Tetrahedron Letters, Vol.31, No.41, pp 5905-5908, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STABLE KETO-TAUTOMER OF TETRAHYDROXYNAPHTHALENE IN ALKALI: THEORETICAL SUPPORT TO THE POST-AROMATIC REDUCTION IN THE BIOSYNTHESIS OF AROMATIC POLYKETIDES

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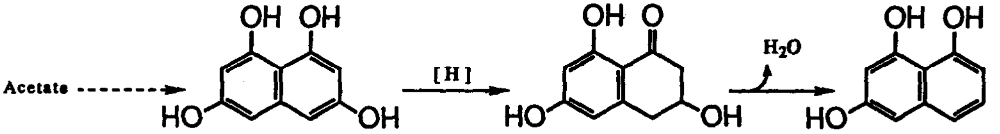
Summary: The structure of the most stable ionic species of 1,3,6,8-tetrahydroxynaphthalene in alkali was investigated by the semi-empirical (AM1) and ab initio (3-21+G//3-21G) molecular orbital calculations. It was concluded that the most stable species was a non-symmetrical keto-tautomer trianion.

Two different mechanisms have been known so far for the removal of acetate-derived oxygens in the biosynthesis of aromatic polyketides of microbial origin. The one is deoxygenation before aromatization,[1] and the other is post-aromatic reduction followed by dehydration (post-aromatic process). The latter is exemplified by the formation of 1,3,8-trihydroxynaphthalene (1,3,8-THN) (3)[2] from 1,3,6,8-tetrahydroxynaphthalene (1,3,6,8-THN) (1) *via* scytalone (2) in the biosynthesis of melanin, a polymer of 1,8-dihydroxynaphthalene, in some phytopathogenic fungi (Chart 1).



1,3,6,8-tetrahydroxynaphthalene (1) scytalone (2) 1,3,8-trihydroxynaphthalene (3)

Chart 1. Biosynthetic Pathway of 1,3,8-THN in Phytopathogenic Fungi.

Previously we reinvestigated a biomimetic reduction[3] of 1,3,6,8-THN (1) to scytalone (2) under a chemical condition of $NaBH_4$ in CH_3ONa-CH_3OH. The NMR spectroscopic studies revealed that a non-symmetrical keto-tautomer (4a or 4b) was stabilized in the alkaline solution of 1,3,6,8-THN (1), in place of naphtholate anion forms (Chart 2).[4] We carried out the theoretical calculations in order to make sure the structure of the most stable anionic species, which was the reactive species for the $NaBH_4$ reduction.

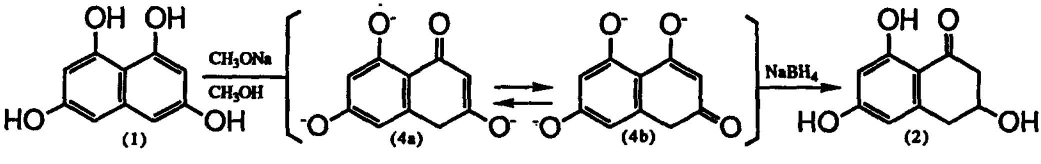


Chart 2. Biomimetic Reduction of 1,3,6,8-THN with $NaBH_4$

Four different anionic species (from -1 to -4) can be formed by the deprotonation of four hydroxyl groups of 1,3,6,8-THN (1), and several isomeric structures are possible for each anionic state. The calculated stabilities of the isomers can be compared only within the same chemical formula, or the same ionic state in this case. Instead of direct comparison of the energy values for all possible isomers in various ionic states, we have determined the most stable species of deprotonated 1,3,6,8-THN (1) in alkali by dividing the calculations into two stages. They are 1) determining the most stable ionic state by a semi-empirical method (AM1[5), 6), 7)]); 2) determining the most stable isomer for the stable ionic state by the AM1 and ab initio[8), 9)] calculations.

