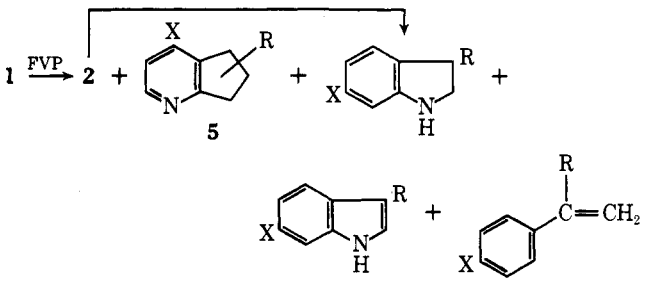
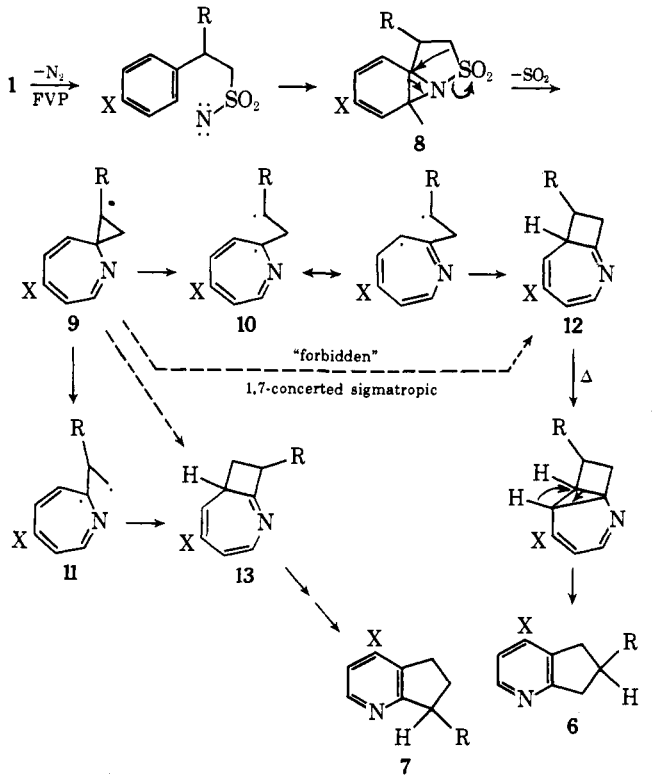


a, X = R = H
b, X = CH_3; R = H
c, X = Cl; R = H
d, X = H; R = CH_3

indoline (75%) and indole (7.7%) but only traces of these compounds at 400°.

The course of the most unusual transformation leading to **5** was investigated. FVP of **1b** (X = CH_3) and **1c** (X = Cl) at 650° gave **5b** (70.2%) and **5c** (62.6%), together with the corresponding 4-X-styrene, 6-X-indoline, and 6-X-indole but no **2** (at 400° some **2** was still formed and lower yields of **5**). The position of the substituent in **5** was established quite unambiguously by nmr spectroscopy.[4] FVP of **1d** (X = H, R = Me) at 650° gave a mixture of 6-methyl- (**6**) (63%) and 7-methyl-6,7-dihydro-5*H*-1-pyrindine (**7**) (9%)[5] (**7**-picrate, mp 128.5–129°) (**6**/**7** ratio = 7). The NMR spectrum of the mixture had lines at δ 8.31 (d, 1, $J_{2,3}$ = 5.0 Hz, H_2), 7.45 (d, 1, $J_{3,4}$ = 8.0 Hz, H_4), 6.98 (dd, 1, $J_{2,3}$ = 5.0 Hz, $J_{3,4}$ = 8.0 Hz, H_3), 3.6–1.6 (m, 5, H_5, H_6, and H_7 of **6** and **7**), 1.34 (d, 0.14, J_{7,CH_3} = 7.5 Hz, CH_3 of 7), and 1.15 (d, 0.86, J_{6,CH_3} = 6.1 Hz, CH_3 of **6**). The structure of **6** was confirmed by comparison with an authentic sample prepared (together with the 5-methyl derivative) by a slight modification of the procedure of Lochte and Pittman.[6] **7** was identical with an authentic sample prepared from dihydropyrindine by treatment with lithium diisopropylamide and methyl iodide at −25°.

