Journal of Computer-Aided Molecular Design, 2 (1988) 321–328
ESCOM

J-CAMD 035

Crystallographic studies and semi-empirical MNDO calculations on quisqualic acid and its analogues: Systems containing unusual pyramidal heterocyclic ring nitrogens

David E. Jackson[a], Barrie W. Bycroft[a] and Trevor J. King[b,*]

Departments of [a]Pharmaceutical Sciences and [b]Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

Received 15 February 1988
Accepted 13 June 1988

Key words: Quisqualic acid; Pyramidal amide nitrogen; X-ray crystallography; MNDO calculations

SUMMARY

X-ray crystallographic studies on synthetic DL-quisqualic acid and the corresponding carbon analogue have revealed pyramidal and almost planar geometries respectively for the ring nitrogen atoms carrying the alkyl side chain. Semi-empirical molecular orbital calculations on methyl-substituted model systems predict ring geometries in close agreement with experimentally observed data. The calculated energy barriers between the two enantiomeric forms (invertomers) of the oxadiazolidine systems along with some physical data would suggest that such forms are rapidly interconverting.

INTRODUCTION

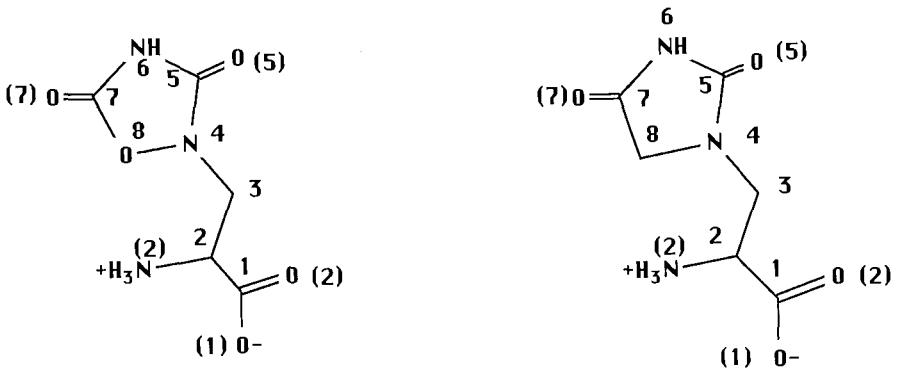
Quisqualic acid is a potent agonist at a number of glutamatergic receptors in both vertebrate and invertebrate systems and has been employed in conjunction with other glutamate analogues to define receptor subtypes [1]. Recently we reported a convenient synthesis of quisqualic acid and a number of its analogues (**1–3**) along with their activities at a well defined glutamatergic synapse [2–4]. Synthetic L-quisqualic acid exhibited, as expected, identical potency to its natural counterpart. D-Quisqualic acid, however, was considerably more active than expected from the known stereoselectivity of this particular receptor sub-type towards L- and D-glutamic acids. The carbon (**2**) and nitrogen (**3**) analogues were both found to be inactive with this system.

METHODS AND RESULTS

In order to provide a molecular input for the interpretation of these structure–activity relationships, the full details of which will be described elsewhere [5], X-ray crystallographic analyses of

*Deceased.

0920-654X/89/$3,50©ESCOM Science Publishers B.V.



Scheme 1. Crystallographic numbering scheme. *Left*: DL-quisqualic acid (**1**); *Right*: 3-(2,4-dioxoimidazolidin-1-yl)-alanine (**2**).

racemic quisqualic acid (**1**) and the carbon analogue (**2**) were undertaken (please refer to Scheme 1 for the crystallographic numbering system used). Crystal structures were solved by direct methods using the MULTAN-80 program [6] and refined by use of the CRYSTALS programs [7] (Table 1). Figures 1 and 2 show computer-generated drawings of the resulting structures.