In the former stage, Na^+ ions were involved[10)] in the calculation as the countercations. Therefore, calculations were performed for the neutralized forms of each anionic state as follows: $C_{10}H_8O_4$ for non-deprotonated species; $C_{10}H_7O_4Na$ for monoanion; $C_{10}H_6O_4Na_2$ for dianion; $C_{10}H_5O_4Na_3$ for trianion; $C_{10}H_4O_4Na_4$ for tetraanion. Before the calculations on these species, it was necessary to assess the basicity of CH_3ONa by the energy value obtained from molecular orbital calculations. This was realized by the deprotonation energy (DE), which is defined as a difference of heat of formation between the native molecule and the sodium salt of its deprotonated species. First, the DEs for several simple compounds, whose observed pKa values are already known, were calculated[11)]. The deprotonation energies and pKa values for ethane, benzene, methanol, phenol and acetic acid are summarized in Table I.

Table I. Deprotonation Energies (DEs) (kcal/mol) and pKa values for Ethane, Benzene, Methanol, Phenol and Acetic acid.

		C_2H_5R	C_6H_5R	CH_3OR	C_6H_5OR	CH_3COOR
Heat of	R= H	-17.4	22.0	-57.0	-22.2	-96.9
Formation	R=Na	-79.3	-49.8	-137.5	-122.4	-208.2
	DE	-61.9	-71.8	-80.5	-100.2	-111.3
	pKa[12)]	50	43	15	10	4.8

In these five compounds, the pKa values decrease linearly as the DE values decrease. These results strongly indicate that the pKa values can be properly estimated by the DE values. Then, we have estimated the DE values for various species on each ionic state of deprotonated 1,3,6,8-THN (1). Figure 1 shows the calculated heats of formation for the most stable isomer[13)] in each ionic state of 1,3,6,8-THN (1) (n=0~4), together with the DE values between two serial ionic states (DE_n: the DE values between n and n+1 ionic states). The direct comparison of these values has not any meanings, although they decrease orderly with the increase of n values. It is the difference of heats of formation between the serial ionic states that represents the required energy to deprotonate from one ionic state to other ionic state.

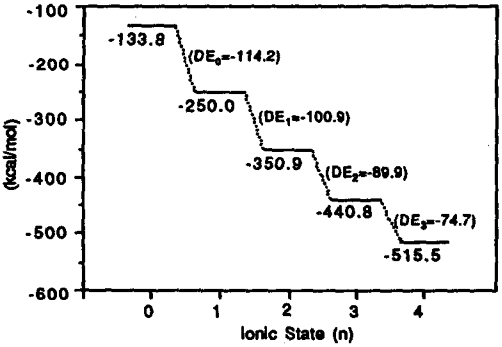


Figure 1. The Heats of Formation of the Most Stable Isomer in Each Ionic State, together with the DE_n values (n=0~3: in parentheses) for 1,3,6,8-THN.

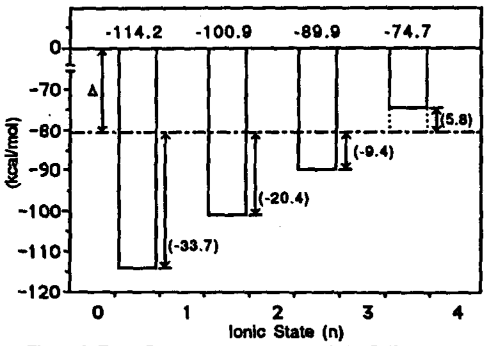


Figure 2. The DE_n values (n=0~3) for 1,3,6,8-THN, together with the Energy Differences (in parentheses) between DE_n and the DE_{MeOH} (Δ: 80.5 kcal/mol).

(1st) $C_{10}H_8O_4 + CH_3ONa = C_{10}H_7O_4Na + CH_3OH + 33.7$ kcal
(2nd) $C_{10}H_7O_4Na + CH_3ONa = C_{10}H_6O_4Na_2 + CH_3OH + 20.4$ kcal
(3rd) $C_{10}H_6O_4Na_2 + CH_3ONa = C_{10}H_5O_4Na_3 + CH_3OH + 9.4$ kcal
(4th) $C_{10}H_5O_4Na_3 + CH_3ONa = C_{10}H_4O_4Na_4 + CH_3OH - 5.8$ kcal

Equation 1. The Thermal Balances for Each Step of the Deprotonation of 1,3,6,8-THN (1).