Scheme I



The above results indicate that C_4 in **1** becomes C_4 in **5**, while C_β in **1** becomes mainly C_6 in **5**, though some "scrambling" occurs and C_β appears to a small extent as C_7 in **5**. A number of reaction sequences can be envisioned to explain these observations, but the one we favor is presented in Scheme I. The first step is the loss of nitrogen to give the nitrene followed by addition to the adjacent benzene ring to give the benzaziridine (**8**).[7] At the lower temperatures and in solution this can ring-open to **2**. At higher temperatures, elimination of SO_2 (which could occur concertedly as shown or *via* a diradical intermediate) gives **9**. This can rearrange to the cyclobutane derivatives **12** and **13** *via* a diradical process as shown. The allowed concerted thermal 1,7-shift requires an inversion at the migration center, and this seems sterically prohibited in this 1-methylspiro[2.6]azanona-4,6,8-triene system.[8,9] A "forbidden" 1,7-suprafacial concerted process[11] cannot be excluded, however. The predominant formation of **6** rather than **7** tends to speak for the diradical process in which a secondary radical (**10**) is formed more readily than the primary one (**11**). Electrocyclic 6π-ring closure followed by cyclopropane ring opening and hydrogen migration leads to the final products.

We have adapted the above FVP to the preparation of gram quantities of the dihydropyrindines and are continuing our studies of the mechanism of their formation.

Acknowledgment. Thanks are due to the National Science Foundation (Grant No. GP-33361X2) for the support of this work.

References and Notes

(1) R. A. Abramovitch, C. I. Azogu, and I. T. McMaster, *J. Am. Chem. Soc.*, **91**, 1219 (1969); R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 1439 (1969); R. A. Abramovitch and W. D. Holcomb, *Chem. Commun.*, 1298 (1969); R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1 (1970).
(2) The best yields of **2** can be obtained by using an "inert" solvent, such as Freon-113 at 135° for 36 hr in these thermolyses: **2a** (28%); **2b** (38.1%), **2c** (1–2%).
(3) R. A. Abramovitch and E. P. Kyba, *J. Am. Chem. Soc.*, **96**, 480 (1974).
(4) **5a**, NMR δ 8.30 (d, 1, $J_{2,3}$ = 5.4 Hz, H_2), 7.46 (d, 1, $J_{3,4}$ = 6.8 Hz, H_4), 6.98 (dd, 1, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 6.8 Hz, H_3), 2.96 (m, 4, H_5 and H_7), and 2.10 (m, 2, H_6); **5b**, NMR δ 8.17 (d, 1, $J_{2,3}$ = 5.6 Hz, H_2), 6.79 (d, 1, $J_{2,3}$ = 5.6 Hz, H_3), 2.91 (m, 4, H_5 and H_7), 2.21 (s, 3, CH_3), and 2.07 (m, 2, H_6); **5c**, NMR δ 8.2 (d, 1, $J_{2,3}$ = 6.7 Hz, H_2), 7.03 (d, 1, $J_{2,3}$ = 6.7 Hz, H_3), 3.05 (m, 4, H_5 and H_7), and 2.08 (m, 2, H_6). All H_2 in these compounds showed marked nuclear quadrupole broadening and $J_{2,3}$ was measured after addition of 1 drop of CF_3CO_2H.
(5) All the new compounds were completely characterized by microanalysis and infrared, NMR, and mass spectroscopy.
(6) H. L. Lochte and A. G. Pittman, *J. Org. Chem.*, **25**, 1462 (1960).
(7) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968); R. A. Abramovitch, T. D. Bailey, T. Takaya, and V. Uma, *J. Org. Chem.*, **39**, 340 (1974).
(8) For inversion to occur at the migrating center the latter would have to swing out and away from the ring and hence from the π system. A similar rearrangement has been observed in 1-phenylspiro[2.6]nona-4,6,8-triene,[9] and it and a related[10] rearrangement have been formulated as stepwise diradical processes.
(9) E. E. Waali and W. M. Jones, *J. Am. Chem. Soc.*, **95**, 8114 (1973).
(10) R. Mukai, T. Nakazawa, and K. Isobe, *Tetrahedron Lett.*, 565 (1968).
(11) J. A. Berson and L. Salem, *J. Am. Chem. Soc.*, **94**, 8917 (1972).