The data clearly showed a striking difference in the geometries of the nitrogens joining the heterocyclic system to the amino acid side chain. In the hydantoin (**2**) the nitrogen atom is almost planar as expected for an amide group, whereas in quisqualic acid it is clearly pyramidal. Although X-ray crystallographic analysis of naturally occurring L-quisqualic acid had previously been reported [8], the unusual geometry at this position had not been noted. It is particularly noteworthy that our data on racemic quisqualic acid revealed the presence of both enantiomeric forms (invertomers) at the substituted ring nitrogen, corresponding to torsion angles (C3-N4-O8-C7) of + and $-37°$ in the D- and L-isomer, respectively. Furthermore, the L-isomer in the crystal of DL-quisqualic acid had the opposite configuration at the ring nitrogen to that in the crystal of natural L-quisqualic acid ($-137°$ compared with $+144°$), i.e. diastereomeric at this centre. This observation would suggest that both nitrogen configurations are of comparable stability and that the energy barrier for interconversion in solution is small (see Scheme 2). Given this possibility, it was

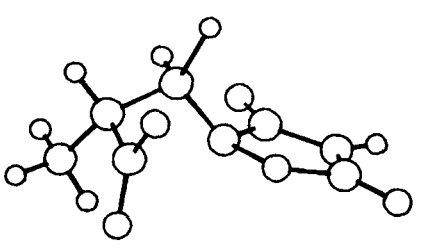


Fig. 1. Crystal structure of DL-quisqualic acid (**1**) clearly showing pyramidal geometry for the side-chain-substituted ring nitrogen.

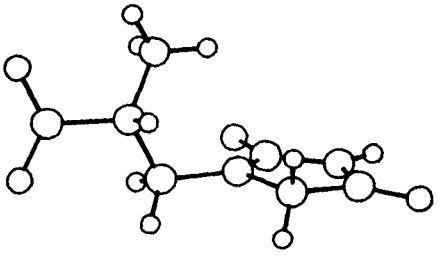


Fig. 2. Crystal structure of 3-(2,4-dioxoimidazolidin-1-yl)-alanine (**2**).

TABLE 1
FRACTIONAL ATOMIC COORDINATES FOR DL-QUISQUALIC ACID (**1**) AND 3-(2,4-DIOXOIMIDAZOLIDIN-1-YL)-ALANINE (**2**)[a,b]

(1)				(2)			
Atom	X/A	Y/B	Z/C	Atom	X/A	Y/B	Z/C
C(1)	− 0.0678(5)	0.1831(1)	0.2450(3)	0(1)	0.8899(3)	0.0855(4)	0.7807
0(1)	0.0481	0.1821(1)	0.1402	0(2)	1.0219(3)	0.1956(3)	0.6027(8)
0(2)	− 0.2969(4)	0.16099(9)	0.2445(2)	0(7)	0.5703(3)	− 0.0 671(3)	− 0.2564(7)
C(2)	0.0811(5)	0.2177(1)	0.3919(2)	0(5)	0. 6798(2)	0.2942(3)	0.1035(8)
N(2)	0.3206(4)	0.2614(1)	0.3669(3)	N(2)	0.9421(3)	0.1580(3)	0.2118(8)
C(3)	0.1440(5)	0.1498(1)	0.5100(3)	N(4)	0.7127(3)	0.0820(3)	0.1743(7)
N(4)	0.3233(5)	0.0859(1)	0.4729(2)	N(6)	0.6138(3)	0.1312(3)	− 0.1191(8)
C(5)	0.4910(5)	0.0447(1)	0.5858(3)	C(1)	0.9371(4)	0.1273(4)	0.6137(8)
O(5)	0.3278(4)	0.0799(1)	0.6870(2)	C(2)	0.8879(3)	0.0840(4)	0.3915(9)
N(6)	0.4738(4)	− 0.0407(1)	0.5527(3)	C(3)	0.7623(3)	0.0986(4)	0.391(1)
C(7)	0.2913(5)	− 0.0558(1)	0.4314(3)	C(8)	0.6836(4)	− 0.0403(4)	0.0750(9)
O(7)	0.2234(4)	− 0.12090(9)	0.3684(2)	C(7)	0.6145(3)	0.0019(4)	− 0.121(1)
O(8)	0.1869(4)	0.02060(9)	0.3808(2)	C(5)	0.6708(3)	0.1803(4)	0.0608(8)
H(1)	0.240(5)	0.172(2)	0.600(3)	H(1)	1.0252	0.1446	0.2153
H(2)	− 0.025(5)	0.262(2)	0.430(3)	H(2)	0.9257	0.2513	0.2324
H(4)	0.280(5)	0.307(2)	0.298(3)	H(3)	0.9126	0.1297	0.0655
H(5)	− 0.017(5)	0.123(2)	0.525(3)	H(4)	0.9052	− 0.0091	0.3556
H(6)	0.441(8)	0.223(2)	0.332(4)	H(5)	0.7420	0.1858	0.4502
H(7)	0.409(6)	0.290(2)	0.457(4)	H(6)	0.7281	0.0326	0.4960
H(8)	0.553(6)	− 0.083(2)	0.611(3)	H(7)	0.7540	− 0.0892	0.0266
				H(8)	0.6413	− 0.0970	0.1775
				H(9)	0.5762	0.1853	− 0.2340

