cationic (**2**) structures. It has been well established theoretically and experimentally that the difference in stability between tautomers of 2-pyridone in the unimolecular state is quite small (0.1—0.6 kcal/mol) in favor of 2-pyridone,[13] and the AM1 method well reproduces the small difference in stability between 2-pyridone and 2-pyridinol.[14] Thus, it was found that the substituent effects of the 4′-pyridyl function and its cation at the 5-position on the tautomeric equilibria of 2-pyridones are small.

Taking into account the above calculated results and the strong predominance of the pyridone tautomer in the tautomeric equilibria of 2-pyridones in solutions due to the stabilization by hydrogen bonding,[15] it is clear that **1** exists mainly as the 2-pyridone tautomers (**a**) in both the neutral (**1**) and cationic (**2**) states in solutions.

Conformational Properties in Neutral and Cationic Structures As shown in Table I, the equilibrium conformations of the neutral structures, **1a** and **1b**, are distinctly twisted with torsional angles of 38.3° and 38.1°, respectively, which are nearly the same as the values for amrinone calculated by the *ab initio* STO-3G[6a] and the NDDO methods.[6b] On the other hand, the equilibrium conformations of the ionic structures, **2a**, **2b** and **3**, are more planar, with torsional angles of 21.5°, 25.4° and 18.4°, respectively, than those of the neutral structures. Thus, the experimental values for the conformation of amrinone seem to be better reproduced in the calculated results for the ionic structures than in those for the neutral structures.

Taking into account the apparent significance of the cationic structure in bipyridine cardiotonics, the torsional potentials of **1** and its cation (**2**) were investigated in detail. Also, the torsional potentials of 3,4′-bipyridine (**4**) and its cation, 1′-hydro-3,4′-bipyridinium cation (**5**), were calculated for comparison, since the conformational behaviors of bipyridines[16] and bipyridinium dications[17] have been well investigated experimentally and theoretically in connection with various aspects of physical and chemical technology. However, no conformational study of the monocations of bipyridines has been reported as far as we are aware.

The calculated torsional potentials are shown in Fig. 2. The potential curves for the neutral structures, **1a**, **1b** and **4**, are all nearly the same and the rotational barriers are quite low. On the other hand, those for the cationic structures, **2a**, **2b** and **5**, are apparently different from each other and the barriers are far higher than those in the neutral structures.[18] Also, an interesting feature is that the barrier height in the abundant pyridone tautomer (**2a**) is highest among the examined cationic structures.

Relationships between Torsional Potentials and Electronic Properties It is well known that the torsional potentials of conjugated molecules depend on a balance between conjugative and steric interactions and that the π-conjugative effects on the conformational properties of unsaturated compounds are correlated with the bond length and bond order of the bond concerned. Since the steric interactions of the cationic structures, **2a**, **2b** and **5**, are considered to be rather similar, the differences in the conformational behavior among the cations may be due to the differences in electronic properties.

The bond lengths and bond orders of the inter-ring CC bond in the planar conformation were compared among the neutral structures, **1a**, **1b** and **4**, and among the cationic structures, **2a**, **2b** and **5**. As shown in Table II, the differences in the inter-ring CC bond length and in the bond order among the structures are apparently larger in the cationic structures than in the neutral ones and among the cationic structures, the pyridone structure (**2a**) has the shortest bond length and the greatest bond order. Thus, the differences in bond order are mainly due to those in π-bond order.

The π-bond orders of the inter-ring CC bond in the cations, **2a**, **2b** and **5**, are considered to be associated to the π-electron-donating abilities of the pyridone, pyridinol and pyridine rings (these are hereafter referred to as ring

Table II. Bond Length, Bond Order and π-Bond Order of the Inter-Ring CC Bond in a Planar Structure

Ionic state	Compd.	Bond length (Å)	Bond order	π-Bond order
Neutral	**1a**	1.4561	1.0249	0.2732
	1b	1.4581	1.0214	0.2659
	4	1.4595	1.0185	0.2615
Cationic[a]	**2a**	1.4284 (−0.0277)	1.1552 (0.1303)	0.4460 (0.1728)
	2b	1.4363 (−0.0218)	1.1133 (0.0919)	0.3986 (0.1327)
	5	1.4440 (−0.0155)	1.0802 (0.0617)	0.3585 (0.0970)

a) Relative values to the neutral structure are given in parentheses.

