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Reactivity of the B–H Bond in Tris(pyrazolyl)hydroborato Zinc Complexes: Unexpected Example of Zinc Hydride Formation in a Protic Solvent and Its Relevance towards Hydrogen Transfer to NAD^+ Mimics by Tris(pyrazolyl)hydroborato Zinc Complexes in Alcoholic Media

Catherine Bergquist, Lawrence Koutcher, Amanda L. Vaught, and Gerard Parkin*

Department of Chemistry, Columbia University, New York, New York 10027

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Solutions of the zinc hydroxide complex $[Tp^{Bu^t,Me}]ZnOH$ in alcohols (ROH; R = Me, Et, Pr^i) achieve hydride transfer to the NAD^+ model, 10-methylacridinium perchlorate. Deuterium labeling studies, however, demonstrate that the source of the hydride is not the alcohol but, rather, the B–H group of the $[Tp^{Bu^t,Me}]$ ligand. A further example in which a $[Tp^{Bu^t,Me}]$ ligand acts as a hydride donor is provided by the reaction of the aqua complex $\{[Tp^{Bu^t,Me}]Zn(OH_2)\}[HOB(C_6F_5)_3]$ with MeOH to generate the zinc hydride complex $[Tp^{Bu^t,Me}]ZnH$. The present study therefore provides a caveat for the often assumed inertness of the B–H group in tris(pyrazolyl)hydroborato ligands, especially in the presence of reactive cationic species.

Liver alcohol dehydrogenase (LADH) is the zinc enzyme that is responsible for the oxidation of alcohol in humans.[1] The oxidation involves several components, which include (i) displacement of an aqua ligand by an alcohol, (ii) deprotonation of a coordinated alcohol, and (iii) formal hydride transfer from the zinc alkoxide to the NAD^+ cofactor. In this paper, we focus on aspects of this chemistry in a synthetic analogue system based on the tris(pyrazolyl)hydroborato ligand and demonstrate that while alcoholic solutions of $[Tp^{Bu^t,Me}]ZnOH$ do indeed achieve hydride transfer to a NAD^+ mimic, namely 10-methylacridinium, the transfer does not involve the alcohol but, rather, results from cleavage of the B−H group of the tris(pyrazolyl)hydroborato ligand.

We recently reported the first evidence that a series of simple tetrahedral zinc alkoxide complexes may be obtained by alcoholysis of a zinc hydroxide complex. Specifically, the zinc alkoxide complexes $[Tp^{Bu^t,Me}]ZnOR$ (R = Me, Et, Pr^i) were generated by the reaction of $[Tp^{Bu^t,Me}]ZnOH$ with corresponding aliphatic alcohol.[2] We also demonstrated that hydride transfer from a $[Tp^{Bu^t,Me}]ZnOR$ derivative is feasible by the observation that $[Tp^{Bu^t,Me}]ZnOEt$ reacts with an activated aldehyde, ArCHO (Ar = p-$C_6H_4NO_2$), in benzene to give $[Tp^{Bu^t,Me}]ZnOCH_2Ar$ and MeCHO,[2a] via a Meerwein−Ponndorf−Verley type of reaction.[3] Since an aldehyde is a rather poor model for NAD^+, we sought to obtain a more realistic system by employing nicotinamide and acridinium derivatives which conserve the pyridinium ring present in NAD^+ (Figure 1).[4] 1-Benzylnicotinamide chloride, (BNA)Cl, in particular, has previously been investigated as a hydride acceptor in zinc chemistry but was found to be inefficient.[5] For example, Vahrenkamp recently reported that hydride transfer from $[Tp^{Cum,Me}]ZnOPr^i$ to (BNA)Cl was

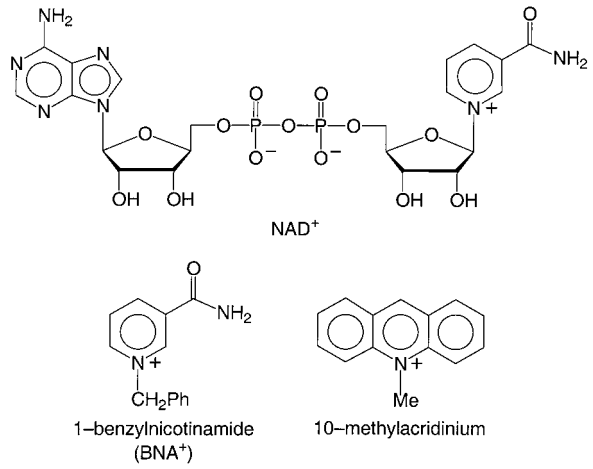

Figure 1.

