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STERIC ACCELERATION OF REDUCTIVE DESULFONATION OF 1,8-NAPHTHALENEDISULFONATE BY AN NADH MODEL COMPOUND

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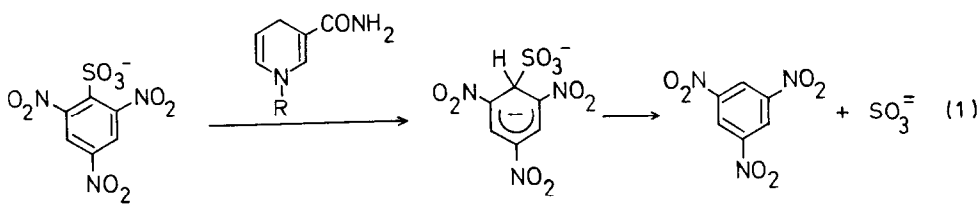
1,8-Naphthalenedisulfonate was reductively desulfonated by N-benzyl-1,4-dihydronicotinamide, whereas no desulfonation was observed for the 1,6-isomer. The high reactivity of the 1,8-isomer is attributed to the steric-strain that enforces the shift of the initial state with the sp^2-carbon close to the transition state with the sp^3-carbon.

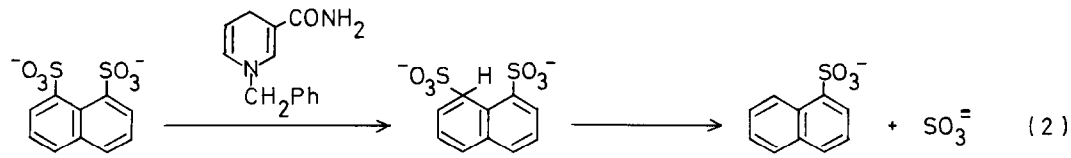
It is known that it would be advantageous for an enzyme to have greatest affinity for the transition state of the reaction that it catalyzes. The compounds termed "transition state analogues" have structures reasonably similar to transition states and are potent enzyme inhibitors.[1,2] This concept suggests that the substrate bound to enzyme may be deformed so that the structure may be closely similar to that of the transition state. In dihydronicotinamide(NADH model) reduction of 1,3,5-trinitrobenzene nucleus or 2,4,6-trinitrobenzenesulfonate(TNBS), an sp^2-carbon of the substrates is converted to an sp^3-carbon in the transition state by accepting hydride (or its equivalent) from dihydronicotinamide.[3-5]



(1)

Thus, if the sp^2-orbital of the starting substrate is partially deformed to the sp^3-orbital, the reduction would be markedly facilitated.

To test the hypothesis, we conducted the reductive desulfonation of 1,8-naphthalenedisulfonate(1,8-NDS) by N-benzyl-1,4-dihydronicotinamide(BNAH)(eq. 2).



(2)

As attested by numerous examples in the literatures, close proximity of substituents in 1,8(peri)-positions of naphthalene often results in out-of-plane deformations.[6] The CPK model suggests that two sulfonate groups of 1,8-NDS are displaced to opposite sides for the mean naphthane plane. In fact, the IR wavenumber ($\nu_{SO_3^-}$: KBr disk) of 1,8-NDS is greater by 20 cm^{-1} than that of 1,6-NDS (Table 1), indicating that the resonance between SO_3^- and naphthalene is inhibited at least partially. It is expected, therefore, that the 1-(or 8-)carbon which should originally adopt the sp^2-orbital has the characteric of the sp^3-orbital (at least partially). If the reductive desulfonation of 1,8-NDS by BNAH is specifically facilitated relative to other isomers, it strongly suggests that the rate acceleration is caused by the steric strain which deforms the substrate structure to the transition state analogue.

The preparations of pure 1-naphthalenesulfonate(1-NS), 2-NS, 1,6-NDS, and 1,8-NDS were described previously.[7] The reaction of BNAH with 1-NS, 2-NS, and 1,6-NDS did not give the expected, desulfonated products (i.e., naphthalene from 1- and 2-NS, and 1- and 2-NS from 1,6-NDS) at all, and the starting materials were recovered (>90%).[8] On the other hand, the reaction of BNAH with 1,8-NDS under the identical reaction conditions resulted in 1-NS in 5-10% yield (based on BNAH).[8] Clearly, 1,8-NDS is specifically sensitive to the reductive desulfonation by BNAH.