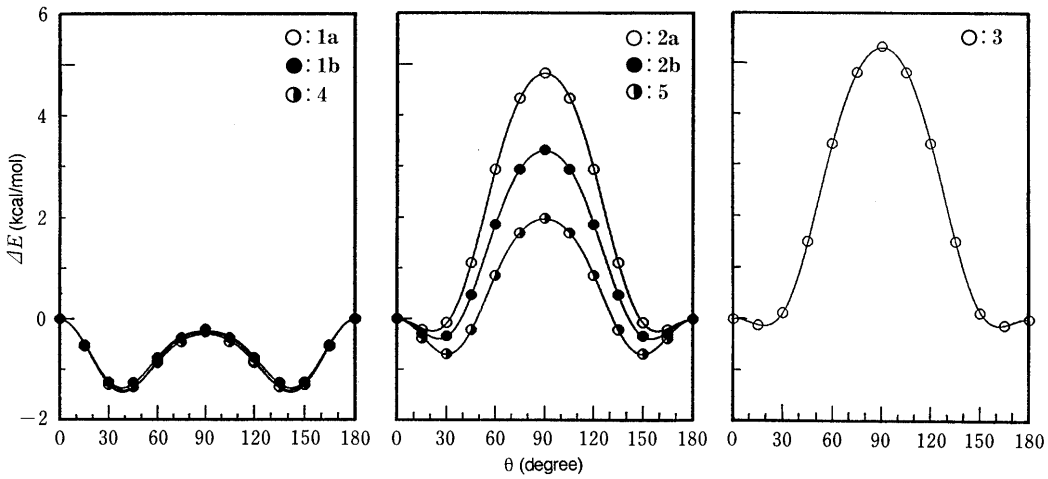


Fig. 2. Torsional Potentials for the Tautomeric and Ionic Structures of **1** and for 3,4′-Bipyridine (**4**) and Its Cation (**5**) According to AMI Calculations

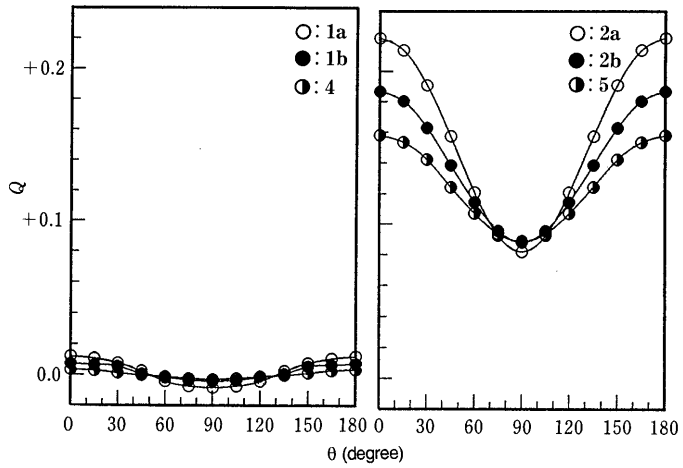


Fig. 3. Plot of Sum of Net Atomic Charges (Q) on the 4′-Pyridyl Ring of **1a**, **1b** and **4** and on the Pyridinium-4′-yl Ring of **2a**, **2b** and **5** as a Function of Torsional Angle (θ)

