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Regioselectivity of Biomimetic Reduction of Tetrahydroxynaphthalene. Location of Transition Structures for Hydride Addition with Theoretical Calculations

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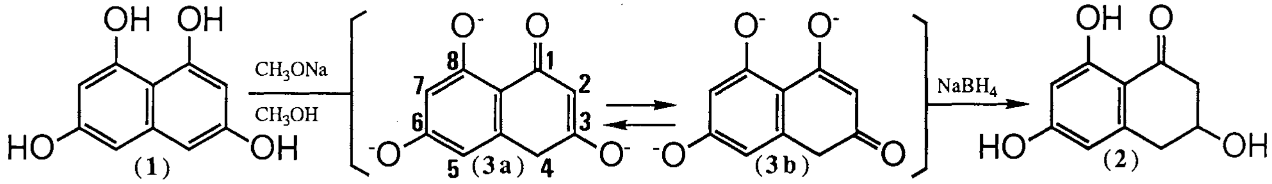
The regioselectivity of a biomimetic reduction of 1,3,6,8-tetrahydroxynaphthalene (THN) was investigated by semi-empirical (AM1) molecular orbital calculations. Transition state structures and stabilities were simulated for the hydride attack models to the carbonyl carbons at C-1 and C-3 of the stable trianionic speices of THN. The results suggested that C-3 carbon was more favorable for the reduction, which agreed with the experimental fact.

In our previous investigations using NMR spectroscopy[1)] and theoretical calculations,[2)] the keto-tautomeric trianion, THN4H (**3a** or **3b**) was identified as the most stable ionic species of 1,3,6,8-tetrahydroxynaphthalene (1,3,6,8-THN) (**1**) in CH_3ONa-CH_3OH. This paper deals with the theoretical investigations to get further information on the regioselectivity of a biomimetic reduction[3)] of 1,3,6,8-THN (**1**) by $NaBH_4$ in an alkaline condition (Scheme 1). The same regioselective reduction of 1,3,6,8-THN (**1**) is observed in the biosynthesis of scytalone (**2**).[4)]



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

From the extensive studies[5)] performed on the mechanism of the borohydride reduction of ketone, following three mechanisms have been so far proposed: (a) four-center; (b) linear; (c) six-membered ring. However, there has been no satisfactory explanation for the mechanism. As the right way of theoretical treatment of the reduction has not yet been established for the time being, we simulated the structures and stabilities of the transition state on the basis of the simplest model,[6)] that a hydride ion attacks to a carbonyl carbon. As we reported previously, the stable keto-tautomeric trianion, THN4H has an almost planar geometry. The attack of hydride to the ring plane was here assumed to occur from an axial direction at *re*-face or *si*-face.

Transition structures were searched by adopting the distance between the carbonyl carbon and a hydride ion as a reaction coordinate, according to the procedure reported by McIver and Komornicki[7)] using a semi-empirical (AM1)[8-11)] method. The distance was varied by a step of 0.5

Å or 0.2 Å within a range of 1.0 Å to 3.0 Å. At each distance of the hydride and the carbonyl carbon, structures were energy-minimized in terms of all the other geometrical parameters. Then, starting from the approximate transition structure, the saddle point structures were obtained by minimizing[12) the gradient norm so that the diagonalized[13) force-constant (Hessian) matrix had only one negative eigenvalue.