Each step of deprotonation requires -114.2, -100.9, -89.9 and -74.7 kcal/mol, respectively. The smaller the DE value for each deprotonation step, the more the stabilization of the step. In the deprotonation of 1,3,6,8-THN (1) by CH_3ONa, each deprotonation step proceeds only when the DE_n is smaller than the DE_{MeOH} (-80.5 kcal/mol). Figure 2 depicts the DE_n values (n=0~3) for 1,3,6,8-THN (1), together with the differences (kcal/mol) between DE_n and DE_{MeOH}. The positive value (5.8 kcal/mol) indicates that the corresponding fourth deprotonation does not proceed by CH_3ONa. Equation 1 shows the thermal balances for each deprotonation step of 1,3,6,8-THN (1). Accordingly, it is suggesed that 1,3,6,8-THN (1) can be deprotonated upto trianionic state (n=3) in CH_3ONa-CH_3OH.

For the second stage of the study, the most stable structure among isomeric ones were investigated by the calculations. Among five trianionic isomers, three naphthalene type and two keto-tautomers, the naphthalene-type isomers were less stable than two keto-tautomers by ca. 10 kcal/mol. The most stable isomer was keto-tautomer THN4H (heat of formation: 13.3 kcal/mol) and the second stablest was keto-tautomer THN2H (15.1 kcal/mol) by AM1 method with geometry optimization. In order to compare the stabilities of the two keto-tautomeric structures precisely, the both AM1-optimized structures were further optimized by ab initio calculations with the 3-21G basis set. Then the single-point calculations were perfomed for the both keto-tautomers using the diffuse function-augmented 3-21+G basis set[14] for the more accurate description of the oxygen lone pairs. In Figure 3 and 4, the final geometries of THN4H (5) and THN2H (6) are shown, respectively. The energetic results were summarized in Table II, which compares the stability of THN4H (5) to THN2H (6).

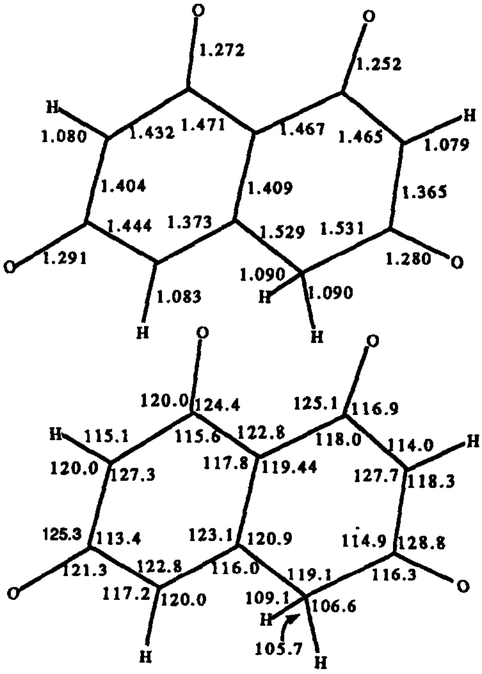


Figure 3. 3-21G Optimized Structures for THN4H (5). Upper: Bond length (Å); Lower: Bond Angle (°)