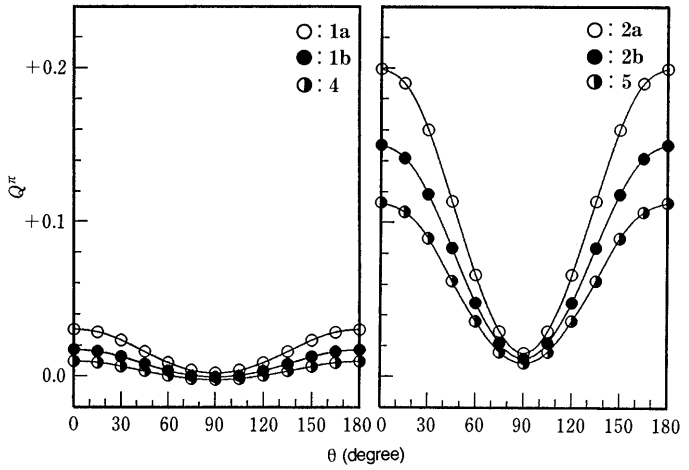


Fig. 4. Plot of Sum of π-Charges (Q^π) on the 4′-Pyridyl Ring of **1a**, **1b** and **4** and on the Pyridinium-4′-yl Ring of **2a**, **2b** and **5** as a Function of Torsional Angle (θ)

A), respectively, toward the pyridinium cation ring. So, the changes in electron density on ring A associated with the torsional angle were examined. The changes in net atomic charge and π-charge are shown in Figs. 3 and 4, respectively. The changes in electron density on the ring A with rotation are for the most part due to those in π-electron density. The changes are apparently larger in the cationic structures than in the neutral structures and the magnitudes of the change in the cationic form are in the order of **2a** > **2b** > **5**, in accordance with the order of those in the torsional barrier. Thus, the high torsional barrier in **2a** is attributed to the great stabilization of the planar conformation due to the strong π-electron-donating property of the pyridone ring.

π-Electronic Interaction and Molecular Orbital Features The differences in the π-electronic interaction among the cations, **2a**, **2b** and **5**, were investigated from the viewpoint of orbital interactions between π-orbitals of the two rings.

We first investigated the π-orbitals of the basic molecules, 2-pyridone, 2-pyridinol, pyridine and pyridinium cation, constructing the bipyridines concerned. The two higher occupied and two lower unoccupied π-molecular

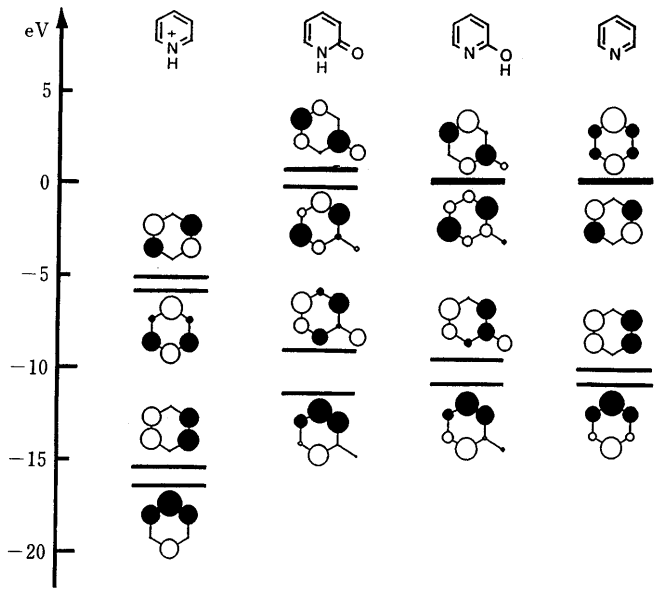


Fig. 5. Two Higher Occupied and Two Lower Vacant π-Molecular Orbitals of Basic Molecules Constructing the Bipyridines of Interest

orbitals are shown in Fig. 5. The LUMO of the pyridinium cation and the π-HOMO's of 2-pyridone, 2-pyridinol and pyridine have large orbital coefficients at the positions corresponding to the inter-ring carbon atoms of the examined bipyridines, and the energies of the π-HOMO's increase in the order of pyridine, 2-pyridinol and 2-pyridone. From these orbital features, it appears that the differences in π-electronic interaction between the two rings among the cations (**2a**, **2b** and **5**) can be well explained on the basis of the features of the frontier orbitals.

