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Evaluation of a Radical Mechanistic Probe for NADH-dependent Horse Liver Alcohol Dehydrogenase Reactions by Computer Graphics Modeling

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The feasibility of the reduction of nortricyclanone (**1**) as a chemical probe for testing the proposed radical mechanism for NAD-dependent horse liver alcohol dehydrogenase (HLADH) reactions has been examined using computer graphics modeling. The results of this study suggest that the radical ring-opening of this probe molecule may involve too substantial a geometry reorganization for the molecule to serve as a chemical probe in detecting the possible presence of the radical intermediates in the HLADH reactions. This result suggests that one should exercise caution in extrapolating results obtained from chemically based radical probes in the solution phase to the topologically constrained systems such as enzyme-substrate reactions.

The detailed description of chemical mechanism and the transition state structure for the hydrogen transfer step in the NADH-dependent alcohol dehydrogenase reactions has been a subject of continuing debate. The key mechanistic question is whether the hydrogen transfer between the coenzyme and the substrate carbonyl functionality occurs in a single step as a hydride or in two steps as an electron followed by a hydrogen atom. The structural and kinetic data, and *in vitro* modeling information available on this enzyme-coenzyme system, while substantial, has not yet resulted in a general consensus in support of one of the proposed mechanisms.[1]

Definitive interpretations of various kinetic data obtained for the actual enzyme reactions have been problematic since the hydrogen transfer step is not always the rate-determining

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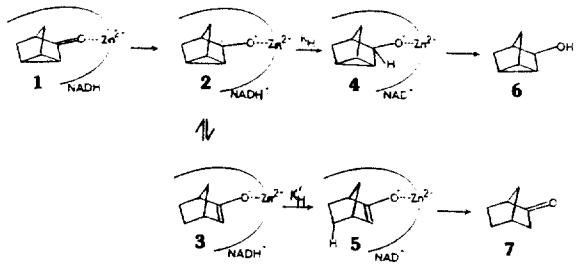
step. Although the recent study on the HLADH reaction with benzyl alcohol by means of intrinsic deuterium and ^{13}C isotope effect measurements has been interpreted to favor the hydride transfer process,[2] various *in vitro* model studies have clearly shown that a one-electron redox process is quite possible between suitable combinations of dihydro-pyridines and substrates.[3,4]

We[5] and others[6] have previously attempted to approach this mechanistic problem by devising chemically based mechanistic probes which are expected to reveal the presence of radical or radical ion intermediates in the enzyme reaction. These chemically based mechanistic probes were designed to exploit the extremely fast molecular processes taking place only in radical or radical ion intermediates,[7] e.g. ring opening of cyclopropyl carbinyl radicals, cyclization of hexenyl radicals and loss of stereochemical integrity of radicals derived from α,β-unsaturated aldehydes.

In these studies,[5,6] no evidence has been found which would implicate radical intermediates in the redox reactions of HLADH with the probe substrates. This observation can be taken as evidence against any involvement of a well-developed radical species. However, this observation may conceivably be due to the differential hydrogen atom transfer rate between the geometrically constrained coenzyme and the presumed radical intermediate, as previously pointed out.[5]

As illustrated in Scheme 1 for the nortricyclanone probe



Scheme 1

(**1**), the involvement of the two-step process of electron and subsequent hydrogen atom transfers might not be reflected in the product formation, if there is a large difference in the hydrogen atom transfer rate: i.e., if $k_H \gg k_H'$ the pathway **2-4-6** would be much more favorable than the pathway **3-5-7**. Therefore, we have now examined the hydrogen transfer geometry of the HLADH reaction by means of computer graphics modeling in order to evaluate the effects of molecular binding of nortricyclanone to the enzyme on the hydrogen transfer step. The nortricyclanone probe(**1**) was selected in this study because of its known efficiency as a radical probe and its conformational simplicity. We have modelled the substrate(**1**) itself and the expected ring-opened product, norcamphor(**7**), in the enzyme active site but have not attempted to model radical intermediates(**2** and **3**).

