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Theoretical conformational study of the molecular structures of some bipyridine cardiotonics

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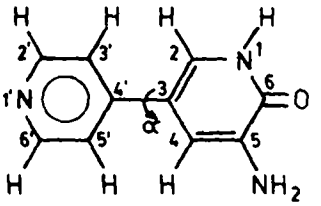
Abstract. Conformational features of amrinone and milrinone have been examined via *ab initio* (at STO–3G and 3–21G levels) MO theory. The calculated results suggest twisted structures for both the molecules. The higher barrier to rotation of the pyridine ring and restricted conformational flexibility of milrinone are observed to be two significant factors responsible for its greater cardiotonic activity as compared to that of amrinone.

Keywords. Bipyridine cardiotonics; conformational features; amrinone; milrinone.

1. Introduction

In recent years considerable attention has been focussed on the conformations of bipyridine cardiotonics on account of their potential inotropic and peripheral vasodilatory properties (Miller *et al* 1981; Taylor *et al* 1982; Ward *et al* 1983). Amrinone (5-amino-3,4′-bipyridine-6-one) (1) and its analogue milrinone (1,6-dihydro-2-methyl-6-oxo-3,4′-bipyridine-5-carbonitrile) (2) are two such bipyridine cardiotonics being commonly used as a new class of drugs having both these properties. Milrinone has been reported to have greater cardiotonic potency as compared to amrinone (Ward *et al* 1983). Crystallographic studies on the structures of these two molecules (Robertson *et al* 1986) have shown two remarkable differences between them: amrinone is approximately planar having a torsional angle of 1·3° whereas the same angle is 52·2° for milrinone. Large structural differences between these molecules in solution were also postulated by these workers on the basis of NMR studies. Although several experimental studies (Suzuki 1967; Lambert *et al* 1976) have been made earlier to rationalise the conformational changes on the basis of crystal forces, little work has been done to support the experimental observations with theoretical conformational analysis which might help to reveal the important structural prerequisities for understanding the structure–activity relations.



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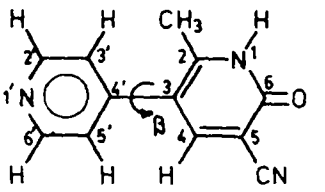

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In continuation of our interest on theoretical conformational studies of potential drug molecules (Bhattacharjee 1989; Bhattacharjee and Doucet 1989) we report here a theoretical investigation on the molecular structure of amrinone and milrinone by *ab initio* methods, calculated at both STO–3G and 3–21G levels.

2. Methods

Ab initio quantum chemical calculations can provide substantial structure and energy information, provided the basis set opted for has sufficient flexibility. Recent studies on comparatively larger systems (Rondan *et al* 1981; Lieu and Hopkinson 1984; Cossé-Barbi *et al* 1990) have shown that optimisation of geometries employing minimal STO–3G basis sets followed by single point computations with split valence basis sets (e.g; 3–21G) provide a good compromise between economy and accuracy. This procedure has therefore been followed.

Calculations were done in both the STO–3G and 3–21G basis sets. The 'Berny' optimisation scheme for the energy as given in the Gaussian 82 program package (Binkley *et al* 1983) was used. We have used the optimised geometries for pyridine and 2-methyl-pyridine-6-one (Sutton 1965) as the starting point of the geometry optimisation of amrinone and milrinone. The amino-nitrile interchange at the C_5 position is found to have practically no influence on the overall conformational profile of the molecules. Therefore, the amino and cyano groups were not taken into consideration for our calculations.

All computations were performed on a VAX-11/780 computer of the Institut de Topologie et de Dynamique des Systemes de l'Université, Paris 7, France.

3. Results and discussion

Tables 1 and 2 present the calculated optimised structural parameters of amrinone and milrinone respectively. Contrary to the crystallographic findings, the calculated torsional angles between the interaromatic planes are found to be $\sim 37°$ and $\sim 67°$ for amrinone and milrinone, respectively. The torsional angle of 1·3° for amrinone as reported from crystallographic studies is probably due to the influence of crystal forces on the fixation of the planar structure in the solid state, whereas the considerable steric interaction due to the bulkier methyl group at the C_2 position probably accounts for the large torsional angle in milrinone, both in the solid as well as in the isolated state, as considered in the calculations.

The computational results on both these molecules indicate that their structures are considerably twisted. Although crystallographic studies also indicate a large difference in their torsional angles, it is far less in magnitude than the calculated results. Thus in order to assess the activity differences between the molecules, their conformational flexibilities are studied and an optimisation of their planar geometries carried out (tables 1 & 2). The energy profiles of the compounds along the α or β axes (rotation of the pyridine ring) are shown in figure 1. The planar conformer of amrinone is about 8·0 and that of milrinone about 49·0 kJ per mole more unstable respectively than their preferred conformers (figure 1). Thus amrinone is much more flexible over a wide range of torsional angles, α. The structural parameters of the

Table 1. Minimum energy and planar conformations of amrinone in the STO-3G and 3-21G basis sets[a].

	Minimum energy		Planar	
Structural parameters	STO-3G $E = -559.970496$	3-21G $E = -560.724687$	STO-3G $E = -559.967284$	3-21G $E = -560.721451$
Bond length				
(C_3C_4)	1·507(1·475)[b]	1·511	1·512	1·515
(C_2H)	1·084	1·081	1·083	1·082
(C_4H)	1·083	1·085	1·081	1·083
(C_3-H)	1·080	1·079	1·078	1·076
(C_5-H)	1·080	1·079	1·079	1·077
Bond angle				
C_3C_2H	124·47	124·51	125·30	124·80
C_3C_4H	117·90	117·84	119·10	118·75
C_4-C_3-H	121·20	121·12	122·24	122·00
C_4-C_5-H	121·23	121·20	122·44	122·08
Torsional angle (α)	37·6(1·3)[b]	36·9	0·0	0·0

[a] Bond lengths are in Å; E(energy) is in a.u.; bond angles and torsional angles (α) are in degrees
[b] Crystallographic data (Robertson *et al* 1986).