The changes in energy and orbital distribution of the molecular orbitals of the cations (**2a**, **2b** and **5**) associated with the conformation are shown in Fig. 6. The HOMO's and the LUMO's at the torsional angle of 90° are almost completely localized to ring A and the pyridinium ring, respectively, and are quite similar in orbital distribution and in nodal property to those of the basic molecules shown in Fig. 5, although the energies of the occupied orbitals are lower by *ca.* 2.5 eV than those in the basic compounds due to the electron inductive effect of the cationic pyridinium ring.

As expected from the energy separation between the HOMO's and LUMO's the change in orbital energy associated with the change in conformation from orthogonal to planar is greatest in **2a** among the cations. However, in contrast to the expectation based on the orbital distribution, the changes in energy of the vacant orbitals associated with the conformation are greater in the next LUMO's which have no appreciable orbital coefficient on the inter-ring carbon atoms, than in the LUMO. Also, no apparent difference in orbital distribution on the pyridinium ring among the HOMO's is shown in the planar conformation. Thus, although a correlation between the π-electron donating property and the HOMO energy was found, the differences in the π-electronic interaction among the cations could not be attributed to any specific orbitals.

Differences in Conformational Properties between Amrinone and Milrinone The calculated torsional potentials of **1** described above show that the conformation is more