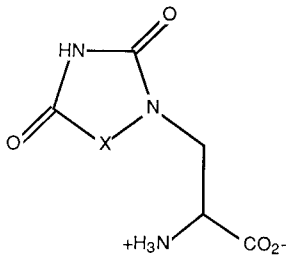
[a]Crystal data for (**1**): $C_5H_7N_3O_5$; M = 189.13, monoclinic, space group Cc, a = 5.253 (1), b = 15.674 (2), c = 9.244 (1) A, Beta = 100.56 (1), U = 748.2 A^3, Z = 4, D_c = 1.67 g/cm^3, R = 2.40, R_w = 2.56 for 767 reflections with $\theta < 76$, $I > 3\delta(I)$, Cu-K_α radiation (λ = 1.54178 A).

Crystal data for (**2**): $C_6H_9N_3O_4$; M = 187.14, orthorhombic, space group $P2_12_12_1$, a = 11.958 (1), b = 10.442 (2), c = 6.083 (1) A, U = 759.5 A^3, Z = 4, D_c = 1.64 g/cm^3, R = 3.85, R_w = 4.45 for 596 reflections with $\theta < 66$, $I > 3\delta(I)$, Cu-K_α radiation (λ = 1.54178 A). (Data from one enantiomorph selectively crystallised from the racemate).

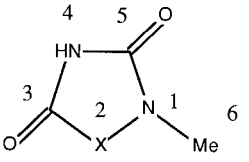
[b]Lists of structure factors and anisotropic thermal parameters are available on request.

of interest to establish whether semi-empirical MO calculations were capable of predicting the pyramidal nature of the ring nitrogen and estimating the barrier for inversion at this centre.

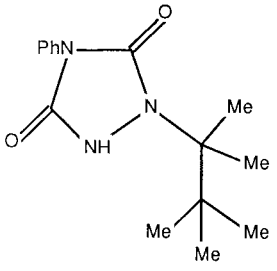
Theoretical calculations were initiated on the model systems (**4–6**) with starting geometries obtained using sketch facilities and molecular mechanics minimisation to generate template files for submission to MNDO geometry optimisation [9,10]. The torsion angle 3-2-1-6 was fixed in 10° increments between −100 and +100° and the molecule subjected to MNDO geometry optimisation. The resulting energy profiles are shown in Fig. 3A–C. The results from full MNDO geometry optimisation on (**4–6**) starting with unrestrained torsion angles on either side of 180° are shown in Tables 2 and 3. For the *N*-methyl dioxo-oxadiazolidine (**4**) two energy minima are observed at ±140°. These values accord with two pyramidal nitrogen configurations and are in excellent