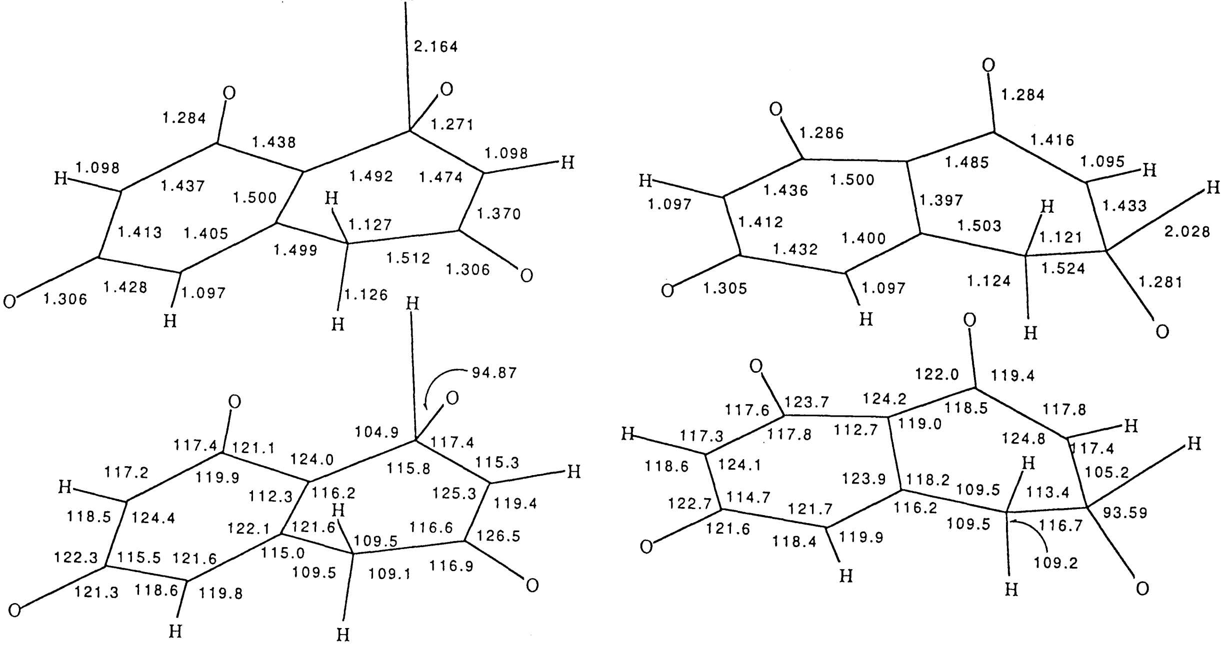


Fig. 1. Transition structures for the attack of hydride to THN4H.
Left: Attack at C-1; Right: Attack at C-3,
Upper: Bond length (Å); Lower: Bond angle (°).

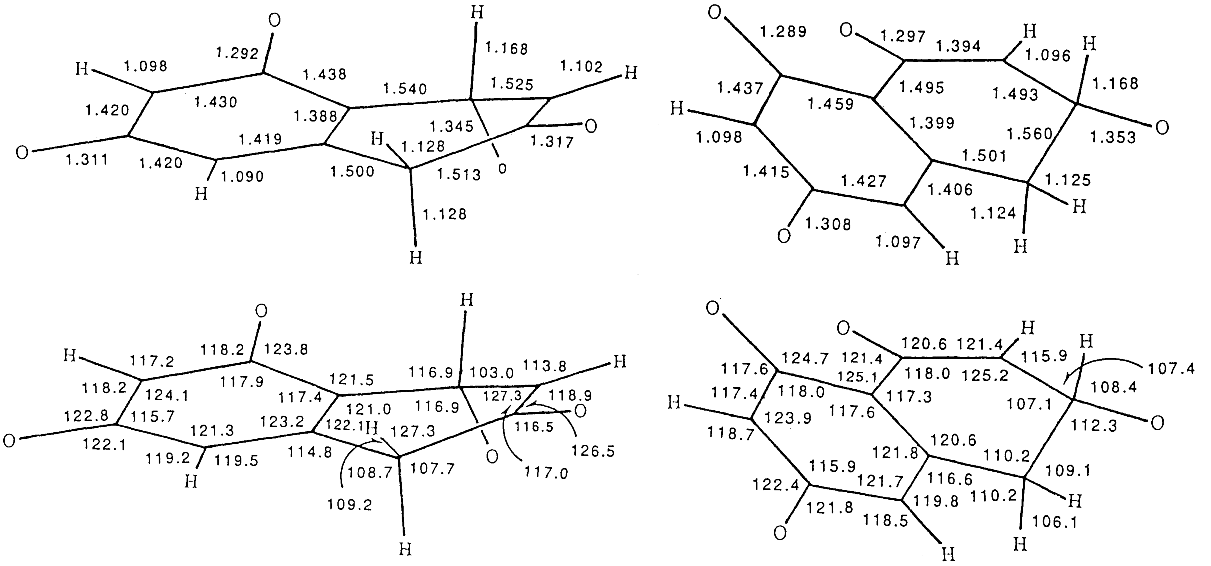


Fig. 2. Structures for the Hydride adduct of THN4H
Left: Attack at C-1; Right: Attack at C-3,
Upper: Bond Length (Å); Lower: Bond Angle (°).

The optimized structures for the transition states resulted from the two cases (*re*-face and *si*-face) have molecular configurations which are mirror images of each other. The transition structures for the attack at *si*-face are shown in Fig. 1, and the respective hydride-adducts are depicted in Fig. 2.

The distance between hydride and the reactive carbon was 2.028 Å for the addition at C-3, and a newly formed alcoholic carbon-oxygen bond is no longer on the ring plane (the dihedral angle of C3-C2-C1-O is 143.2°) and more tetrahedrally coordinated, indicating that the transition structure is product-like. On the other hand, hydride was located at a distance of 2.164 Å from the reactive carbon for the addition at C-1, and the corresponding carbon-oxygen bond was almost on the ring plane (the dihedral angle of C1-C2-C3-O is -179.9°), showing the transition structure to be reactant-like.

