Lewis Acid Catalysis in Heterolysis Reactions of Glycol Ether Radicals Mimicking Diol Dehydratase-Catalyzed Reactions
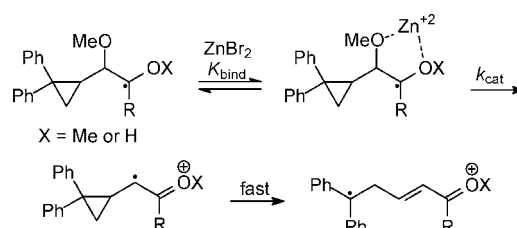
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ABSTRACT

Zinc bromide-catalyzed heterolysis reactions of glycol ether radicals were studied by laser flash photolysis methods, which gave the binding constants and catalytic rate constants for fragmentation. The Lewis acid-catalyzed heterolysis reactions mimic a putative reaction pathway in diol dehydratase-catalyzed reactions and are potentially useful polar processes for incorporation into conventional radical chain reaction sequences.

Coenzyme B_{12}-dependent diol dehydratase enzymes catalyze the conversion of a glycol to an aldehyde plus water via radical intermediates.[1,2] The reaction sequence (Scheme 1)

Scheme 1
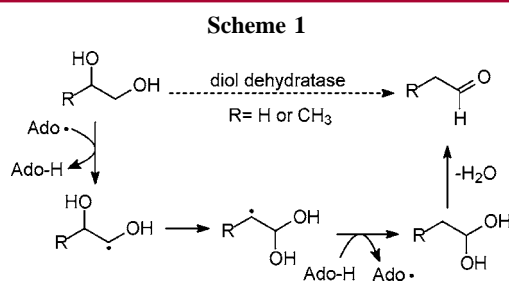
is a radical nonchain process initiated by homolysis of the Co−C bond in coenzyme B_{12} (Ado-Cbl) to give the 5′-deoxyadenosin-5′-yl radical (Ado•). H-atom abstraction from glycol substrate by Ado•, rearrangement of the glycol radical to a β,β-dihydroxyalkyl radical, and H-atom transfer from 5′-deoxyadenosine gives a closed-shell aldehyde hydrate and Ado•, which recombines with cobalt to regenerate coenzyme B_{12}. The aldehyde hydrate subsequently dehydrates to give the aldehyde product.

Although specific acid catalysis of glycol radical reactions has been known for decades,[3,4] the mechanistic details of the conversion of the glycol radical to the β,β-dihydroxyalkyl radical in diol dehydratase enzymes are not known.[1,2] The hydroxy group migration could occur in a concerted process or by heterolytic fragmentation of the β-hydroxy group to give hydroxide and an intermediate radical cation that subsequently collapse to give the β,β-dihydroxy radical. Irrespective of the mechanism, the rearrangement of a glycol

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radical to an aldehyde hydrate radical appears to have attractive potential in the context of synthetic analogues. Specifically, conversions of glycol ether radicals to acetal radicals or their equivalents might be useful additions to radical-based synthetic methodology.
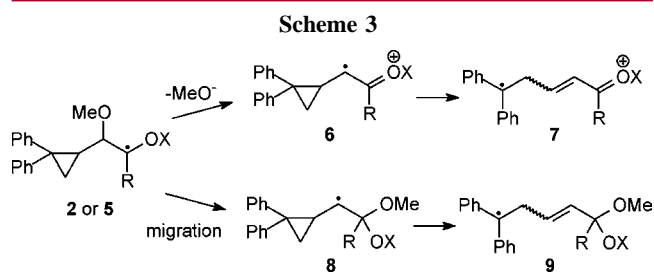
Potassium ion or other Lewis acids are essential for coenzyme B_{12}-dependent diol dehydratase,[5,6] and X-ray crystal structures of a resting enzyme with bound substrate show that potassium is complexed to both hydroxy groups of glycol.[7] The structure suggests that the Lewis acid has a catalytic role in the enzyme, serving to stabilize hydroxide in a fragmentation reaction. This possible reaction pathway inspired us to study Lewis acid catalysis of radical reactions of glycol ether radicals, and we report here $ZnBr_2$-catalyzed radical heterolysis reactions that mimic the putative fragmentation step of diol dehydratase.