Table 2. Minimum energy and planar conformations of milrinone in the STO-3G and 3-21G basis sets[a].

	Minimum energy		Planar	
Structural parameters	STO-3G $E = -598.553006$	3-21G $E = -599.308166$	STO-3G $E = -598.534269$	3-21G $E = -599.289062$
Bond length				
(C_3C_4)	1·511(1·513)[b]	1·513	1·537	1·536
(C_2C)	1·530(1·465)[b]	1·532	1·540	1·538
(C_4H)	1·085	1·084	1·080	1·081
(C_3-H)	1·081	1·081	1·079	1·077
(C_5-H)	1·081	1·081	1·059	1·061
Bond angle				
C_3C_2C	124·90 (128·7)[b]	126·10	133·30	133·25
C_3C_4H	118·00	117·60	119·05	118·95
C_4-C_3-H	121·25	120·95	122·45	122·15
C_4-C_5-H	121·40	121·05	125·10	124·80
Torsional angle (β)	67·15 (52·2)[b]	66·95	0·0	0·0

[a] Bond lengths are in Å; E(energy) is in a.u.; bond angles and torsional angles (β) are in degrees
[b] Crystallographic data (Robertson *et al* 1986).

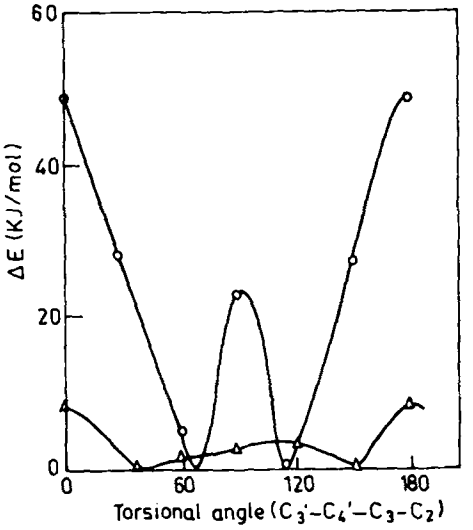

Figure 1. Calculated energy profile along the torsional angle ($C_{3'}$-$C_{4'}$-C_3-C_2) for amrinone (△), and milrinone (○).

planar conformation of amrinone indicate (table 1) that the molecule is capable of adjusting the destabilisation to a remarkable extent by a relatively small increase in the central C–C bond length and the ortho-hydrogen bond angles. The approximate planar structure ($\alpha = 1{\cdot}3°$) in the solid state could be attributed to crystal forces which are expected to be strong enough to surmount this low rotational barrier. However, in the case of milrinone the structural parameters show marked changes in the planar conformation. Thus, considerable increase in the central C–C bond length and the ortho-hydrogen bond angles along with the shortening of the ortho-hydrogen bond lengths (table 2) could be accounted for by the steric hindrance due to the methyl group at the C_2 position in the molecule. Therefore, milrinone is found to be a rather rigid molecule with limited conformational flexibility in comparison to amrinone.

4. Conclusion

The computational results of this theoretical investigation clearly indicate the greater flexibility of amrinone when compared with that of milrinone. Hence, greater cardiotonic potency of milrinone is most likely due to the reduced conformational flexibility because of the 2-methyl group. Finally, it should be noted that, if a molecular recognition pattern of these compounds were to be deduced from an electrostatic potential analysis for the purpose of understanding the biological activity of these analogues, the effect of this torsional angle on the contour maps would be crucial. The torsional angle C_2-C_3-$C_{4'}$-$C_{3'}$, would affect the relationship of the hydrogen atom to the negative potential regions around the 2-methyl group. This angle would also affect the spatial orientation of the potential region around the 2-methyl group with respect to the potential region around the conjugated bonds in the molecules. An analysis of the molecular electrostatic potential of these molecules based on the results presented here is being carried out.

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References

Bhattacharjee A K 1989 *J. Comput. Chem.* (communicated)

Bhattacharjee A K and Doucet J P 1989 *J. Chem. Soc., Perkin Trans. 2* (to be published)

Binkley J S, Frish M J, De Frees D J, Raghavachari K, Whiteside R A, Schlegel H B, Fluder E M and Pople J A 1983 Gaussian 82, Release A, Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pa

Cossé-Barbi A, Bhattacharjee A K, Doucet J P and Dubois J E 1990 *J. Mol. Struct. (Theochem)* **204** 67

Lambert J B, Shurvell H F, Verbit L, Cooks R G and Stout G H 1976 *Organic structural analysis* (New York: MacMillan)

Lieu H and Hopkinson A C 1984 *Can. J. Chem.* **62** 922

Miller R P, Palomo A R, Brandon B S, Hartley C J and Quinones M A 1981 *Am. Heart J.* **102** 500

Robertson D W, Beedle E E, Swartzendruber J K, Jones N D, Elzey T K, Kauffman R F, Wilson H and Hayes J S 1986 *J. Med. Chem.* **29** 635

Rondan N G, Paddon-Row M N, Caramella P, Houk K N 1981 *J. Am. Chem. Soc.* **103** 2436

Sutton L E 1965 *Chem. Soc. Spec. Publ. Suppl.* 18

Suzuki H 1967 *Electronic absorption spectra and geometry of organic molecules* (New York: Academic Press)

Taylor S H, Silke B and Nelson G I C 1982 *Eur. Heart J.* **3** 19

Ward A, Brogden R N, Heel R C, Speight T M and Avery G S 1983 *Drugs* **26** 468