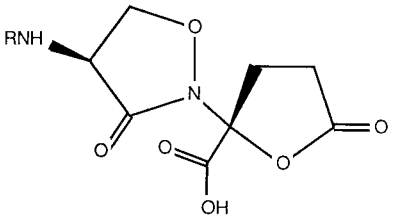
(1) X=O
(2) X=CH_2
(3) X=NH



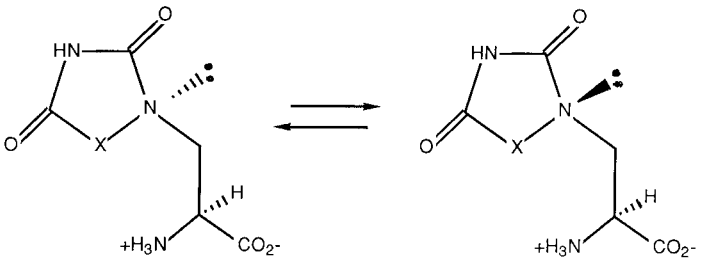
(4) X=O
(5) X=CH_2
(6) X=NH



(7)



(8) R=COMe
(9) R=H



Scheme 2

agreement with the corresponding torsion angles observed in the crystal lattice for L- and DL-quisqualic acid (Table 3). Figure 3A shows the two invertomers as energy wells with a theoretical inversion barrier of approximately 3.5 kcal mol^{-1}. This accords with experimentally determined values for simple pyramidal nitrogen systems and supports the view that the two forms rapidly equilibrate at room temperature.

Figure 3B shows the corresponding energy profile for the model hydantoin (**5**). Clearly, the MNDO calculations predict extremely shallow energy wells close to an angle of 180° according