R. A. Abramovitch,* W. D. Holcomb
Department of Chemistry, University of Alabama University, Alabama 35486
Received September 23, 1974

A Model Dehydrogenase Reaction. Charge Distribution in the Transition State

Sir:

Nonenzymatic reductions by nicotinamide coenzymes in aqueous solutions may serve as models for the action of the NAD^+-dependent dehydrogenases. We report here the ef-

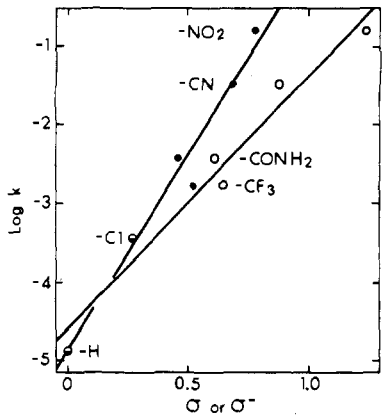
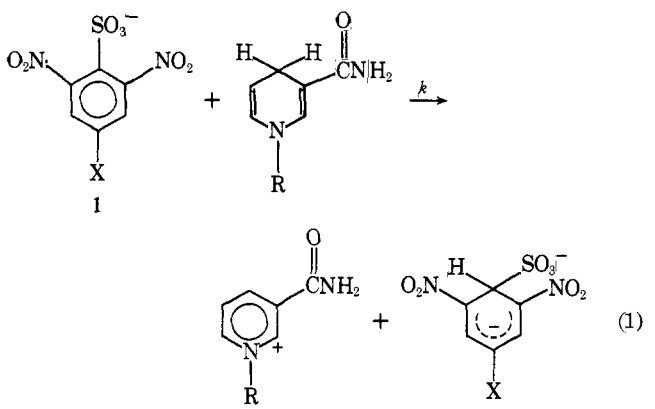


Figure 1. Linear free-energy correlations of the rate of NADH reduction of 2,6-dinitro-4-X-benzene sulfonates with σ (●) and σ^- (○).

fect of para substituents in the oxidant on the rate of such a nonenzymic reduction. The resultant linear free energy relationship indicates extensive transfer of negative charge from NADH in formation of the activated complex. Enzymatic catalysis of the model reduction by a dehydrogenase makes valid comparisons more likely.

The reduction of trinitrobenzene sulfonate by NADH to yield the trinitrobenzene-sulfite σ complex and NAD^+ has been reported[1] previously (eq 1, X = NO_2). It has been



(1)

shown that bovine liver glutamate dehydrogenase (L-glutamate: $NAD(P)^+$ oxidoreductase (deaminating) EC 1.4.1.3) serves as a powerful catalyst for the reaction.[1] For both enzymic and nonenzymic reactions, incorporation of deuterium from the 4 position of the dihydropyridine into the reduced product has been demonstrated.[1] No exchange with solvent (unlabeled reactants in D_2O) was observed.[1] These observations suggest that a two-electron transfer preceded or followed by proton abstraction is not involved.

Preliminary measurements have shown that the isotope effect on the rate of reaction of the *p*-nitro compound with 4-B-^{2}H-NADH is large,[2] so that the hydrogen nucleus is very likely being transferred in the rate-determining step.

The substituent effect on the second-order rate constant for reduction of 2,6-dinitro-4-X-benzene sulfonates, **1**, by NADH was investigated. Substrates in which X = NO_2, CN, $CONH_2$, CF_3, Cl, and H were synthesized or obtained commercially. Elemental analyses and ir spectra were consistent with the proposed structures, **1**. The reaction was studied in aqueous potassium phosphate buffers, pH 8.10, I = 0.12 at 25.0 ± 0.1°. Rates were measured by following the disappearance of the dihydropyridine absorbance at 340 nm. Initial velocities were obtained from <5% of the expected change. Corrections for the degradation of the coenzyme were applied when necessary.

Hammett plots for the correlation with σ and σ^- are shown in Figure 1. The least-squares lines of best fit yield ρ values of 4.97 ± 0.31 and 3.24 ± 0.31, respectively, both with correlation coefficients of 0.982.[3,4] The extent of charge transfer in the activated complex can be estimated through comparison with the analogous ρ values obtained for two extensively studied processes, phenol ionization (equilibrium), and aromatic nucleophilic substitution (rate). These processes are known to involve transfer of negative charge into the ring and into para substituents such as NO_2 and CN. For phenol ionization in aqueous solution ρ = 2.23,[5] and for displacement of halogen from 1-halogeno-2,6-dinitrobenzenes by methoxide in methanol (for which addition of methoxide is rate-determining[6]), ρ = 3.6 for the correlation with σ^-.[7] Transfer of this latter reaction from methanol to water should decrease the ρ value.[8]

Comparison of our value of ρ to the values for these two model processes thus implies extensive transfer of negative charge into the aromatic nucleus in the transition state.

Thus, it is possible to eliminate mechanisms in which atom transfer is rate-determining followed by electron transfer to form products. Little or no electronic substituent effect is to be expected in such a process.[9] Although large substituent effects have occasionally been observed for rate-determining formation of an anionic free radical transition state,[10] the deuterium isotope effect measurements[2] (if confirmed for other compounds in the series) would exclude such a mechanism.

