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A Semiempirical Study of Intramolecular Hydrogen Bonding in Some Naphthazarin Derivatives*

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Structural and energetic properties of some derivatives of naphthazarin are considered by the semiempirical AM1 method. It is shown that these systems, possessing intramolecular hydrogen bonds, are qualitatively well described at the AM1 level of theory. This conclusion is supported by a good qualitative agreement with available experimental data. The strength of the intramolecular hydrogen bond is briefly discussed. It appears that their energies are roughly additive.

INTRODUCTION

Intramolecular hydrogen bonding considerably aids the flexibility of biological macromolecules, thus enabling their important role in life processes.[1] In contrast to numerous theoretical studies of intermolecular hydrogen bonds,[2] internal stabilization of molecular systems by X–H$\cdots$Y interactions was rarely attacked by quantum chemical methods. This is partly a consequence of the fact that systems of interest involving internal hydrogen bonding are relatively large. Hence, they require use of semiempirical methods which, in turn, are not quite suitable in general. We have shown, however, that the AM1 method provides a good description of hydrogen bond bridges O–H$\cdots$O between oxygen atoms – at least at the qualitative level.[3-6] The main result of these calculations is a strong indication that asymmetric H-bond(s) is (are) energetically preferred over symmetric arrangement of atoms. Energy partitioning gave an interesting insight into the origin of the relative stabilities of isomers or tautomers and provided some useful information about the strength of the internal hydrogen bond. It is the purpose of the present communication to give further evidence that the AM1 method offers a qualitatively correct picture of intramolecular hydrogen bond(s) in aromatic β-hydroxy ketones. Its results are checked against available experimental (predominantly structural) data.

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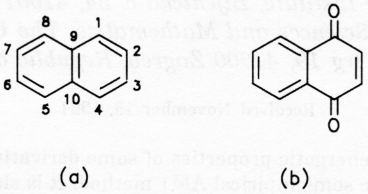
RESULTS AND DISCUSSION

The AM1 method is applied in its standard form[7] and all independent geometric parameters are varied until minimum energy is obtained. Since we are interested in naphthazarin isomers,[3] performance of the AM1 approach in reproducing structural units of parent naphthalene and α-naphthoquinone systems (Figure 1) is discussed first. The bond distances of naphthalene are compared to the X-ray, E.D. (electron diffraction) and *ab initio* results in Table I. It appears that the AM1 semiempirical scheme successfully reproduces the main structural characteristics of the studied compounds, as evidenced by the average absolute errors Δ_{av}, which for X-ray and E.D. data are 0.003 Å and 0.002 Å, respectively. An equally good accordance is obtained with *ab initio* results (Δ_{av} = 0.003 Å). It is obvious that this kind of quantitative agreement is fortuitous, particularly since theoretical, X-ray and E.D. equilibrium bond distances have somewhat different definitions. Besides, pure hydrocarbons do not provide a



(a) (b)

Figure 1. Schematic representation and numbering of atoms in naphthalene (a) and α-(1,4)naphthoquinone (b).

TABLE I

Comparison of AM1 bond distances in naphthalene and α- naphthoquinone with available ab initio *and experimental data (in Å)*

Atomic pairs	AM1	*AB INITIO*	X-RAY	E.D.
Naphthalene				
C(1)–C(2)	1.373[a]	1.371[b]	1.364[c]	1.371[d]
C(2)–C(3)	1.416	1.420	1.415	1.412
C(9)–C(10)	1.419	1.415	1.418	1.420
C(1)–C(9)	1.422	1.425	1.421	1.422
α-naphthoquinone				
C(1)–C(2)	1.478[a]	–	1.465[e]	–
C(2)–C(3)	1.337	–	1.310	–
C(1)–C(9)	1.479	–	1.445	–
C(9)–C(10)	1.407	–	1.390	–
C(8)–C(9)	1.392	–	1.375	–
C(7)–C(8)	1.396	–	1.420	–
C(6)–C(7)	1.393	–	1.370	–
C(1)–O(1)	1.238	–	1.210	–