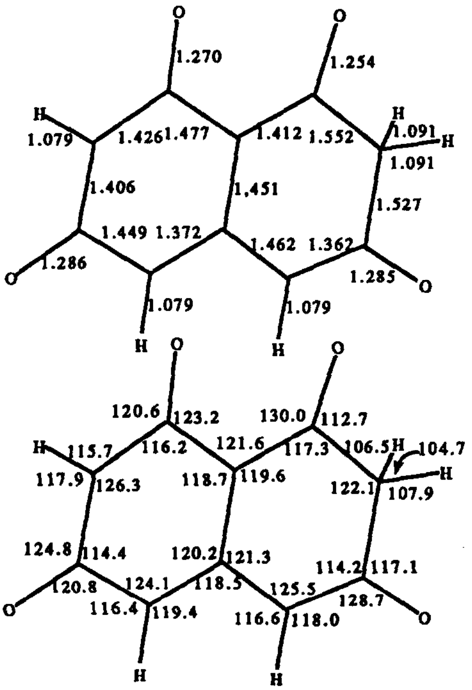


Figure 4. 3-21G Optimized Structures for THN2H (6). Upper: Bond length (Å); Lower: Bond Angle (°)

Table II. Comparison of Energy Values between Two Keto-tautomeric Trianions of 1,3,6,8-THN.

Methods	THN4H (5)	THN2H (6)	$\Delta^{b)}$
AM1 (kcal/mol)	13.3	15.1	1.8
3-21G (a.u.)	-676.865792979	-676.861645328	0.004137651 (2.60 kcal/mol)
3-21+G$^{a)}$//3-21G (a.u.)	-677.046198419	-677.043108629	0.003711212 (2.33 kcal/mol)

a) The diffuse sp orbital exponent (0.0845) was augmented to oxygen.
b) The differences between the value of THN4H and that of THN2H.

Consequently, it was concluded that the keto-tautomeric trianion, THN4H (5), was the most stable ionic species of 1,3,6,8-THN (1) in alkali, which is supposed to be the reactive species in the $NaBH_4$ reduction to scytalone (2) in alkaline condition. These results are in good agreement with our previous observations[4)] by NMR spectroscopy that 1,3,6,8-THN (1) forms a stable non-symmetrical keto-tautomeric structure in CD_3ONa-CD_3OD. Further theoretical investigations on the regioselectivity of a biomimetic reduction of 1,3,6,8-THN (1) to scytalone (2) are now in progress basing on the results of this study.

ACKNOWLEDGEMENT The authors are grateful to Dr. K. Tanabe and Mr. S. Tsuzuki for valuable discussion of National Chemical Laboratory for Industry of Agency of Industrial Science and Technology, MITI.

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5) The calculations were carried out using the MOPAC program system. All geometries were fully optimized with the standard Broden-Fletcher-Goldfarb-Shanno (BFGS) method.
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8) The calculations were performed with the Gaussian 86 program system. All geometries were fully optimized using the Berny gradient method at the split-valence RHF/3-21G basis set.
9) Gaussian 86: M.J. Frisch, J.S. Binkley, H.B. Schlegel, K. Raghavachari, C.F. Melius, R.L. Martin, J.J.P. Stewart, F.W. Bobrowicz, C.M. Rohlfing, L.R. Kahn, D.J. Defrees, R. Seeger, R.A. Whiteside, D.J. Fox, E.M. Fleuder and J.A. Pople, Carnegie-Mellon University.
10) The four hydroxyl groups of 1,3,6,8-THN were replaced by O^-Na^+groups, the number of which was based on that of the ionic state. To each oxygen atom, X (H or Na) atom was placed on the ring plane at the following position: the C-O-X angle is 110°; the O-H distance is 1.1Å; the O-Na distance is 1.5 Å. All the combinations corresponding to the sites of deprotonated hydroxyl groups and the torsional ambiguities of X atoms (0° or 180°) were taken into account. As regards the X atoms attaching to the O1 or O8 oxygens, they were arranged to form a six-membered cyclic hydrogen bond or ligation system, considering the energetical preference. We have also prepared such models as one Na atom interacts with O1 and O3 (O6 and O8) bifurcately from above and beneath the ring plane. After all, the number of calculated models for each ionic state of deprotonated 1,3,6,8-THN were as follows: 13 for non-deprotonated species; 116 for monoanion; 129 for dianion; 49 for trianion; 4 for tetraanion.
11) In the AM1 calculations the imaginary element sparkle "+" was used as a pure ionic charge for Na atom because the parameter for Na has not yet been provided with the AM1 program.
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(Received in Japan 11 July 1990)