We studied the models for glycol radicals shown in Scheme 2 in laser flash photolysis (LFP) experiments. The

Scheme 2
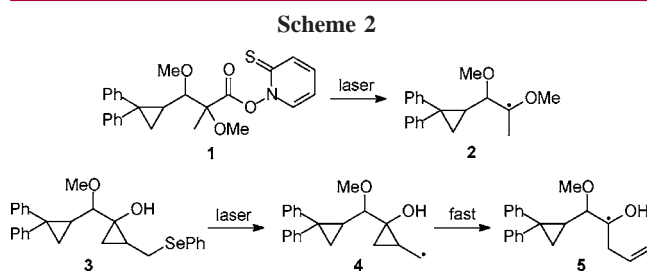
α,β-dimethoxy radical **2** was produced by 355 nm photolysis of the PTOC ester precursor **1**,[8,9] which gave an acyloxyl radical that rapidly decarboxylated to give radical **2**.[10] The α-hydroxy-β-methoxy radical **4** was formed from phenylselenyl precursor **3** by 266 nm photolysis to give cyclopropylcarbinyl radical **4** that rearranged to radical **5** in a fast ($k \approx 10^{10}$ s^{-1})[11,12] fragmentation reaction.

Radicals **2** and **5** contain diphenylcyclopropane reporter groups for UV detection.[13] Heterolysis of the β-methoxy group in these radicals will give radical cation products (**6**) that are expected to fragment rapidly to UV-detectable distonic radical cations **7** (Scheme 3). This heterolysis reaction sequence is known to occur for radical **2** in general acid-catalyzed reactions.[10] Alternatively, a migration reaction

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(8) Acronym PTOC is for pyridine-2-thioneoxycarbonyl. PTOC esters were originally developed by Barton's group and are also known as Barton esters.[9]

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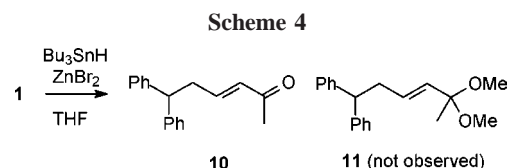
Scheme 3

in radicals **2** and **5** would give radicals **8**, which are expected to ring open to radicals **9** with rate constants of $k \approx 5 \times 10^{11}$ s^{-1}.[14]

When radical **2** was produced in the absence of a catalyst in various solvents, no signal from product radical **7** was observed.[10] In acetonitrile or in THF with $ZnBr_2$ added, however, results such as those shown in Figure 1A were
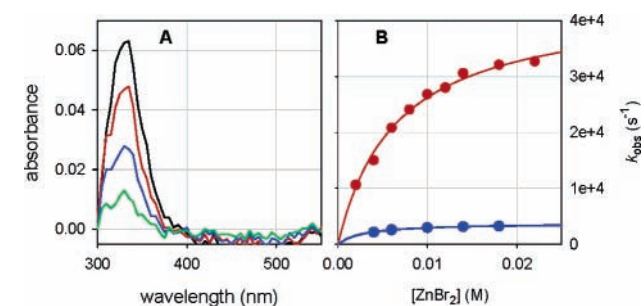
Figure 1. (A) Time-resolved growth spectrum from reaction of radical **2** in CH_3CN containing 0.01 M $ZnBr_2$. (B) Observed rate constants for reactions of **2** in CH_3CN (red) and in THF (blue) in the presence of $ZnBr_2$; the lines are fits for the binding constants and catalytic rate constants listed in the text. For the THF results, the concentrations of $ZnBr_2$ are 10 times the actual concentrations.

obtained. The growing signal with $\lambda_{max} \approx 335$ nm is consistent with that expected for distonic radical cation **7** and quite similar to that observed from **2** in Brønsted acid-catalyzed heterolysis reactions.[10] The heterolysis reaction of radical **2** was confirmed by conducting preparative reactions with **1** in THF with 0.01 M $ZnBr_2$ and Bu_3SnH or octadecane-1-thiol. The α,β-unsaturated ketone **10** and 1,2-dimethoxy-1-(2,2-diphenylcyclopropyl)propane (from reduction of radical **2**) were found in ca. 70% GC yield for the thiol reaction (Scheme 4).