[a] This paper
[b] H. Sellers and J. Boggs, *J. Mol. Struct.* **74** (1981) 137.
[c] D. W. J. Cruickshank and L. A. Sparks, *Proc. Roy. Soc.* **A258** (1960) 270.
[d] S. N. Ketkar and M. Fink, *J. Mol. Struct.* **77** (1981) 139.
[e] J. Gaultier and C. Hauw, *Acta Cryst.* **18** (1965) 179.

severe test for any theory because of a lack of lone pair electrons, which are very difficult to tackle. Rather, the former family of molecules and their properties represent a necessary but not sufficient test for appraisal of an adopted theoretical approach. It is, therefore, not unexpected that the AM1 method gives less accurate structural parameters for compounds involving oxygen atoms. This is evident from a comparison between the AM1 and X-ray results in α-naphthoquinone (Table I). The average error is 0.023 Å, which is a relatively high discrepancy. It should be mentioned, however, that the X-ray data are related to a molecular crystal, thus reflecting intermolecular interactions, whereas calculation is related to a single molecule. The AM1 results are in qualitative agreement with the observed distances in the quinone fragment. In particular, a highly pronounced localization is predicted for the C(2)–C(3) bond. This is in harmony with the E.D. data for a free benzoquinone[7] where the corresponding value reads 1.344 Å. In addition, the theoretical values for C(1)–C(2) and C(1) = O(1) bond distances of 1.478 Å and 1.238 Å compare well with the E.D. data of 1.481 Å and 1.225 Å, respectively. We note in passing that a fragment involving atoms O(1) = C(1)–C(2) = C(3)–C(4) = O(4) is little changed by annelation of benzene and benzoquinone rings. This is evidenced by the corresponding AM1 distances in benzoquinone which read: $d(\mathrm{C(1)=O(1)})$ = 1.236 Å, $d(\mathrm{C(1)–C(2)})$ = 1.479 Å and $d(\mathrm{C(2)=C(3)})$ = 1.338 Å. They are very close to those in α-naphthoquinone. Apparently, two sets of aromatic π-electron sextets try to avoid each other and π-delocalization is not increased by annelation. Interestingly, the AM1 method predicts practically equal CC distances in the unsubstituted benzene fragment in α-naphthoquinone system. They are very close to a free benzene value. This contradicts the X-ray data (Table I) which exhibit a strong localization within the benzene moiety too. It is interesting to point out that the AM1 results are in harmony with measurements of ^4J(Me–C–C–H) proton-proton coupling constants[8] which provide a certain probe of π-bond orders. It turned out that spin-spin coupling constants did not reveal any appreciable bond fixation within the benzene nucleus in **1b**. Hence, much more sophisticated *ab initio* calculations, employing very good basis sets, would be desirable in the future as well as perhaps some additional experimental structural studies. As a corollary of the AM1 calculations, we can say that AM1 might just overemphasize the role of aromaticity and delocalization. On the other hand, it should be stressed that in Mills-Nixon systems involving benzene fused to small ring(s) the AM1 method gives a very strong localization within the allegedly aromatic benzene moiety, the former being the correct answer.[9]

We turn our attention to structural properties of naphthazarin (Figure 2) and compare the AM1 results with the X-ray and neutron diffraction data of Herberstein *et al.*[10] (Table II). The most stable isomer of naphthazarin discussed here has a 1,4-quinoid structure as evidenced by various experimental techniques[11,12] and semiempiri-

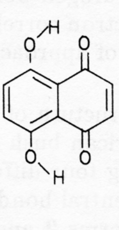


Figure 2. Schematic representation and numbering of atoms in the most stable tautomer of naphthazarin.