The existence of some kind of intermediate has been implicated in the dihydronicotinamide reductions of *N*-methylacridinium ion[11] and trifluoroacetophenone.[12] In these cases kinetic anomalies detected in deuterium isotope effect experiments[13] were explained by a mechanism in which neither of the elementary steps leading to and from the intermediate is clearly rate determining (i.e., the two transition states have nearly the same standard free energies). In the present case, the linearity of the free energy relationship does *not* suggest a change in rate-determining step over the range of reactivities examined and therefore is consistent with the presence of an intermediate in the reaction only if the transition states are very similar in structure (i.e., similar in the response of their standard free energies to changes in substituent).

It is clear from the results reported here that substantial charge transfer has occurred in formation of the activated complex of this model dehydrogenase reaction. While it remains to be proven conclusively that the transfer of the hydrogen nucleus is concerted with that of the negative charge, we suggest that this coenzyme-substrate transition state is analogous to that pictured for SN2 nucleophilic aromatic substitution with a hydride ion as the displacing nucleophile.

Acknowledgment. We are grateful for the many helpful suggestions provided by Professors Joseph L. Kurz and George Drysdale and for the financial support provided by the National Science Foundation (GB 26483X) and the National Institutes of Health (AM 13332 and GM 43163-01 (L.C.K.)).

References and Notes

(1) D. J. Bates, B. R. Goldin and C. Frieden, *Biochem. Biophys. Res. Commun.*, **39**, 502 (1970).
(2) D. J. Bates, Ph.D. Thesis, Washington University, St. Louis, Mo., 1972. The isotope effect for the enzymic reaction is unambiguously primary (5–7) while that for the nonenzymic reaction is near maximal (1.8).
(3) As substrates for glutamate dehydrogenase the reactivity of these compounds spans a range of four powers of ten. Only one factor of ten can be accounted for by substrate binding (K_m, 2–20 m*M*) with the remainder appearing in the maximal velocity (V_{max}, 1–0.0002 μM sec^{-1} μM active $site^{-1}$). The magnitude of the substituent effect on the enzymatically catalyzed rate is thus comparable to that on the uncatalyzed rate

discussed here and leaves little doubt as to the appropriateness of the uncatalyzed reaction as a model.
(4) Omission from these calculations of the data for the p-CF_3 compound results in $\rho = 5.08 \pm 0.13$, $r = 0.998$ for the correlation with σ and $\rho = 3.25 \pm 0.31$, $r = 0.986$ for the correlation with σ^-.
(5) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(6) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N.Y., 1968, p 146.
(7) J. Miller, *ibid.*, p 78.
(8) O. Exner in "Advances in Linear Free Energy Relationships," N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, p 26.
(9) P. Neta and R. H. Schuler, *J. Am. Chem. Soc.*, **94**, 1056 (1972). A ρ of -0.45 was observed.
(10) M. Mohammad and E. M. Kosower, *J. Am. Chem. Soc.*, **93**, 2709 (1971). A ρ of $+14$ was observed.
(11) D. J. Creighton, J. Hajdu, G. Mooser, and D. S. Sigman, *J. Am. Chem. Soc.*, **95**, 6855 (1973).
(12) J. J. Steffens and D. M. Chipman, *J. Am. Chem. Soc.*, **93**, 6694 (1971).
(13) A detailed investigation of isotope effects on the reactions reported here is in progress.

Linda C. Kurz, Carl Frieden*
Department of Biological Chemistry
Division of Biology and Biomedical Sciences
Washington University
St. Louis, Missouri 63110
Received November 14, 1974

Hydrozirconation. III. Stereospecific and Regioselective Functionalization of Alkylacetylenes via Vinylzirconium(IV) Intermediates

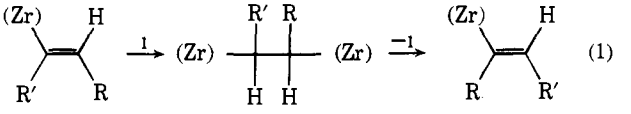
Sir:

Di(η^5-cyclopentadienyl)(chloro)alkylzirconium(IV) complexes have been shown to be useful intermediates in the transformation of olefins into a variety of organic derivatives.[1,2] We have now observed that hydrozirconation of disubstituted acetylenes proceeds stereospecifically with high regioselectivity to yield vinylic Zr(IV) complexes which are, as well, valuable as precursors of trisubstituted olefins.