The energy diagram for the two cases are shown in Fig. 3. Activation energies for both cases are calculated as $\Delta E_1^{\neq}=213.38$ kcal/mol (C-1) and $\Delta E_3^{\neq}=197.69$ kcal/mol (C-3). The former reaction pathway requires more activation energies ($\Delta E_{TS}=15.09$ kcal/mol) than the latter. It is also recognized from this diagram that the hydride-adduct at C-3 is more stable than that at C-1 by 9.17 kcal/mol.

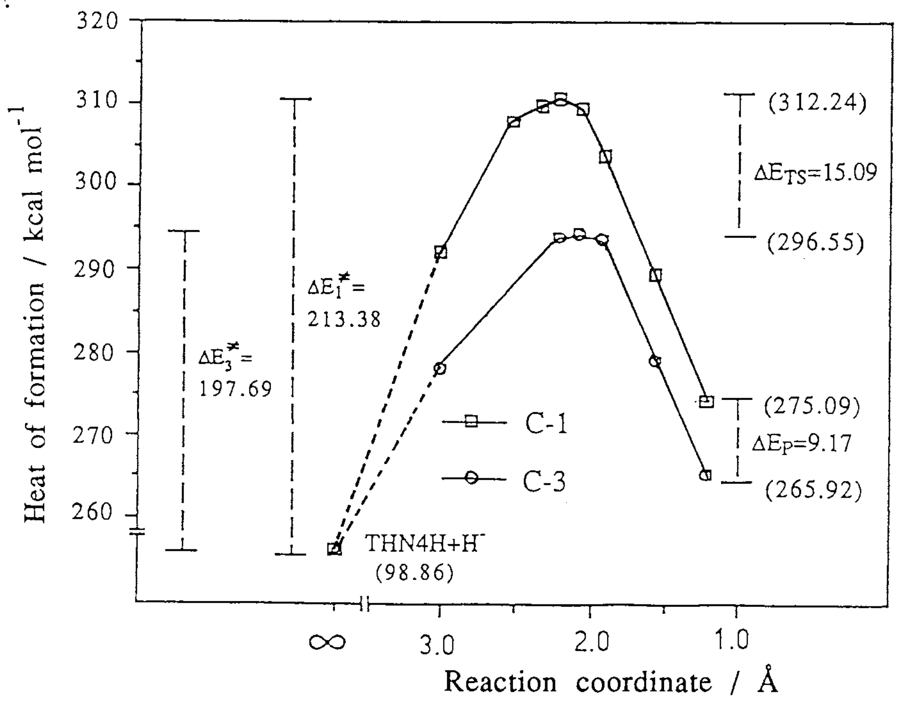


Fig. 3. Energy diagram for the addition of hydride to C-1 and C-3 of THN4H.

From all these investigations, it is suggested that the hydride addition at C-3 predominates over that at C-1. These results are in good agreement with the experimental results on the regioselectivity.

The regioselectivity has been here discussed in terms of their stabilities of transition structure and product, but the electronic nature of the reactive species, THN4H should also be considered. Sodium borohydride is a "Soft" reagent,14) and HOMO-LUMO interaction15) might be an important factor which determines reactivity. The LUMO eigenvectors for THN4H were calculated with ab initio (3-21+G//3-21G) method.[16,17] The eigenvector[18] for C-1 was larger than that for C-3: (C-1) 2Pz(I)=0.25007, 2Pz(O)=0.43213; (C-3) 2Pz(I)=-0.21370, 2Pz(O)=-0.40165, suggesting that the addition of hydride at C-1 occurs predominantly. A result to indicate the same tendency was obtained also by the semi-empirical calculation (AM1). This contradicts with the experimental results and the perfect predominancy of the C-3 addition throughout the reaction pathway. However, this result only suggests the electronic properties of THN4H itself are favorable to the attack of hydride to C-1, not taking into account the accessibility of the hydride. Hydride access to C-1 seems to be heavily interfered mainly by the electrostatic repulsion[19] with the oxygen at C-8. The effect should be reflected to the relative stability of the two pathways including the transition states. The relative difference of the reactivities to hydride between the two positions is estimated quantitatively and sufficiently in our studies. Therefore, this is an example where the selectivity can be determined not by the HOMO-LUMO coefficiencies but by the energetic predominance throughout the whole reaction pathway.

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17) 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.
18) The eigenvector (Hartree) showed here is involved in the 2Pz orbital (π-electron orbital) of THN4H: (I) and (O) correspond to inner and outer orbitals of the 3-21G basis set, respectively.
19) The calculated Mulliken atomic charges of THN4H, where those of the hydrogens are summed into those of the attached carbons, are as follows: 0.641181 (C-1); -0.355487 (C-2); 0.572635 (C-3); -0.110378 (C-4); -0.266153 (C-5); 0.568694 (C-6); -0.345008 (C-7); 0.616357 (C-8); 0.010197 (C-4a); -0.362341 (C-8a); -0.888399 (O-1); -1.019145 (O-3); -1.077979 (O-6); **-0.984174 (O-8)**.

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