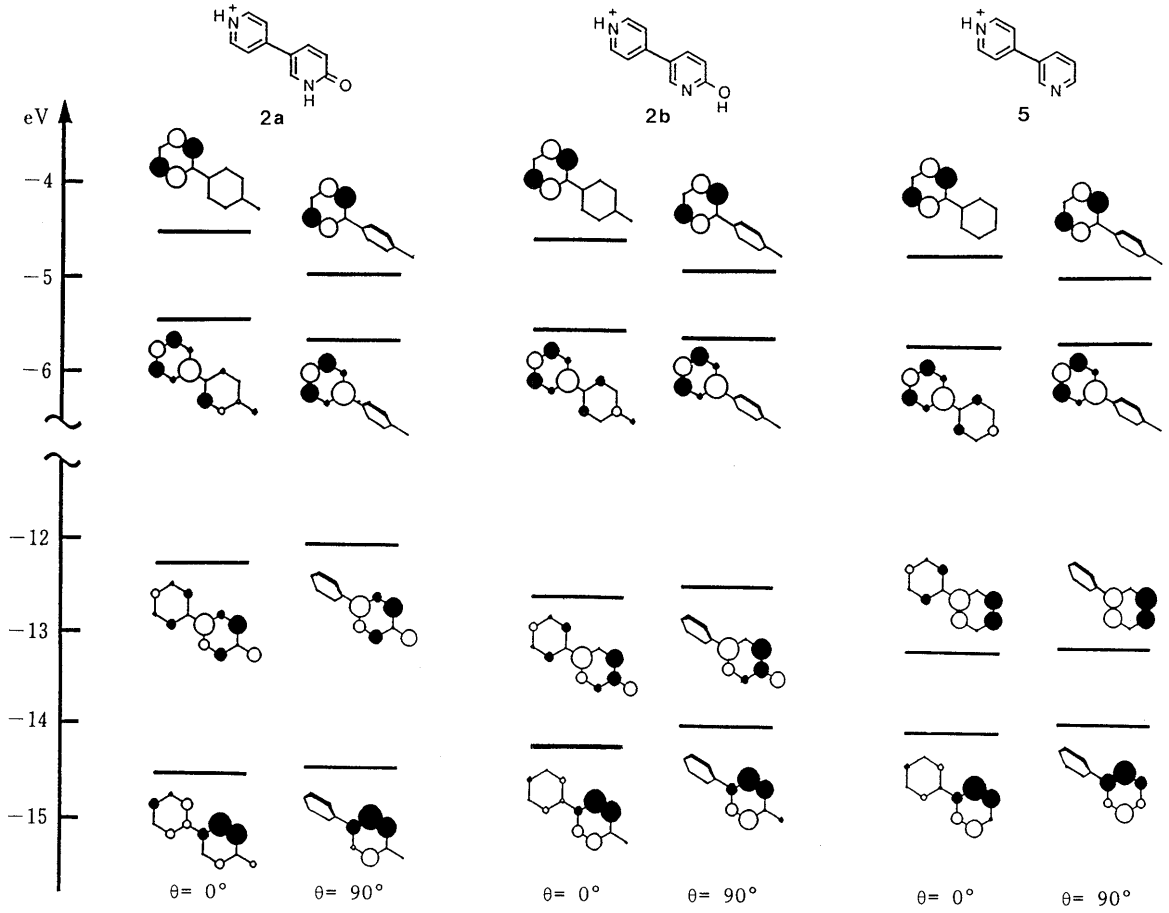


Fig. 6. Two Higher Occupied and Two Lower Vacant π-Molecular Orbitals of Cations (**2a**, **2b** and **5**) in Planar ($\theta=0°$) and Twisted ($\theta=90°$) Conformations

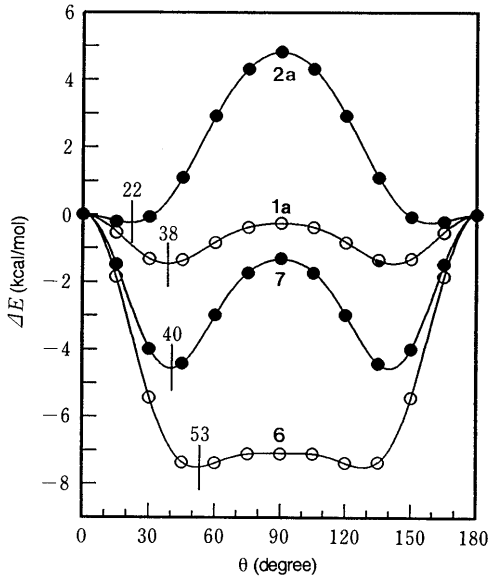


Fig. 7. Comparisons of Torsional Potential between the Model Compounds (**1a** and **6**) of Amrinone and Milrinone and between the Cationic Structures (**2a** and **7**)

○, neutral; ●, cation.

planar and more rigid in the cationic pyridone structure than in the neutral structures. This suggests that the difference in conformation between amrinone and milrinone, which was not well-defined in the calculations for the neutral structures,[6] may be more distinct in the cationic pyridone structures. So, the conformational properties of amrinone and milrinone were compared based on the results of the calculations for the model compounds, **1a** and the 2-methylated compound (**6**), respectively, and for their cationic structures, **2a** and **7**.[19]

As shown in Fig. 7, **6** has a higher torsional barrier at $\theta=0°$ and a larger equilibrium torsional angle than **1a**, due to the steric effect of the 2-methyl group. These conformational features of the neutral structures, **1a** and **6**, are in fundamental agreement with the *ab initio* results for amrinone and milrinone presented by Hoffmann *et al.*,[6] although the barrier height (*ca.* 7.5 kcal/mol) for **6** is far smaller than the *ab initio* value (*ca.* 12 kcal/mol). In the cationic structures (**2a** and **7**), the torsional barriers at $\theta=0°$ and $\theta=90°$ are lower and higher, respectively, due to the π-electronic stabilization of the planar conformation, and so the equilibrium torsional angles are smaller, compared to those in the neutral structures. However, the formation of the highly twisted conformation revealed in the neutral **6** is still seen in the cationic structure **7**. In addition, the formation of the planar conformation in amrinone is more apparent in the torsional potential of the cationic model structure (**2a**) than in that of the neutral **1a**. Overall, the difference in conformation between amrinone and milrinone seems to be more clear-cut in the cationic structures than in the neutral structure.