Results and Discussion

The starting geometry of HLADH enzyme was taken from the X-ray crystal structure containing the dimeric enzyme complexed with NADH and an inhibitor molecule, DMSO.[8] The nortricyclanone(**1**) and norcamphor(**7**) structures were built and refined using the molecular mechanics algorithms of the MacroModel Molecular Modeling System.[9]

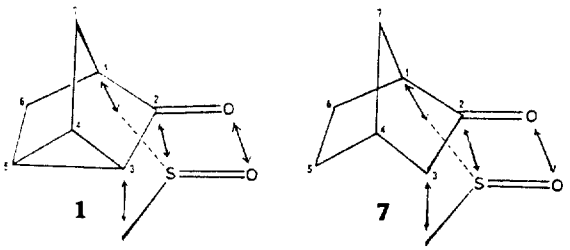


Figure 1. Four atom pair superpositions of substrates **1** and **7** onto DMSO in the crystal structure of the enzyme.

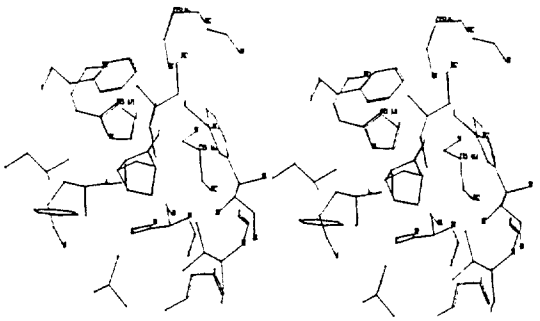


Figure 2. Stereodiagram of the active site of HLADH containing substrate (**1**).

Since molecular mechanics parameters for the zinc ion present in the active site of the enzyme are not available, the substrate molecule was placed into the active site via its superposition onto the DMSO molecule which is present in the active site of the crystal structure by employing a superimposition algorithm (Figure 1).[10] The DMSO molecule and the zinc atom were then deleted from the active site (Figure 2). Since it is impractical to include all atoms of the enzyme in the energy calculation, we selected only those atoms within 7A distance of any atom of the substrate. In the absence of force field parameters for the zinc ion the substrate was geometrically constrained inside the active site of the enzyme by the following approximations. Relative movements among the subset of atoms included in the calculations are muted and limited by their attachments to non-participating rigid atoms in the enzyme (>7A from substrate atoms). This makes "large" distortions of the active site geometry energetically unfavorable. Assuming therefore that atomic movements of zinc bound atoms with respect to the reference coordinate system will be quite small we have positionally constrained the substrate carbonyl oxygen by fixing its reference coordinates (X,Y,Z). In this manner we approximate the geometry of the metal-bound atoms in the active site while permitting movement during minimization. (Comparisons of pair-wise interatomic distances of zinc-bound atoms in pre- and post-minimized structures qualitatively confirm the integrity of the enzyme active site in post-minimized structures). The total AMBER force field potential energy[11] of the substructure set (the substrate and all atoms within the 7A distance of the substrate atoms) was minimized to the preset convergence criterion (the RMS energy gradient ≤ 0.05 KJoule/A). Conformations were initially minimized using the self correcting conjugate gradient (SCCG) method[12], and then followed by block diagonal Newton-Raphson (BDNR) treatment.[13] A set of starting orientations of the substrate (**1**) in the enzyme active site cavity was generated by systematic

Table 1. Distance between H_A and the C-atoms of substrate(1).

Rot(°)	Em[a]	H_A-C_1	H_A-C_2	H_A-C_3	H_A-$C_{4/5}$[b]	H_A-$C_{6/7}$[b]	$\Delta(2,5)$[c]
0	923.37	4.530	3.641	4.510	5.857/5.419	4.995/5.772	1.778
30	948.46	3.974	3.706	5.183	5.816/6.040	5.237/4.886	2.107
90	948.46	3.974	3.709	5.183	5.816/6.040	5.237/4.886	2.107
120	945.04	5.043	3.617	3.846	4.904/5.390	5.886/5.203	1.287
270	945.04	5.043	3.618	3.847	4.904/5.390	5.886/5.203	1.286
300	947.87	4.455	3.629	4.538	5.402/5.858	5.731/4.876	1.773
330	947.87	4.451	3.628	4.539	5.401/5.857	5.729/4.872	1.773

[a] Minimized energy in KJoule/mole. [b] Because of the symmetry element present in *1* (plane of symmetry formed by C_1, C_3 and O), C_4 and C_5, and C_6 and C_7 are indistinguishable, respectively. [c] The difference of the distances: $[H_A\text{-}C_4/C_5]\text{-}[H_A\text{-}C_2]$. The shorter of the distance $H_A\text{-}C_4/C_5$ is used in the calculation of $\Delta(2,5)$.