TABLE II

Comparison of AM1 bond distances in naphthazarin with available ab initio *and X-ray data (in Å)*

Atomic pair	AM1	*AB INITIO*	X-RAY
C(1)–C(2)	1.475[a]	1.508[b]	1.478(3)[c]
C(2)–C(3)	1.335	1.320	1.348(3)
C(1)–C(9)	1.472	1.500	1.468(3)
C(9)–C(10)	1.429	1.407	1.433(3)
C(8)–C(9)	1.399	1.403	1.404(3)
C(7)–C(8)	1.426	1.413	1.420(3)
C(6)–C(7)	1.335	1.374	1.382(3)
C(1)–O(1)	1.243	1.239	1.246(3)
C(8)–O(8)	1.366	1.378	1.343(3)
O(8)–H(8)	0.971	0.995	0.995(5)
O(1)···H(8)	1.950	1.577	1.577(7)
O(1)···O(8)	2.731	2.505	2.620(8)

[a] Z. B. Maksić, M. Eckert-Maksić, and D. Kovaček, *Croat. Chem. Acta* **62** (1989) 623.

[b] J. R. de la Vega, J. H. Busch, J. H. Shauble, K. L. Kunze, and B. E. Haggert, *J. Amer. Chem. Soc.* **104** (1982) 3295.

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cal calculations.[3] The AM1 results show that intramolecular hydrogen bonds assume asymmetric positions as established by Herberstein *et al.*.[10] Naphthazarin, however, appears in crystal in several forms and the molecules are deformed because of different intermolecular environments. Hence, the experimental data given in Table II refer to average bond distances. Perusal of the results shows a good overall agreement between semiempirical theory and experiment. The average deviation is 0.013 Å, which is rather small if it is taken into account that intermolecular hydrogen bonding is present in the crystal. Performance of the AM1 method is better than that of the *ab initio* STO-3G approach, which has an absolute error of 0.017 Å. It follows that the AM1 scheme offers an economical, slightly better than the STO-3G *ab initio* method, procedure when qualitative information is desired. Some caution should be exercised, however, if O···O contacts are in question. The AM1 method overestimates this nonbonded distance and some empirical adjustments are necessary.[6] A crude offset value of –0.20 Å should be applied. It brings the corrected AM1 estimate of the O···O distance of 2.53 Å relatively close to the *ab initio* result (2.51 Å) and X-ray measurement (2.62 Å). It should be pointed out that a satisfactory quantitative description of the intramolecular (internal chelate[13]) hydrogen bond requires highly sophisticated basis sets and explicit calculation of the electron correlation effect if structural and energetic properties[3] are considered. This type of approach is clearly not feasible for such large molecules at present.

Finally, we shall focus on the structure of cordeauxia-quinone (Figure 3) which gives rise to the red colour of the African bush *Cordeauxia edulis*. This molecule is a derivative of naphthazarin, possessing four different substituents at positions 2, 3, 6 and 7. Distribution of the two O–H central bonds yields four different forms **1**–**4** (Figure 3). AM1 calculations show that forms **2** and **3** are energetically more favourable, the latter being the most stable (Table III). They have either 1,4- or 5,8- quinoid structure, as intuitively expected. This is compatible with the results obtained earlier on the parent naphthazarin.[3] Forms **1** and **4** are less stable by some 7 kcal/mol. The question arises which of these forms appears in molecular crystals. Fehlmann and Niggli interpreted their X-ray measurements in terms of form **1** although a contribution of form **3** could not be completely ruled out.[14] Our calculated AM1 bond distances are compared with the experimental data in Table III. In order to quantify (dis)agreement we also give individual and average absolute errors. The average absolute error Δ_{av} is smallest for the form **1** thus offering a support to a conjecture of Fehlmann and Niggli.[14] Hence we conclude that molecular crystal of cordeauxia- quinone is built (at least predominantly) from the form 1, which in turn is not the most stable isomer. Apparently, it is additionally stabilized by the intermolecular forces. It should be pointed out in this connection that adjacent molecules form infinite chains by intermolecular hydrogen bonds between hydroxyl and O–CH_3 groups.[14]