The calculated torsional potentials for the cationic structures, **2a** and **7**, are in essential agreement with the

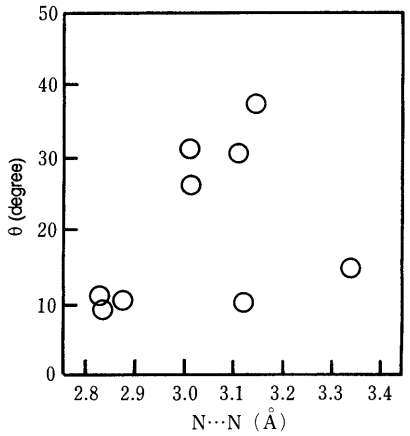


Fig. 8. Plot of Torsional Angle (θ) *versus* N···N Hydrogen-Bond Length in the Crystal Structure of Amrinone

The crystal structural data were taken from ref. 5*a*.

crystal structural data for the hydrochloride salts of amrinone and milrinone.[3] Also, as shown in Fig. 8, the inspection of the crystal structural data for neutral amrinone[5a] reveals that the torsional angles are small and concentrated in a narrow range ($9-11°$) for molecules with a strongly hydrogen-bonded pyridyl group but dispersed over a wide range ($10-37°$) for those with a weakly hydrogen-bonded pyridyl group. These structural features are in good correspondence with the features of the calculated torsional potentials for the neutral and cationic models, **1a** and **2a**, *i.e.* the small torsional angles and the conformational rigidity in the strongly hydrogen-bonded amrinone molecules correspond well to the smaller equilibrium torsional angle and the higher torsional barriers in the cationic structure, **2a**, compared to those in the neutral structure, **1a**.

In conclusion, a clear difference in conformation between amrinone and milrinone is apparent from the conformational properties of the cationic structure, which is considered to be a usual structure in biological environments including acid-base and hydrogen-bonding interactions.