The reaction of (η^5-C_5H_5)ZrH(Cl) (**1**) with 1-butyne gives trans vinylic derivative **2** which establishes that Z-H addition to the acetylene occurs cis.[3] We have found that addition of **1** to various unsymmetrically *disubstituted* acetylenes occurs readily[4] to give mixtures of vinylic derivatives in which the steric bulk of the alkyl substituents dictates the direction of Zr-H cis β-addition to the triple bond. Thus, for each unsymmetrical acetylene, two vinylzirconium(IV) compounds can be formed which differ only in the point of attachment of the metal to the double bond. We have also observed that, over a period of several hours, this initial mixture of vinylic species can be converted to one with higher regioselectivity, at room temperature, through catalysis with **1** (see Table I). In no case were products derived from allylic rearrangements observed.[5] The regioselectivity found was generally higher than that observed for hydroboration with hindered boranes.[6] The chemical reactivity of these vinylzirconium(IV) compounds renders them useful as intermediates in the facile and selective conversion of dialkylacetylenes to trisubstituted olefins.

The two-step conversion of an acetylene to a functionalized olefin is illustrated as follows. 5-Methyl-2-hexyne (670 mg, 6.67 mmol) was stirred with 1.58 g (6.13 mmol) of **1** in benzene[8] for 2 hr. Removal of the solvent in vacuo gave the vinylic complex (**2d** and **3d**, 55:45)[7] as a pale red oil. The mixture of **2d** and **3d** was redissolved in benzene. Reanalysis of this mixture by NMR[7] after several hours at room temperature revealed that its composition had not changed. However, addition of several milligrams of **1** to this solution resulted in its conversion, slowly to a new mixture of isomers containing >95% **2d** and <5% **3d**.[9] Treatment of a solution of the vinylic complexes with *N*-bromosuccinimide gave, rapidly, the corresponding vinylic bromides in good yield, with retention of (C=C) stereochemistry[10] and with the same composition of positional isomers as that observed for the organometallic precursor (see Tables I and II). In this way, vinylic chlorides were prepared from **2**, **3** and NCS, and iodides from **2**, **3**, and I_2. The yield of vinylic halides so produced was at least as high as that reported for the hydrohalogenation of acetylenes via vinylalanes.[11]

It is interesting to note that, whereas alkylzirconium(IV) complexes positionally rearrange rapidly,[1] no such process occurs for their purified vinylic analogs. We believe that this rearrangement, observed to be catalyzed by **1**, occurs through a dimetalated alkyl intermediate as shown in reaction 1.

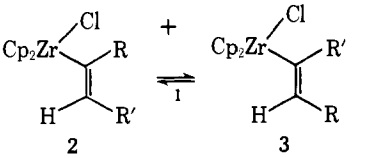

(1)

Because of the mildness of reaction conditions and high yields of products formed stereospecifically and with high regioselectivity, hydrozirconation is an attractive method

Table I

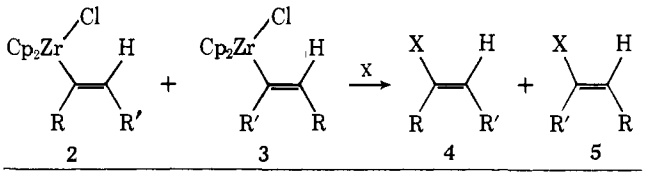
$Cp_2Zr(H)Cl$ + RC≡CR′ ⟶

1


2 3

Acetylene	Product ratio (2:3)[7] Initially observed	After treatment with 1
a, R = H; R′ = n-C_4H_9–	>98 : 2	
b, R = CH_3; R′ = CH_3CH_2–	55 : 45	89 : 11
c, R = CH_3; R′ = $CH_3CH_2CH_2$–	69 : 31	91 : 9
d, R = CH_3; R′ = $(CH_3)_2CHCH_2$–	55 : 45	>95 : <5
e, R = CH_3; R′ = $(CH_3)_2CH$–	84 : 16	>98 : <2
f, R = CH_3; R′ = $(CH_3)_3$–	>98 : 2	

Table II


2 3 4 5

Vinylic complex (ratio 2:3)		X	Product composition[12] (4:5)	Yield[13] (%)
2a + 3a	>98:<2	NBS	>98:<2	75
		NCS	>98:<2	∼100
2b + 3b	72:28[a]	NBS	72:28	97
		NCS	71:29	53
2d + 3d	>95:<5[b]	NBS	>95:<5	75
		NCS	>95:<5	71
2e + 3e	84:16[c]	NBS	83:17	95

[a] Reaction with X performed on aliquot taken during treatment of the complexes with **1**. [b] Reaction performed on aliquot taken after treatment of 2d and 3d with **1**. [c] Reaction performed on aliquot taken before treatment of 2e and 3e with **1**.