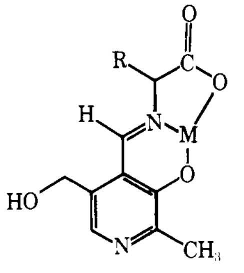
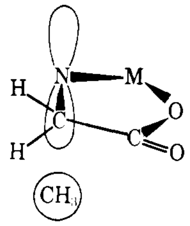
Differential Reactivity of the α-Methylene Protons of Bis(pyridoxylideneglycinato)cobalt(III)—Inferences for Vitamin B_6 Catalyzed Reactions

Sir:

A wealth of mechanistic information on vitamin B_6 model reactions has resulted from the study of amino acid-pyridoxal Schiff bases and their metal complexes, I.[1] Most of the work has focused on mechanistic and spectroscopic properties of these systems. Relatively less work has been directed at the question of how the enzymes bring about enhancement of the reactivity of these Schiff bases. Dunathan has suggested that selective catalysis of cleavage of a bond to the amino acid α-carbon atom can be accomplished by correctly orienting that bond with respect to the π system of the azomethine group.[2] Pointing out that most vitamin B_6 reactions involve the flow of electrons into the π system of the Schiff base, he has postulated that catalysis will occur when the bond to be cleaved best overlaps the π system. We have been designing model systems to test his hypothesis. Herein we report a preliminary kinetic study of a reaction of bis(pyridoxylideneglycinato)-cobalt(III).[3] In this complex the methylene protons of the glycine moiety are forced into different conformations with respect to the azomethine π system, as illustrated in II where the view is of the α-carbon atom projected against the azomethine nitrogen and the methyl group is the methyl group from the other coordinated Schiff base.[4] Furthermore, the complex is inert to ligand substitution during the time span of the vitamin B_6 model reactions.



I



II

The reaction that we have investigated is the deuterium exchange of the glycine moiety's α proton, monitoring the reaction with ^{1}H NMR. For amino acid Schiff bases, this reaction could proceed either by mechanism III → IV → III or by III → IV → V → IV → III.[5] However, in this case, the latter mechanism can be excluded. No loss of the azomethine C-H proton signal is observed during the time that complete exchange is observed for α-CH_2 protons of the glycine moiety. Therefore no interchange between V and IV is occurring. As in a recent study of the exchange of the α-CH_2 group in a bis(salicylideneglycinato)cobalt(III) complex,[6] excellent biphasic kinetics are observed for the disappearance of the two protons. Measurement of these rates over a suitable temperature difference results in activation profiles as shown in Figure 1. Variation of total complex concentration shows that at a given temperature the rate is essentially second order in complex. General base catalysis is normally observed in proton transfers of coordinated Schiff bases like these.[6,7] Therefore the second-order rate law is consistent with a mechanism which involves the base-catalyzed proton exchange of one complex by the pyridine nitrogen of another complex. This is a plausible mechanism given the basicity of the pyridine nitrogen atom and the high complex concentration required for study of the reactions.

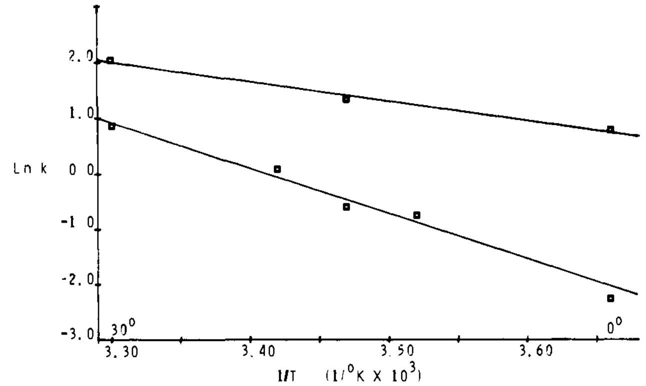
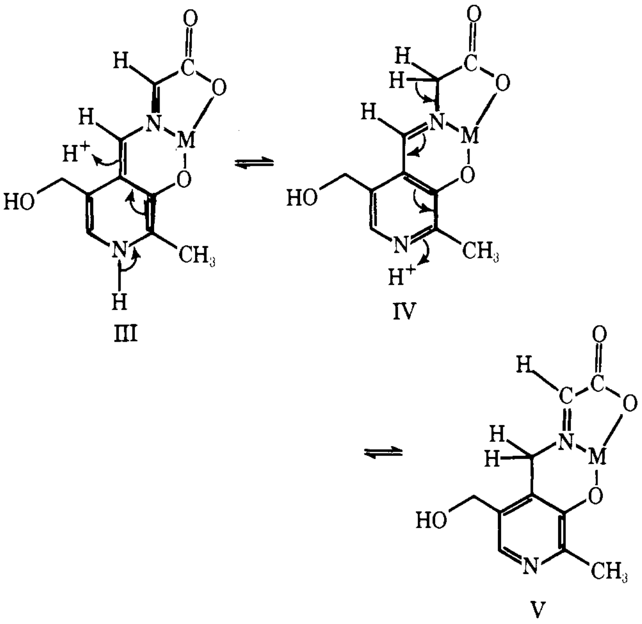