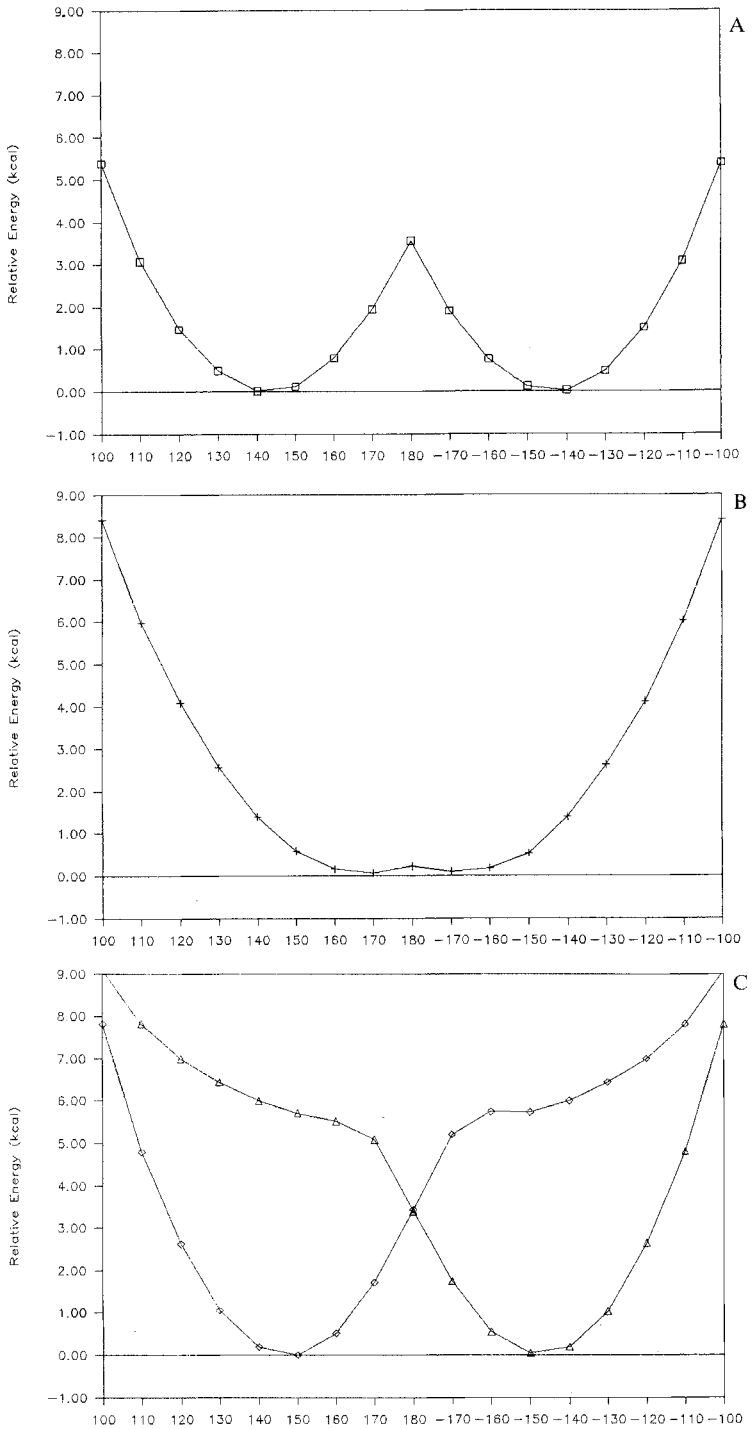


Fig. 3. Relative energy profiles (kcal mol^{-1}) for model systems (**4–6**) with respect to defined torsion angle 3-2-1-6. (A) Oxygen analogue (**4**); (B) Carbon analogue (**5**); and ((C) Nitrogen analogue (**6**).

TABLE 2
COMPARISON OF THE OBSERVED (X-RAY DATA) AND CALCULATED (MNDO) BOND LENGTHS IN THE RING SYSTEM OF QUISQUALIC ACID (**1**) WITH THE OXAZOLIDINEDIONE (**4**), AND OF THE CARBON ANALOGUE OF QUISQUALIC ACID (**2**) WITH THE HYDANTOIN (**5**)

(1)		(4)		(2)		(5)	
X-ray data		MNDO		X-ray data		MNDO	
C3-N4	1.456	N1-C6	1.494	C3-N4	1.456	N1-C6	1.463
N4-C5	1.393	N1-C5	1.462	C8-N4	1.455	C2-N1	1.474
N4-08	1.435	N1-02	1.345	C8-C7	1.515	C2-C3	1.536
C5-05	1.202	C5-05	1.215	C7-07	1.216	C3-03	1.219
C5-N6	1.372	C5-N4	1.411	C7-N6	1.350	C3-N4	1.415
N6-C7	1.354	N4-C3	1.412	C5-05	1.223	C5-05	1.221
C7-07	1.195	C3-03	1.216	C5-N4	1.334	C5-N1	1.418
C7-08	1.363	C3-02	1.384	C5-N6	1.387	C5-N4	1.417

with an almost planar geometry for the ring nitrogen and close to the corresponding torsion angle observed in (**2**) (Table 3). However, for the dioxo-triazolidine (**6**) the MO calculations reveal much more complex energy profiles. These can be interpreted in terms of pyramidal configurations for both N-1 and N-2, with energy wells corresponding to minimal lone pair interactions, i.e., the lone pairs *trans*-disposed. The transition from one energy well to the other must therefore involve concomitant inversion at both nitrogens. Defining the H-N2-N1-C6 torsion angle as 0° and subjecting (**6**) to further geometry optimisation gives an estimated barrier to inversion of 6.5 kcal mol^{-1}. Although X-ray analyses on (**3**) or (**6**) have not as yet been carried out, a recent communication on the complex dioxo-triazolidine (**7**) indicated that both the adjacent ring nitrogens were indeed pyramidal [11] with the lone pairs trans disposed, as predicted by the above semi-empirical MO calculations for (**6**).

TABLE 3
MNDO OPTIMISED GEOMETRY FOR TORSION ANGLE 3216 IN (**4–6**) AND CORRESPONDING DATA FROM X-RAY CRYSTALLOGRAPHY

Cpd	X	MNDO-optimised geometry	Barrier to inversion (kcal)	Cpd	X-ray data
4	O	+140, −140	3.55	1	+144[a], ±137[b]
5	CH_2	+164, −165	0.22	2	+168[c]
6	NH	+149, −148	6.49	7	+146[d]

[a]L-Quisqualic acid (see Ref. 8).
[b]DL − (**1**).
[c]One of the enantiomorphs selectively crystallised from the racemate.
[d](**7**) (see Ref. 11).