Some structural features of individual molecules deserve more attention. All forms **1–4** possess a roughly planar naphthazarin moiety. However, $CH_3C{=}O$ and O–CH_3 groups deviate considerably from the plane of naphthazarin skeleton. This is in accordance with X-ray observations.[14] More specifically, the methyl group of the O–CH_3 fragment is rotated out of the molecular plane by some 60°. Analogously, the plane of the $CH_3C{=}O$ fragment is rotated by roughly 70° in all four forms. Further, bond distances of **1** are in qualitative agreement with the experimental data, with a couple of notable exceptions. For example, the central C(9)–C(10) bond should be relatively long if structure **1** is in question. Experiment, on the contrary, yields a very low value of 1.37 Å, which is (fortuitously?) equal to the bond distance of the C(8)–C(9) bond. The AM1 method gives 1.380 Å for the latter bond, thus being in harmony with the X-ray measurements. But, we cannot help saying that the experimental bond distances of C(5)–C(6) and C(5)–C(10) covalent bonds are too short, to a considerable extent, as evidenced by a comparison with their C(1)–C(2) and C(1)–C(9) counterparts. It follows that refined X-ray measurements would be well advised.

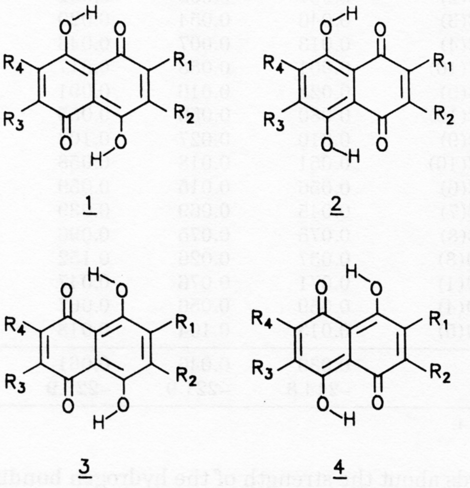


Figure 3. Schematic representation and numbering of atoms in four possible forms of cordeauxia-quinone. Substituents are $R_1 = CH_3CO$, $R_2 = CH_3$, $R_3 = OCH_3$ and $R_4 = OH$.

TABLE III

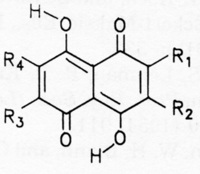
Comparison of AM1 bond distances in Cordeauxia-quinone with X-ray data (Å) and heat of formation (in kcal/mol) of its forms **1**–**4**.

Atomic pairs	X–ray[a]	**1**	**2**	**3**	**4**
C(1)–C(2)	1.48	1.473	1.477	1.428	1.458
C(2)–C(3)	1.40	1.354	1.346	1.380	1.354
C(3)–C(4)	1.48	1.467	1.487	1.434	1.481
C(4)–C(10)	1.38	1.379	1.468	1.397	1.461
C(1)–C(9)	1.49	1.467	1.474	1.399	1.382
C(9)–C(10)	1.37	1.450	1.426	1.425	1.450
C(8)–C(9)	1.37	1.380	1.397	1.472	1.465
C(5)–C(10)	1.42	1.471	1.402	1.478	1.385
C(5)–C(6)	1.41	1.466	1.425	1.469	1.452
C(6)–C(7)	1.32	1.365	1.389	1.359	1.365
C(7)–C(8)	1.39	1.465	1.465	1.486	1.483
C(2)–C(11)	1.40	1.491	1.493	1.491	1.493
C(11)–C(H_3)	1.44	1.493	1.493	1.493	1.493
C(3)–C(H_3)	1.45	1.482	1.481	1.481	1.480
C(6)–O(6)	1.42	1.385	1.384	1.386	1.385
O(6)–C(H_3)	1.45	1.431	1.431	1.431	1.431
C(7)–O(7)	1.41	1.364	1.365	1.362	1.362
C(8)–O(8)	1.39	1.353	1.364	1.238	1.243
C(1)–O(1)	1.32	1.249	1.244	1.367	1.360
C(4)–O(4)	1.30	1.359	1.244	1.367	1.249
C(5)–O(5)	1.26	1.247	1.364	1.242	1.355
O(4)···O(5)	2.57	2.702	2.700	2.720	2.696
O(1)···O(8)	2.51	2.701	2.683	2.717	2.701