Figure 1. Temperature dependence for the pseudo-first-order rate constants for exchange of the α-methylene protons of bis(pyridoxylideneglycinato)cobalt(III). The complex concentration was 0.2 M and sufficient KNO_3 was present to give an ionic strength of 1.0. The pD was adjusted to 8.9. The units of the pseudo-first-order rate constant are h^{-1}.



The particularly interesting feature of Figure 1 is the difference in temperature dependence for the two proton exchanges. The relatively small slope for the faster reaction is indicative of a relatively low $\Delta H^{\ddagger}$ and relatively negative $\Delta S^{\ddagger}$. For the slow reaction $\Delta H^{\ddagger} = 16 \pm 2$ kcal/mol and $\Delta S^{\ddagger} = -19 \pm 5$ eu.

For the fast reaction $\Delta H^{\ddagger} = 5 \pm 3$ kcal/mol and $\pi S^{\ddagger} = -50 \pm 15$ eu. The values for the fast reaction are far less precise than those for the slow reaction because of the small temperature dependence and the more inconvenient rate under the experimental conditions. For the purposes of the present communication, we wish only to emphasize the qualitative comparison between the temperature dependencies of the fast and slow reactions illustrated in Figure 1.

We interpret our results as being consistent with the Dunathan suggestion of catalysis arising from overlap of the bond to be cleaved with the azomethine π system. For the fast reaction overlap is possible and $\Delta H^{\ddagger}$ is very much reduced. The reaction is, however, base catalyzed and the requirement that the base approach colinear with the π system imposes a very

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unfavorable $\Delta S^{\ddagger}$. For the slower reaction $\Delta H^{\ddagger}$ is less favorable because overlap with the π system cannot readily occur. Restrictions must also be relaxed on the angle of approach of the base in the slow reaction because $\Delta S^{\ddagger}$ is not so unfavorable as in the rapid reaction.

For enzymes, the potential significance of the activation parameters for the fast reaction is substantial and the following speculation is therefore warranted. Correct positioning of an auxiliary base at the active site of the enzyme could make $\Delta S^{\ddagger}$ much less negative. For the low value of $\Delta H^{\ddagger}$ observed by us and $\Delta S^{\ddagger} = 0$, the reaction would occur at a rate more rapid than is generally observed for reactions catalyzed by vitamin B_6 enzymes. It appears that the Dunathan hypothesis not only can explain the selectivity of vitamin B_6 enzymes but also may explain the magnitude of the rate enhancements observed with these enzymes.

Acknowledgment. The authors gratefully acknowledge support of this research by Grant AM 21568 from the National Institutes of Health.

References and Notes

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(2) H. C. Dunathan, *Proc. Natl. Acad. Sci. U.S.A.*, **55**, 712 (1966).
(3) The bis(pyridoxylideneglycinato)cobalt(III) complex was prepared by air oxidation of the Co(II) complex at 0 °C with activated charcoal in methanol. It was isolated as the sodium salt. Anal. Calcd for $NaCoC_{20}H_{20}N_4O_8{\cdot}H_2O$: C, 43.8; H, 4.1. Found: C, 43.83; H, 4.36. NMR was referenced to hexamethyldisiloxane (pD 8.9): 1.18, (2-CH_3), 4.52 (5-CH_2), 4.95 (glycine α H), 7.38 (6-H), 8.65 ppm (azomethine C-H).
(4) Evidence for different environments of the two protons comes from NMR studies. The glycine moiety's CH_2 proton resonance appears as an AB pattern, consistent with different environments for the two protons. For each, the pseudo-allylic 4-bond coupling could be measured to the azomethine C–H proton. These couplings were $J = 1.85$ and 0.95 Hz. The larger coupling constant is consistent with the greatest angle to the plane of the π system (M. Barfield et al., *J. Am. Chem. Soc.*, **97**, 1482 (1975)) and it is this proton which exchanges most rapidly. NMR spectra showing these changes were supplied to the referees.
(5) S. W. Tenenbaum, T. H. Witherup, and E. H. Abbott, *Biochem. Biophys. Acta*, **362**, 308 (1974).
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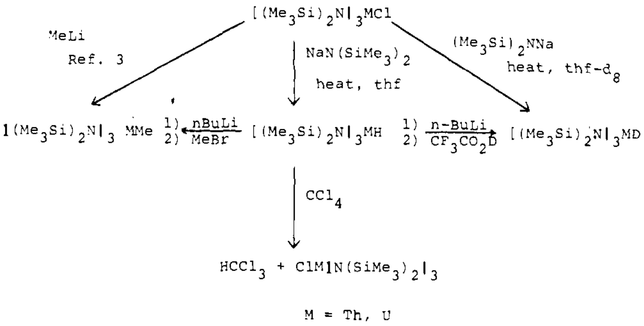
Hydrido[tris(hexamethyldisilylamido)]thorium(IV) and -uranium(IV)