Table 2. Distance between H_A and the C-atoms of substrate(+)-7a.

Rot(°)	Em[a]	H_A-C_1	H_A-C_2	H_A-C_3	H_A-C_4	H_A-C_5	H_A-C_6	H_A-C_7	$\Delta(2,5)$[b]
0	177.59	4.193	3.111	3.226	4.405	5.578	5.477	4.296	2.467
30	177.59	4.195	3.112	3.225	4.406	5.579	5.478	4.298	2.467
60	173.69	4.252	2.957	2.541	3.799	3.948	4.304	4.826	0.991
90	197.63	4.113	2.869	2.476	3.683	3.768	4.106	4.715	0.899
120	195.18	3.089	3.296	4.743	5.054	4.717	3.314	4.558	1.421
150	195.18	3.089	3.296	4.743	5.054	4.717	3.314	4.588	1.421
180	176.00	3.538	3.359	4.618	5.117	4.618	3.434	5.040	1.259
240	176.00	3.528	3.355	4.615	5.111	4.611	3.424	5.031	1.256
270	196.61	4.386	3.163	3.094	4.396	5.545	5.559	4.496	2.382
300	196.61	4.386	3.163	3.094	4.396	5.545	5.559	4.496	2.382
330	202.24	4.619	3.457	3.838	5.143	6.125	5.854	5.033	2.668

[a] Minimized energy in KJoule/mole. [b] The difference of the distances: $[H_A\text{-}C_5]\text{-}[H_A\text{-}C_2]$. [c] The energy minimized conformations of the starting rotational conformation for 270°-0°-30° range give the correct spatial arrangement for the *exo*-face delivery of the pro-R(H_A) hydrogen of NADH.

Table 3. Distance between H_A and the C-atoms of substrate(−)-7b.

Rot(°)	Em[a]	H_A-C_1	H_A-C_2	H_A-C_3	H_A-C_4	H_A-C_5	H_A-C_6	H_A-C_7	$\Delta(2,5)$[b]
0	173.17	3.077	3.241	4.624	5.017	5.449	4.308	4.040	2.208
90	173.17	3.077	3.242	4.625	5.017	5.448	4.308	4.040	2.207
120	196.98	5.162	3.706	3.910	5.398	5.780	5.658	5.970	2.074
150	177.69	5.106	3.631	3.689	5.221	6.021	5.966	5.612	2.390
270	177.69	5.106	3.631	3.689	5.221	6.021	5.966	5.612	2.390
300	173.17	3.077	3.241	4.624	5.017	5.449	4.308	4.040	2.208

[a] Minimized energy in KJoule/mole. [b] The difference of the distances: $[H_A\text{-}C_5]\text{-}[H_A\text{-}C_2]$. [c] The energy minimized conformations of the starting rotational conformation for 300°-0°-90° range give the correct spatial arrangement for the *exo*-face delivery of thepro-R(H_A) hydrogen of NADH.

rotation along the C = O vector in 30° increments within the originally selected 7A substructure shell. All the rotational orientation were similarly energy-minimized. For each of the resulting minimum-energy conformers, the distance between the pro-R(H_A) hydrogen of NADH and the carbon atoms of the substrate was graphically measured. The energies and selected interatomic distances of the nortricyclanone (**1**) conformers in the active site of HLADH are listed in Table 1.

Next, similar calculations and energy minimizations were performed for the ring-opened product, norcamphor (**7**) in the active site of HLADH. It is known that only (+)-[1S,4R]-enantiomer of norcamphor (**7a**) is readily reduced by the enzyme, while the antipode (**7b**) is left intact.[14] First, the correct enantiomer (**7a**) was brought into the active site cavity of the enzyme through the superimposition procedure described above. The results of the energy calculations and distance measurements are presented in Table 2. The antipode (**7b**) geometry was generated from **7a** within the originally selected 7A substructure shell of the enzyme, by inversion of the substrate atomic coordinates. Similar calculations and distance mappings were performed and the results are shown in Table 3.