* To whom correspondence should be addressed. E-mail: parkin@chem.columbia.edu.

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(3) See, for example: Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Harlow, Essex, England, 1989.

(4) For a review of model studies employing nicotinamide derivatives, see: Yasui, S.; Ohno, A. *Bioorg. Chem.* **1986**, *14*, 70−96.

(5) For reduction of (BNA^+) with transition-metal hydride complexes, see: Kobayashi, A.; Takatori, R.; Kikuchi, I.; Konno, H.; Sakamoto, K.; Ishitani, O. *Organometallics* **2001**, *20*, 3361−3363.

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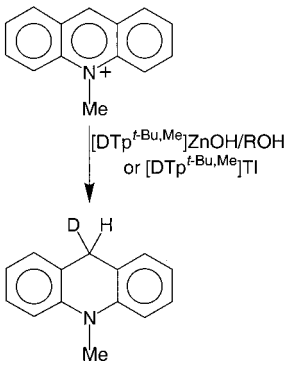
Scheme 1



rather ineffective, giving (BNA)H in only 14% yield, with the zinc complex being converted to the inactive chloride derivative $[Tp^{Cum,Me}]ZnCl$.[6] Kimura has examined the ability of $[(tacd)ZnOH]_3(TfO)_3 \cdot TfOH$ (tacd = 1,5,9-triazacyclododecane) as a reagent to mediate hydride transfer from Pr^iOH to (BNA)Cl but likewise observed only low conversion (17%), and the fate of the zinc complex was not addressed.[7]

In an effort to obtain a system that models quantitatively the hydride transfer step of the LADH catalytic cycle, we sought to employ substrates for which (i) the pyridinium nucleus is more susceptible to reduction and (ii) the counteranion shows a reduced tendency to coordinate to zinc, compared to that of chloride. Thus, we turned our attention to 10-methylacridinium perchlorate,[8] which would be expected to be more reactive than 1-benzylnicotinamide on the basis of its reduction potential: 10-methylacridinium (−0.43 V) and 1-benzylnicotinamide (−1.08 V).[9]

Indeed, 10-methylacridinium perchlorate was efficiently reduced to 10-methylacridan by solutions of $[Tp^{Bu^t,Me}]ZnOH$ in ROH (R = Me, Et, Pr^i) at 80 °C (Scheme 1).[10] While the formation of 10-methylacridan was encouraging, ^1H NMR spectroscopy indicated that the equilibrium mixture of $[Tp^{Bu^t,Me}]ZnOH$ and $[Tp^{Bu^t,Me}]ZnOR$ decomposed over the course of the reaction. Despite this decomposition, the yield of 10-methylacridan was ca. 85%, based on the amount of $[Tp^{Bu^t,Me}]ZnOH$ originally present.

An unanticipated result, however, was the observation that the reactions employing deuterated solvents, i.e. d^4-methanol, d^6-ethanol, and d^8-isopropanol, generate 10-methylacridan that is devoid of deuterium. Such absence of deuterium incorporation clearly calls into question the notion that the reduction of 10-methylacridinium in this system could involve hydride transfer via a zinc alkoxide complex with a mechanism analogous to that employed by LADH. Since $[Tp^{Bu^t,Me}]ZnOH$ and $[Tp^{Bu^t,Me}]ZnOR$ decomposed during the reaction, it was postulated that the B−H group could be the hydride source. Indeed, after this group was selectively labeled with deuterium, the reaction of $[DTp^{Bu^t,Me}]ZnOH$ with 10-methylacridinium perchlorate in protioethanol generated 10-methylacridan with deuterium located in the methylene group (Scheme 1), as demonstrated by NMR spectroscopy. Further evidence that the alcohol plays no significant role in the reduction of 10-methylacridinium is provided by the observation that treatment of 10-methylacridinium perchlorate with $[Tp^{Bu^t,Me}]ZnOH$ in d^8-THF also generates 10-methylacridan. Likewise, evidence that the zinc plays no significant role and that the reduction centers on the reactivity of the B−H bond is provided by the observation that the thallium complex $[Tp^{Bu^t,Me}]Tl$ is also able to perform the hydride transfer under similar conditions (Scheme 1). We therefore speculate that the mechanism involves hydride transfer from the $[Tp^{Bu^t,Me}]^-$ ligand[11] to 10-methylacridinium to generate 10-methylacridan and $B(pz^{Bu^t,Me})_3$; proteolytic cleavage of $B(pz^{Bu^t,Me})_3$ with ROH would be expected to release the pyrazole, $Hpz^{Bu^t,Me}$.