Sir:

Metal hydrides are known for most of the metals. The 4f- and 5f-block metals, except those of the man-made ones, form rather stable metallic, binary hydrides of the type MH_2 and MH_3.[1] In contrast, only one molecular hydride of the f-block metals has been described, viz., $(Me_5C_5)_4M_2H_4$ where M is thorium or uranium.[2] We describe here the first monomeric, monohydride derivatives of these metals, viz., $HTh[N(SiMe_3)_2]_3$ and $HU[N(SiMe_3)_2]_3$.

Reaction of chloro[tris(hexamethyldisilylamido)]thorium(IV)[3] with 1 molar equiv of sodium hexamethyldisilylamide in refluxing tetrahydrofuran yields hydrido[tris(hexamethyldisilylamido)]thorium as white needles from pentane:[4] mp 145–147 °C; IR ν_{ThH} 1480 cm^{-1}; ^{1}H NMR (PhH) δ 0.90 and 0.40 due to the hydride and trimethylsilyl resonances, respectively. The deuteride, $DTh[N(SiMe_3)_2]$, ν_{ThD} 1060 cm^{-1}, can be prepared by refluxing $ClTh[N(SiMe_3)_2]_3$ and $NaN(SiMe_3)_2$ in perdeuteriotetrahydrofuran. The uranium hydride and deuteride were prepared similarly. Hydrido[tris(hexamethyldisilylamido)]uranium was crystallized from pentane as brown-yellow needles:[4] mp 97–98 °C; IR ν_{UH} 1430 cm^{-1}, ν_{UD} 1020 cm^{-1}. We have been unable to locate the hydride signal in the ^{1}H NMR spectrum of this paramagnetic ($\mu_B = 2.6$ BM in benzene solution) substance, though the trimethylsilyl groups resonate at δ −19.5. The hydrides can also be prepared from $ClM[N(SiMe_3)_2]_3$ and *tert*-butyllithium or lithium triethylhydridoborate in pentane.

Scheme I



The metal-bound hydrides were further characterized by their reaction chemistry; see Scheme I. The hydrides react with carbon tetrachloride yielding chloroform (identified by its NMR spectrum) and $ClM[N(SiMe_3)_2]_3$ (M is thorium or uranium). The latter were identified by melting point, mixture melting point, and IR and NMR spectra. Further, addition of *n*-butyllithium to a pentane solution of the hydrides, followed by methyl bromide, yields $MeM[N(SiMe_3)]_3$[3] (M = Th or U quantitatively). The product from reaction of *n*-butyllithium with the hydride derivatives affords $HM[(N(SiMe_3)_2]_3$ or $DM[N(SiMe_3)_2]_3$ (M = Th or U) upon addition of trifluoroacetic acid or deuteriotrifluoroacetic acid, respectively.

The uranium and thorium hydrides have also been characterized by a single-crystal X-ray analysis, though the hydrogen atom was not located.[5]

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References and Notes

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(4) All new compounds gave satisfactory elemental analysis for C, H, and N and molecular ions (M − 2) in the mass spectrometer.
(5) Zalkin, A., personal communication.

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A New Approach toward the Synthesis and Chemistry of Fluoroxy Compounds

Sir:

Since the pioneering investigations of Barton and Hesse[1] in which electrophilic fluorination was developed, work in this new area has been restricted to the use of fluoroxytrifluoromethane (CF_3OF).[2,3] Recently reactions have been developed in which a fluorine molecule acts as an electrophile, replacing tertiary hydrogens in organic substrates.[4]

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