From these data, several observations are noteworthy. First the rotational conformations of both nortricyclanone(**1**) and norcamphor(**7**) over a wide range of the rotational angle, readily converge to a limited number of energy minimized conformations: For substrate **1**, starting conformations generated over the range of 30°-90° all converge to one local minimum energy conformation. Similarly, the 120°-270° and 300°-330° rotational conformations converge respectively to

one local minimum energy conformation each. Similarly, the twelve rotational starting conformations for substrate **7a** and **7b** yield 7 and 3 local minimum energy conformations each. These observations suggest (1) that there are relatively few discrete local energy minima in these molecular systems, and (2) that given the constraints of our model the substrate molecules retain significant rotational flexibility in the active site cavity.

An additional important observation is that the differences of the hydrogen atom transfer distances (Δ2,5) between C2 and C5 of the substrate (**1**) are relatively large (1.3-2.1A) in all of the energy minimized conformations. A similar situation is observed with the ring-opened product (**7**), although the difference is as small as 0.9-1.0A in a couple of conformers of **7a**. If one assumes that the hydrogen atom transfer distances for the radical intermediates **2** and **3** in the enzyme active site are reasonably approximated by the distances calculated for substrates **1** and **7**, the pathway leading to the normal reduction product (**6**) is expected to be more favorable than the one leading to the ring-opened product (**7**) because of the shorter H atom transfer distance. Although it is difficult to accurately evaluate the distance dependency of the hydrogen atom transfer rate, it is expected to be substantial by analogy to the distance dependency calculated for electron transfer[15] and experimentally observed for proton transfer rates.[16] Therefore, it seems quite likely that even if the radical ion species are actually involved in the alcohol dehydrogenase reactions, the radical probes involving a large geometry change e.g. 1, would not reveal it because of the large rate difference in the hydrogen atom transfer rates ($k_H \gg k_H'$ in Scheme 1).

Another interesting aspect of the interactions between the substrate ligand (**7**) and the enzyme active site is the possible correlations between the calculated energies of the minimized conformations and the enantio- and facial-selectivities observed for the ketone substrate. In addition to the enantioselectivity mentioned above, norcamphor (**7a**) is also known to be reduced by the *exo*-hydrogen approach to yield *endo*-2-norbornanol.[14] The data in Tables **2** and **3** clearly show that our hope for reasonable correlations between the calculated energies and the observed selectivities for the enzymic reduction of **7** has not been realized in these calculations. For example, the total AMBER energeis of the lowest energy conformers are virtually identical for both the correct (173.69KJ/mole for **7a**-60°) and incorrect (173.17KJ/mole for **7b**-0°) enantiomers. Moreover, the orientation of the lowest energy conformer (60°) of **7a** predicts the hydrogen transfer from the *endo* face of the substrate instead of the observed *exo* face.

The precise reasons for the poor correlation between the calculation and the experimental observations are not yet known. It is possible that the selective recognition of the ligand by HLADH occurs only in the transition state rather than in the initial Michaelis complex.[17] Another possibility that could-modify the active site geometry substantially is that the catalytically relevant enzyme-coenzyme-substrate complex may carry a water molecule as the fifth ligand.[18] This possibility is under examination. The force field calculations may possibly be flawed in this case, because they do not take into proper consideration the role of the zinc ion in the active site, nor is the dihydropyridine moiety of the coenzyme rigorously handled. In the absence of appropriate zinc ion parameters, we attempted a second approach to constrain the substrate in order to mimic the ligand binding effect. A limited number of calculations were performed in which the distances between the zinc ion and each metal-coordinated atom (substrate oxygen, His-67, Cys-46 and Cys-174) were fixed. No improvement in the correlations of energies with selectivities was observed by this approach. A number of other possibilities that would overcome the zinc ion problem are under exploration, and results of these studies will be reported in the due course.