While hydride transfer from the $[Tp^{R,R'}]$ ligand is not of relevance to the catalytic cycle of LADH, it is of interest because it is an unprecedented form of reactivity for the ubiquitous $[Tp^{R,R'}]$ ligand system,[12,13] despite the well-known ability of borohydride derivatives to act as reducing agents.[14] Undoubtedly the observation that $[Tp^{R,R'}]$ ligands do not generally act as hydride donors is a result of the steric bulk around boron in such species.[15,16]

A more dramatic illustration of the $[Tp^{Bu^t,Me}]$ ligand to participate in hydride transfer reactions is provided by the reactivity of $\{[Tp^{Bu^t,Me}]Zn(OH_2)\}[HOB(C_6F_5)_3]$[17] towards alcohols. Specifically, ^1H NMR spectroscopy demonstrates that dissolution of $\{[Tp^{Bu^t,Me}]Zn(OH_2)\}[HOB(C_6F_5)_3]$ in CD_3OD results in the immediate generation of $[Tp^{Bu^t,Me}]ZnH$[18] and $Hpz^{Bu^t,Me}$ (Scheme 2).[19] The formation of the zinc hydride

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(10) It should be noted that solutions of 10-methylacridinium in methanol generate 9-methoxy-10-methyl-9,10-dihydroacridine in the presence of $[Tp^{Bu^t,Me}]ZnOH$, analogous to its formation in the presence of NaOH. See: Ivanov, G. E.; Izmail'skii, V. A. *Chem. Heterocycl. Compd.* **1970**, *6*, 1045−1047.
(11) The transfer could occur from either a coordinated or dissociated $[Tp^{Bu^t,Me}]^-$ ligand.
(12) (a) Trofimenko, S. *Scorpionates: The Coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press: London, 1999. (b) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943−980.
(13) Hydride transfer and B−H insertion reactions of bis(pyrazolyl)hydroborato derivatives are, nevertheless, known. See, for example: (a) Gorrell, I. B.; Looney, A.; Parkin, G.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 4068−4069. (b) Looney, A.; Han, R. Y.; Gorrell, I. B.; Cornebise, M.; Yoon, K.; Parkin, G.; Rheingold, A. L. *Organometallics* **1995**, *14*, 274−288. (c) Dowling, C.; Parkin, G. *Polyhedron* **1996**, *15*, 2463−2465. (d) Ghosh, P.; Parkin, G. *J. Chem. Soc., Chem. Commun.* **1998**, 413−414. (e) Paolucci, G.; Cacchi, S.; Caglioti, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1129−1131.
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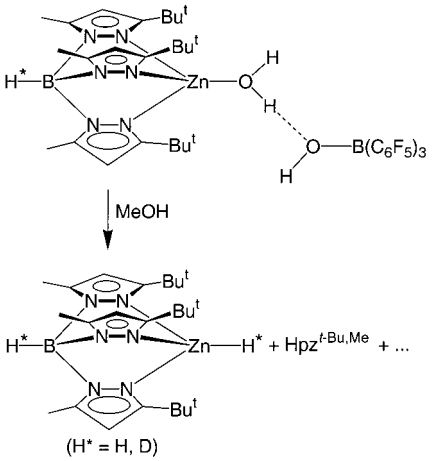
(15) Decomposition of tris(pyrazolyl)hydroborato ligands due to cleavage of B−N bonds, forming pyrrole, is certainly precedented. See for example: (a) Chia, L. M. L.; Radojevic, S.; Scowen, I. J.; McPartlin, M.; Halcrow, M. A. *J. Chem. Soc., Dalton Trans.* **2000**, 133−140 and references therein. (b) Cano, M.; Campo, J. A.; Heras, J. V.; Pinilla, E.; Rivas, C.; Monge, A. *Polyhedron* **1994**, *13*, 2463−2465.
(16) For an interesting example of B−H bond activation in a ruthenium tris(2-mercapto-1-methylimidazolyl)hydroborato complex, see: Hill, A. F.; Owen, G. R.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2759−2761.
(17) Bergquist, C.; Parkin, G. *J. Am. Chem. Soc.* **1999**, *121*, 6322−6323.
(18) $[Tp^{Bu^t,Me}]ZnH$ has been prepared independently.[2a]