DISCUSSION

These theoretical results and experimental observations clearly indicate that heterocyclic systems of the types (**1, 3, 4** and **6**) which would at first sight be expected to be pseudo-aromatic and hence planar, are in fact substantially distorted from planarity. However, it must be said that with the inherent inaccuracies of the semi-empirical MNDO calculations on such heterocyclic ring systems, the quantitative aspect of the inversion barriers as predicted by these calculations must be viewed with some caution and at best should be regarded as approximate. Nevertheless, all our physical data lend support to the general notion that such systems are non-planar and can rapidly invert in solution at room temperature. In the case of quisqualic acid (**1**) the presence of a pyramidal ring junction nitrogen would appear to mimic the sp^3 carbon atom at position 4 of glutamic acid, and with the potential for inversion at this centre may be advantageous in the dynamics of receptor binding when compared with glutamic acid itself [5].

Preliminary semi-empirical MO calculations on other related heterocyclic systems suggest that this is a general phenomenon. For example, the ring junction nitrogens of the oxazolidinone ring system of cycloserine analogues related to lactivicin (**8**) [12] appear to be pyramidal. A recent X-ray crystallographic report [13] on the structure of 4-aminolactivinic acid (**9**) has revealed a pyramidal geometry for the ring nitrogen; thus providing in part a rationalisation of the β-lactam-like activity of this group of compounds.

CONCLUSION

In conclusion we suggest that heterocyclic systems with a potential pyramidal nitrogen which can readily invert may have significant implications with respect to the design of novel receptor ligands and transition state analogue enzyme inhibitors.

ACKNOWLEDGEMENTS

We thank Dr. J.G. Vinter and colleagues (Smith, Kline & French Research, Welwyn) for valuable assistance and discussions.

REFERENCES

1 Watkins, J.C. and Evans, R.H., Annu Rev. Pharmacol., 21 (1981) 165–204.
2 Bycroft, B.W., Chhabra, S.R., Grout, R.J. and Crowley, P.J., J.Chem. Soc., Chem. Comm., (1984) 1156–1157.
3 Bycroft, B.W., Chowdhury, A.K. and Chhabra, S.R., in preparation.
4 Boden, P., Bycroft, B.W., Chhabra, S.R., Chiplin, J., Crowley, P.J., Grout, R.J., King, T.J., McDonald, E., Rafferty, P. and Usherwood, P.N.R., Brain Res., 385 (1986) 205–211.
5 Bycroft, B.W. and Jackson, D.E., Proceedings of the 2nd Neurotoxicology Meeting, 1988, Elsevier, Amsterdam, in press.
6 Main, P., Fiske, S.L., Hull, S.E., Lessinger, L., Germain, G., Declercq, J.P. and Woolfson, M.M., MULTAN: a System of Computer Programs for Automatic Solution of Crystal Structures from X-ray Diffraction Data, University of York, U.K. and University of Louvain, Belgium.
7 Carruthers, J.R., CRYSTALS Users Manual, Oxford University Computing Laboratory, Oxford 1975.
8 Flippen, J.L. and Gilardi, R.D., Acta Crystallogr., Sect. B, 32 (1976) 951–953.
9 Vinter, J.G., Davis, A. and Saunders, M.R., J. Comput.-Aided Mol. Design, 1 (1987) 31–51.

10 Dewar Research Group, QCPE Bull., 6 (1986) 4 (AMPAC, QCPE506).
11 Baker, R.J., Timberlake, J.W., Alender, J.T., Majeste, R.J. and Trefonas, L.M., Cryst. Struct. Commun., 11 (1982) 763–768.
12 Nozaki, Y., Katayama, N., Ono, H., Tsabotani, S., Harada, S., Okazaki, H. and Nakao, Y., Nature, 325 (1987) 179–180.
13 Wada, Y., Takamoto, M., Tsubotani, S. and Kamiya, K., Acta Crystallogr., Sect. C, 43 (1987) 1786–1788.