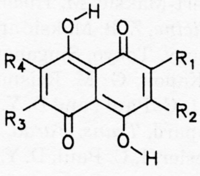
Atomic pairs	Absolute errors (Δ)			
	1	**2**	**3**	**4**
C(1)–C(2)	0.007	0.003	0.052	0.022
C(2)–C(3)	0.046	0.054	0.020	0.046
C(3)–C(4)	0.013	0.007	0.046	0.017
C(4)–C(10)	0.001	0.088	0.017	0.081
C(1)–C(9)	0.023	0.016	0.091	0.108
C(9)–C(10)	0.080	0.056	0.055	0.080
C(8)–C(9)	0.010	0.027	0.102	0.095
C(5)–C(10)	0.051	0.018	0.058	0.035
C(5)–C(6)	0.056	0.015	0.059	0.042
C(6)–C(7)	0.045	0.069	0.039	0.045
C(7)–C(8)	0.075	0.075	0.096	0.093
C(8)–O(8)	0.037	0.026	0.152	0.147
C(1)–O(1)	0.071	0.076	0.047	0.040
C(4)–O(4)	0.059	0.056	0.067	0.051
C(5)–O(5)	0.013	0.104	0.018	0.095
Δav =	0.039	0.046	0.061	0.065
ΔH =	–214.8	–221.9	–223.9	–214.2

[a] Ref. 14.

Finally, a few words about the strength of the hydrogen bonding are in place. We shall adopt here a very simple qualitative model for estimating the hydrogen bond energy. It is provided by a hypothetical structure where the O–H bond of the O–H···O bridge is rotated by 180°. A difference in the enthalpies of formation yields stabilization of the hydrogen bond. Form **1** will be considered for the sake of illustration (Figure 4). Rotation of the O(8)–H bond yielding **1a** rotamer introduces a destabilization of 5 kcal/mol, which is consistent with earlier results in similar systems.[3,4,6] Interestingly, analogous rotation of the O(4)–H bond leads to somewhat higher energy ($\Delta H = -206.2$ kcal/mol). This is easily rationalized by the fact that rotation of the O(8)–H bond leads to a new (albeit very weak) hydrogen bond with O(7) oxygen atom, whereas rotation of the O(4)–H(4) bond increases repulsion between H(4) hydrogen and CH_3 group attached at the C(3) position. Simultaneous rotation of both O(8)–H and O(4)–H bonds yields $\Delta H = -203.8$ kcal/mol, indicating that energies of hydrogen bonding are roughly additive.



1a



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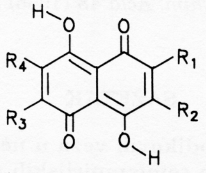

1c

Figure 4. Rotation of O–H bond(s) belonging to hydrogen bridges in form **1** of cordeauxia-quinone.

CONCLUSION

It appears that AM1 provides a satisfactory qualitative description of naphthazarin and related systems involving O–H···O hydrogen bonds, as evidenced by the comparison with available experimental data. Structural and energetic properties of cordeauxia-quinone are discussed. Some inconsistencies in X-ray bond distances within the naphthazarin skeleton are indicated. Relative stabilities of four cordeauxia-quinone isomers are determined. The most stable isomers **3** and **4** possess, loosely speaking, the quinoid fragment as expected (but with a long central C(9)–C(10) bond!). It is shown that the molecular crystal is formed by isomer **1**, indicating that additional stabilization is provided by intermolecular interactions.

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SAŽETAK

Ispitivanje intramolekulskih vodikovih veza u nekim derivatima naftazarina primjenom semiempirijskih metoda

Z. B. Maksić, D. Margetić i M. Eckert-Maksić

Strukturna i energijska svojstva nekih derivata naftazarina razmatrana su s pomoću semiempirijskih metoda AM1 i PM3.

Pokazano je da metoda AM1 opisuje intramolekularne vodikove veze na zadovoljavajući način.