Scheme 4

Acetal **11** was not observed in the preparative reactions, although an authentic sample of **11** was adequately stable

to survive the reaction conditions. This result demonstrates that the reaction involves the heterolysis pathway in Scheme 3 instead of the concerted migration reaction, but it does not permit a complete mechanistic description. Specifically, we cannot determine whether radical cation **6** (X = Me) has a finite lifetime. As an alternative, it is possible that distonic radical cation **7** (X = Me) is formed directly in the Lewis acid-catalyzed heterolysis reaction of **2** by simultaneous cleavage of two bonds.

Kinetic results for radical **2** in acetonitrile and in THF are shown in Figure 1B. The increase in the rate constant for reaction as a function of $ZnBr_2$ concentration shows saturation kinetics behavior consistent with reaction as shown in Scheme 5. Solution of the data by nonlinear regression

Scheme 5
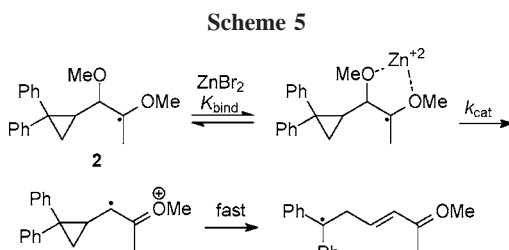
analysis according to eq 1 gave $K_{bind} = 150$ M^{-1} and $k_{cat} = 4.3 \times 10^4$ s^{-1} for reactions in CH$_3$CN. In THF, the data gave $K_{bind} = 3500$ M^{-1} and $k_{cat} = 5 \times 10^3$ s^{-1}.

$$k_{obs} = (k_{cat}K_{bind}[ZnBr_2])/(K_{bind}[ZnBr_2] + 1) \quad (1)$$

The LFP rate constant for heterolysis of the complex of radical **2** in THF was corroborated in an indirect kinetic study.[15] Reaction of PTOC ester **1** in THF with 0.01 M $ZnBr_2$ and 2.5 mM octadecanethiol gave a 40:60 mixture of **10** and 1,2-dimethoxy-1-(2,2-diphenylcyclopropyl)propane. At this concentration of $ZnBr_2$, radical **2** is effectively completely complexed with zinc ion. The rate constant for thiol trapping of the complexed radical is likely to be different than that for reaction of the uncomplexed radical, but, if one assumes that it is not and uses the rate constant for reaction of an α,β-dimethoxy radical with the thiol in THF ($k_H = 2.1 \times 10^6$ M^{-1} s^{-1}),[16] then the rate constant for heterolysis of the $ZnBr_2$ complex of **2** is $k_{cat} \approx 3.5 \times 10^3$ s^{-1}. Alternatively, if the LFP rate constant for heterolysis of the complex is used as the basis rate constant, the calculated rate constant for reaction of the thiol with the $ZnBr_2$ complex of **2** is $k_H \approx 3 \times 10^6$ M^{-1} s^{-1}.

Radical **5** behaved much like radical **2** in CH$_3$CN. No reaction was observed in the absence of catalyst, but reaction was apparent in CH$_3$CN with $ZnBr_2$ present (Figure 2A). The data shown in Figure 2A gives $K_{bind} = 1000$ M^{-1} and
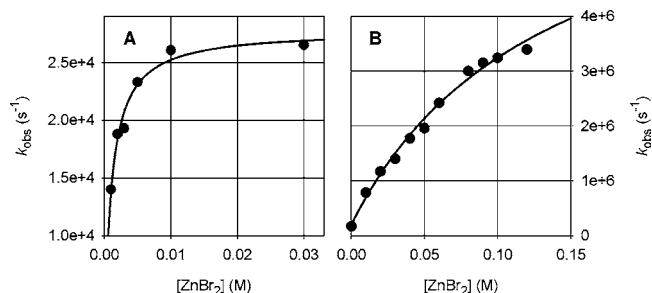
Figure 2. Rate constants for reactions of radical **5** in acetonitrile (A) and for reactions of radical **12** in THF (B); the lines are fits for the binding constants and kinetic values given in the text.