It has been established that the dihydronicotinamide reduction of TNBS is first-order in dihydronicotinamide and TNBS.[4] We confirmed that the reductive desulfonation of 1,8-NDS is also first-order in 1,8-NDS and BNAH.[9] The second-order rate constant (k_2) is recorded in Table 1, together with those for other aromatic sulfonates. The k_2 for 1,8-NDS is smaller by a factor of 470 than TNBS but greater by a factor of 3.9 than o-nitrobenzenesulfonate. The sulfonate group is classified as a weak electron-withdrawing substituent (σ=0.05), but 8-substituent in naphthalene is not the resonant position with 1-substituent. Furthermore, the reductive desulfonation of 1,6-NDS which has an isoelectronic structure with 1,8-NDS does not take place. Therefore, although the reductive desulfonation is facilitated by electron-withdrawing substituent(s),[4] such electronic effect is not the case for 1,8-NDS. These results consistently support that the facile desulfonation of 1,8-NDS is due to the steric deformation.

The above conclusion is further corroborated by the activation parameters (Table 1). The $\Delta S^{\neq}$ value increases in the order, o-nitrobenzenesulfonate < TNBS < 1,8-NDS, suggesting that the initial state of 1,8-NDS is most destabilized entropically. Probably, the sp^2-orbital of the 1-(or 8-)carbon of 1,8-NDS is

Table 1. Second-order rate constants (k_2) for reductive desulfonation (50.6°C) and activation parameters[a)]

Substrate	$\nu_{SO_3^-}$	k_2	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	cm^{-1}	$M^{-1}\ sec^{-1}$	kcal mol^{-1}	eu
1,6-NDS	1034			
1,8-NDS	1054	1.32×10^{-2}	14.6	-22.1
TNBS	1037	6.20	7.90	-30.6
o-Nitrobenzenesulfonate	1032	3.40×10^{-3}	7.28	-47.5

a) [BNAH] = 1.00×10^{-4} M, [substrate] = $(0.50 - 4.83) \times 10^{-3}$ M, pH 9.12 with 0.02 M borate buffer.

considerably deformed owing to the steric crowding, which enforces the shift of the initial state close to the transition state with the sp^3-orbital.

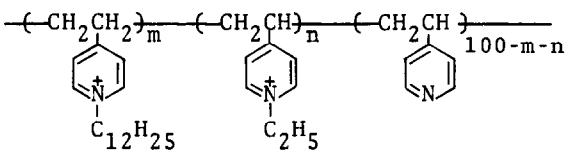
Subsequently, we examined whether desulfonation of 1,8-NDS occurs with natural coenzyme, NADH. As shown in Table 2, the k_2 was smaller by a factor of 19 than that of BNAH. The low reactivity may be ascribed to electrostatic repulsion between two anionic reactants, NADH and 1,8-NDS. This type of the rate suppression can be precluded by the addition of cationic micelles or polyelectrolytes.[10)] In fact, the k_2 value in the presence of 10 mM CTAB(critical micelle concentration, 0.8 mM) was improved by a factor of 3 and those in the presence of cationic polysoaps prepared from poly(4-vinylpyridine)[11)] were further enhanced (18-41 fold).

In conclusion, the present study has demonstrated in the dihydronicotinamide mediated desulfonation of 1,8-NDS that when the reaction center is sterically-strained so that the structure of the initial state may become analogous to that of the transition state, the reaction is markedly accelerated owing to the increase in the $\Delta S^{\ddagger}$. This would be an interesting example for the steric acceleration of NADH model reduction. A similar effect may be also operative in the NADH-dependent enzymes.

Table 2. Second-order rate constants (k_2) for the reaction of NADH and 1,8-NDS[a)]

Additive (mM)	Additive Concentration mM	k_2 M^{-1} sec^{-1}
None		7×10^{-4}
CTAB	10	2.23×10^{-3}
4VP-L-3[b)]	5.0	1.25×10^{-2}
4VP-L-33[b)]	5.0	2.80×10^{-2}

a) [NADH] = 1.00×10^{-4} M. [1,8-NDS] = 3.0×10^{-3} M, pH 9.12 with 0.02 M borate buffer. The concentration of polysoaps is expressed by the total monomeric unit.

b) 

4VP-L-3: m=3, n=96. 4VP-L-33: m=33, n=48

References and Notes

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8) 45-50°C, 24 hr in 12 vol% methanolic solution (pH 9 with 0.018 M borate) under a nitrogen stream, [BNAH] = 6.23×10^{-3} M, and [sulfonate substrate] = 2.67×10^{-2} M. Naphthalene (expected product from 1-NS and 2-NS) was analyzed by GLC, and 1-NS and 2-NS (expected products from 1,8-NDS and 1,6-NDS) were analyzed by high-pressure LC.
9) Under the reaction conditions employed (footnote of Table 1), the decompositi (e.g., acid-catalyzed hydration) of BNAH is negligible in comparison to the net redox reaction.
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