References and Notes

1) A. E. Farah, A. A. Alousi, *Life Sci.*, **22**, 1139 (1978); A. A. Alousi, A. E. Farah, G. Y. Lesher, C. J. Opalka, *Circ. Res.*, **45**, 666 (1979); R. R. Miller, A. R. Palomo, B. S. Brandon, C. J. Hartley, M. A. Quinones, *Am. Heart J.*, **102**, 500 (1981); S. H. Taylor, B. Slike, G. I. C. Nelson, *Eur. Heart J.*, **3**, 19 (1982); A. Ward, R. N. Brogden, R. C. Heel, T. M. Speight, G. S. Avery, *Drugs*, **26**, 468 (1983).
2) A. A. Alousi, J. M. Canter, M. J. Montenaro, D. J. Fort, R. A. Ferrari, *J. Cardiovasc. Pharmacol.*, **5**, 792, (1983); G. Pastelin, R. Mendez, E. Kabela, A. E. Farah, *Life Sci.*, **33**, 1787 (1983); C. S. Maskin, L. Sinoway, B. Chadwick, E. H. Sonnenblick, T. H. Lejemtel, *Circulation*, **67**, 1065 (1983); D. S. Baim, A. V. McDowell, J. Cherniles, E. S. Monrad, J. A. Parker, J. Ederson, E. Braunwald, W. Grossmann, *N. Engl. J. Med.*, **309**, 748 (1983); J. A. Bristol, I. Sircar, W. H. Moos, D. B. Evans, R. E. Weishaar, *J. Med. Chem.*, **27**, 1101 (1984); E. S. Monrad, D. S. Baim, H. S. Smith, A. Lanoue, E. Braunwald, W. Grossmann, *Circulation*, **71**, 972 (1985); K. M. Borow, P. C. Come, A. Neumann, D. S. Baim, E. Braunwald, W. Grossmann, *Am. J. Cardiol.*, **55**, 1204 (1985); S. H. Kubo, R. J. Cody, K. Chatterjee, C. Simonton, H. Rutman, D. Leonard, *ibid.*, **55**, 726 (1985).
3) D. W. Robertson, E. E. Beedle, J. K. Swartzendruber, N. D. Jones, T. K. Elzey, R. F. Kauffman, H. Wilson, J. S. Hayes, *J. Med. Chem.*, **29**, 635 (1986).
4) S. Rakhit, G. Marciniak, G. Lecler, J. Schwartz, *Eur. J. Med. Chem., Chim. Ther.*, **21**, 511 (1986).
5) *a*) G. Reck, V. Hagen, E. Hohne, *Pharmazie*, **41**, 181 (1986); *b*) V. Cody, *Acta Cryst.*, **C43**, 1325 (1987).
6) *a*) H.-J. Hofmann, R. Cimiraglia, *Eur. J. Med. Chem.*, **22**, 569 (1987); *b*) H.-J. Hofmann, P. Birner, *Pharmazie*, **42**, 414 (1987).
7) *a*) M. Kuzuya, A. Noguchi, T. Okuda, *Bull. Chem. Soc. Jpn.*, **57**, 3454 (1984); *b*) *Idem*, *J. Chem. Soc., Chem. Commun.*, **1984**, 435; *c*) *Idem*, *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1423.
8) M. J. S. Dewar, E. G. Zoebisch, E. F. Hearly, J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); J. J. Stewart, MOPAC Ver. 4.0, Program 549, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, U.S.A.
9) G. Y. Lesher, C. J. Opalka, U. S. Patent 4004012 (1977) [*Chem. Abstr.*, **86**, 189725*e* (1977)].
10) W. P. Fang, P. Shieh, M. J. Shiao, *Heterocycles*, **24**, 1585 (1986).
11) W. M. F. Fabian, *J. Comput. Chem.*, **9**, 369 (1988).
12) H. Niedrich, H. Seidert, V. Hagen, B. Mehlis, R. Mitzner, W. Mayer, H. Usbeck, *Pharmazie*, **41**, 176 (1986).
13) P. Beak, F. S. Fry, Jr., *J. Am. Chem. Soc.*, **95**, 1700 (1973); P. Beak, F. S. Fry, Jr., J. Lee, F. Steele, *ibid.*, **98**, 171 (1976); P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977); H. B. Schlegel, P. Gund, E. H. Fluder, *J. Am. Chem. Soc.*, **104**, 5347 (1982).
14) Various AM1 calculations for tautomers of 2-pyridone have been reported by several authors: M. M. Karelson, A. R. Katritzky, M. Szafran, M. C. Zerner, *J. Org. Chem.*, **54**, 6030 (1989); M. Kuzuya, A. Noguchi, S. Kondou, *Gifu Yakka Daigaku Kiyo*, **39**, 49 (1990); W. M. F. Fabian, *J. Phys. Org. Chem.*, **3**, 332 (1990); H. S. Rzepa, M. Y. Yi, M. M. Karelson, M. C. Zerner, *J. Chem. Soc., Perkin Trans. 2*, **1991**, 635.
15) P. Beak, J. B. Covington, J. M. White, *J. Org. Chem.*, **45**, 1347, 1354 (1980).
16) V. Galasso, G. De Alti, A. Bigotto, *Tetrahedron*, **27**, 991 (1971); V. Barone, F. Lelj, C. Cauletti, M. N. Piancastelli, N. Russo, *Mol. Phys.*, **49**, 599 (1983); V. Barone, F. Lelj, L. Commisso, N. Russo, C. Cauletti, M. N. Piancastelli, *Chem. Phys.*, **96**, 435 (1985).
17) E. I. von Nagy-Felsobuki, *J. Heterocycl. Chem.*, **25**, 33 (1988).
18) We also calculated the torsional potential for another isomer (1-hydro-3,4′-bipyridinium cation) in cationic structures of **4**. The calculated potential curve was similar to that of the neutral structure (**4**) and the barrier (1.7 kcal/mol) was only slightly higher than that (1.4 kcal/mol) in **4**.
19) We calculated the conformational behaviors of amrinone, the 5-amino derivative of **1**, and its cationic structure. The calculated torsional potentials were almost the same as those for **1**.