Scheme 2



complex [Tp$^{Bu^t,Me}$]ZnH is most significant, especially considering that it is formed in a protic medium.[20] Deuterium labeling studies confirm that the source of the hydride ligand attached to zinc is the B−H group. Thus, deuterium incorporation into the zinc hydride site does not result when {[Tp$^{Bu^t,Me}$]Zn(OD$_2$)}[DOB(C$_6$F$_5$)$_3$] is dissolved in CD$_3$OD, whereas dissolution of [DTp$^{Bu^t,Me}$]Zn(OH$_2$)}[HOB(C$_6$F$_5$)$_3$] yields [DTp$^{Bu^t,Me}$]ZnD, as demonstrated by both ^{1}H and ^{2}H NMR spectroscopy.

Although sufficient data are not available to define a mechanism for the formation of the zinc hydride complex, we postulate that alcohol solvation disrupts the hydrogen-bonding interaction within {[Tp$^{Bu^t,Me}$]ZnOH$_2$}[HOB(C$_6$F$_5$)$_3$] and the resulting cationic {[Tp$^{Bu^t,Me}$]ZnOH$_2$}$^+$ species, or possibly {[Tp$^{Bu^t,Me}$]Zn}$^+$, scavenges hydride from a [Tp$^{Bu^t,Me}$]$^-$ ligand,[11] thereby resulting in the formation of [Tp$^{Bu^t,Me}$]ZnH with the sacrificial decomposition of a [Tp$^{Bu^t,Me}$]$^-$ ligand.

In conclusion, solutions of the zinc hydroxide complex [Tp$^{Bu^t,Me}$]ZnOH in alcohols achieve hydride transfer to the NAD$^+$ model, 10-methylacridinium perchlorate. However, the source of the hydride is not the alcohol but, rather, the B−H group of the [Tp$^{Bu^t,Me}$] ligand. A further example in which a [Tp$^{Bu^t,Me}$] ligand acts as a hydride donor is provided by the reaction of the aqua complex {[Tp$^{Bu^t,Me}$]Zn(OH$_2$)}-[HOB(C$_6$F$_5$)$_3$] with methanol to generate the zinc hydride complex [Tp$^{Bu^t,Me}$]ZnH. The present study therefore provides a caveat for the often assumed inertness of such ligands towards hydride transfer, especially in the presence of reactive cationic species, as exemplified by 10-methylacridinium and {[Tp$^{Bu^t,Me}$]Zn(OH$_2$)}$^+$. For this reason, alkyl-substituted ligands of the type [RTp$^{R,R'}$][21] are going to play a more important role in studying the chemistry of highly electrophilic systems.

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Supporting Information Available: Text giving experimental details and figures giving NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) [Tp$^{Bu^t,Me}$]ZnH and Hpz$^{Bu^t,Me}$ are formed in an approximately 1:3 ratio, consistent with hydride abstraction resulting in complete decomposition of a [Tp$^{Bu^t,Me}$] ligand. An unidentified pyrazolyl-containing species, possibly {[Tp$^{Bu^t,Me}$]Zn(OH$_2$)}$^+$ or {[Tp$^{Bu^t,Me}$]Zn(ROH)}$^+$, is also present initially. Over a period of hours, small quantities of [Tp$^{Bu^t,Me}$]-ZnF are generated as the mixture containing [HOB(C$_6$F$_5$)$_3$]$^-$ decomposes. Although the initial formation of [Tp$^{Bu^t,Me}$]ZnH is fast, further conversion is slow, possibly due to pyrazole coordination to zinc, thereby tempering its hydride-abstracting capability. For the synthesis of [Tp$^{Bu^t,Me}$]ZnF, see: Kläui, W.; Schilde, U.; Schmidt, M. *Inorg. Chem.* **1997**, *36*, 1598−1601.

(20) [Tp$^{Bu^t,Me}$]ZnH does, nevertheless, react with ROH in benzene solution at elevated temperatures to yield [Tp$^{Bu^t,Me}$]ZnOR. For example, the reaction between [Tp$^{Bu^t,Me}$]ZnH and methanol in benzene solution takes 3 days at 120 °C for completion.[2a]

(21) See, for example: (a) Kisko, J. L.; Fillebeen, T.; Hascall, T.; Parkin, G. *J. Organomet. Chem.* **2000**, *596*, 22−26. (b) Kisko, J. L.; Hascall, T.; Kimblin, C.; Parkin, G. *J. Chem. Soc., Dalton Trans.* **1999**, 1926−1935.