$k_{cat} = 2.8 \times 10^4$ s^{-1}, but we note that the reaction of **5** was suppressed by up to a factor of 2 at higher concentrations of $ZnBr_2$.

Zinc bromide also catalyzed heterolysis of the acetate group in radical **12**. Radical **12** was previously found to react by heterolysis in various organic solvents without catalysts.[10] In THF containing $ZnBr_2$, however, the reaction clearly was catalyzed (Figure 2B). Solution of the data in Figure 2B according to eq 2 gave $K_{bind} = 7.5$ M^{-1}, $k_{cat} = 7.3 \times 10^6$ s^{-1}, and $k_{uncat} = 2 \times 10^5$ s^{-1}. The rate constant found for the uncatalyzed reaction of **12** in THF by this analysis is the same as that previously reported for the uncatalyzed heterolysis.[10]

$$k_{obs} = (k_{uncat} + k_{cat}K_{bind}[ZnBr_2])/(K_{bind}[ZnBr_2] + 1) \quad (2)$$

12
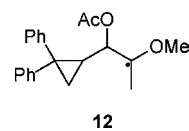
The $ZnBr_2$-catalyzed reaction of **2** appears to display environment effects that are typical for radical heterolysis reactions. The ca. 1 order of magnitude difference in rates for reaction in the modest polarity solvent THF and the medium polarity solvent CH$_3$CN is similar to solvent effects found in heterolysis reactions that give styrene radical cations,[17,18] enol ether radical cations,[19] and alkene radical cations,[20] although relatively stable anionic leaving groups were involved in these reactions. Rate constants for other radical heterolysis reactions correlate with $E_T(30)$ solvent polarity values;[21] if the same holds for $ZnBr_2$-catalyzed heterolysis of methoxide in radical **2**, then the reaction would be expected to have a rate constant of $k_{cat} \approx 1 \times 10^6$ s^{-1} in

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an environment as polar as water, whereas the rate constant in a hydrocarbon solvent would be $k_{cat} \approx 1000$ s^{-1}.

The cyclopropane reporter group in radical **2** has an accelerating effect on heterolysis reactions that is similar to the effects of cyclopropanes in heterolysis reactions of closed-shell molecules. Specifically, when the same reporter group was used in an alkyl radical with a β-phosphate leaving group, the rate of heterolysis was accelerated by a factor of 35 in comparison with that for reaction of an alkyl radical lacking the cyclopropane reporter.[20] Thus, the ZnBr$_2$-catalyzed heterolysis of an α,β-dimethoxy radical without the cyclopropyl reporter group is expected to have a rate constant in the range of 1000−2000 s^{-1} in moderately polar solvents such as acetonitrile and a rate constant exceeding 1 × 10^4 s^{-1} in highly polar media.

Lewis acid catalysis of aminyl radical reactions via complexation at the radical center is known,[22] and Lewis acid catalysis of radical reactions by complexation of a molecule that reacts with a radical is possible.[23] Lewis acids also have been used to influence the stereochemical outcome of radical homolytic substitution reactions, and the Lewis acids appear to catalyze these reactions.[24−27] The ZnBr$_2$

catalysis studied in this work is different in that it results from stabilization of ionic leaving groups in heterolytic radical reactions.

Radical heterolysis reactions involving relatively stable anionic leaving groups have been incorporated into radical chain reaction sequences and display attractive synthetic potential.[28−31] It is possible that related Lewis acid-catalyzed radical heterolysis reactions can be developed, where the leaving group is an inherently stable ether. In a similar manner, Lewis acid catalysis of the acetate fragmentation in radical **12** suggests a potential utility in catalyzing polar reactions of radicals with modestly reactive leaving groups. In regard to the radical rearrangement in diol dehydratase that inspired this study, the demonstration of Lewis acid catalysis in the heterolysis reactions studied here supports the putative reaction pathway involving potassium ion-catalyzed heterolysis.

Supporting Information Available: Experimental details, kinetic data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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