Experimental Methods

The geometry of HLADH enzyme was obtained from X-ray crystal structure (2.9A resolution) of the complexed enzyme with NADH and DMSO, from the Brookhaven Protein Data Bank (6ADH).[8] The substrate structures **1** and **7** were drawn on an Evans-Sutherland PS 330 linked to Vax 11/780, by using the MacroModel Molecular Modeling software (version 1.1-W.C. Still, Columbia University). The total potential energies of the substrate structures were calculated using the AMBER parameters of Kollman,[11] and minimized by the BDNR method:[13] Nortricyclanone (**1**), 901.49 KJ/mole; norcamphor (**7**) 155.70 KJ/mole. The total AMBER potential energy contains the following components: van der Waals, torsion, improper torsion, stretch, bend, hydrogen bond and electrostatic energy. Since the AMBER method used the united-atom field, it was necessary to put hydrogens onto the heteroatoms of the protein structure through the H-Add/H-Del operations in the Organic Input mode.[9] A typical energy minimization of the 7A substructure set of the enzyme/coenzyme/substrate **7a** (113 atoms) takes about 1000 CPU seconds, whereas a similar operation on the 10A substructure set (297 atoms) requires ca. 9000 CPU seconds.

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Direct Transformation of Carboxylic Acids into Aldehydes through Acyloxy-9-borabicyclo[3.3.1]nonane[1]

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New methods for the direct reduction of carboxylic acids to aldehydes through the treatments of B-acyloxy-9-borabicyclo [3.3.1]nonane (acyloxy-9-BBN) with *tert*-butyllithium and 9-borabicyclo[3.3.1]nonane or with lithium 9-boratabicyclo[3.3.1] nonane (Li 9-BBNH) are described. Both these systems provide the corresponding aldehydes from various carboxylic acids in high yields. A mechanism for the reduction through stepwise treatment of acyloxy-9-BBN with *tert*-butyllithium and 9-BBN, which seems to involve the hydride migration through 9-BBN, is proposed and discussed in connection with the reduction through treatment of acyloxy-9-BBN with Li 9-BBNH.

Introduction

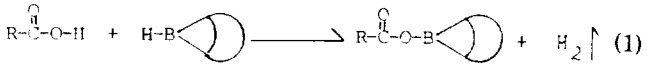
Direct transformation of carboxylic acids into the corresponding aldehydes is of great importance in organic syntheses because of their abundance in nature. A number of methods for the preparation of aldehydes from carboxylic acid derivatives have been developed[2], however, only a few methods are available to get aldehydes directly from carboxylic acids[3,4]. Among them, thexylchloroborane-methyl sulfide[3-a,b] and thexylbromoborane-methyl sulfide[3-c,d] have appeared to be the most promising reducing agents for such direct transformation. Furthermore, the convenient and practical methods for isolation of aldehyde products have been established[3-b]. Although these reagents have their own excellence, these reagents should be prepared by users themselves under the present situation. Consequently, we have centered our efforts to utilize the commercially available 9-borabicyclo[3.3.1]nonane(9-BBN) for such direct conversion.

In this paper, we describe details of such new facile methods for the direct syntheses of aldehydes from carboxylic acids using 9-BBN, which have already reported in form of communications[5], including the mechanistic considerations.

Results and Discussion

Reduction through Treatment of Acyloxy-9-BBN with 9-BBN. It is well known that the reduction of carboxylic acids with boranes(*i.e.*, BH_3-THF[6], BH_3-SMe_2[7], or alkylboranes[8]) proceeds *via* acyloxyboranes formed with evolution of equivalent hydrogen, followed by the hydride transfer to acyloxy group, which indicates that the acyloxyboranes are reactive intermediates for reduction. In this respect, we utilized a commercially available 9-BBN in order to make an acyloxyborane, in the hope of being a reactive intermediate with an adequate structural feature for its acyloxy group being converted to the aldehyde stage.

The reaction of carboxylic acids and 9-BBN provides readily the corresponding acyloxy-9-BBN(**1**) with evolution of 1 equiv of hydrogen (eq 1)[8-c].



1

(H-B ≡ 9-borabicyclo[3.3.1]nonane ≡ 9-BBN)

We attempted to carry out the partial reduction of the acyloxy moiety of **1** to the aldehyde stage with another equiv of 9-BBN. However, the yields of the expected aldehydes were low (Table 1). Shortly, we realized that 9-BBN itself is too weak to attack the carbonyl carbon of acyloxy group.

Reduction through Treatment of Acyloxy-9-BBN with *tert*-Butyllithium. As described above, 9-BBN itself cannot attack the acyloxy group of **1** efficiently. Therefore, we turn-