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Exploiting the Curtin–Hammett Principle—Recognition-Mediated Acceleration of an Aldol Reaction

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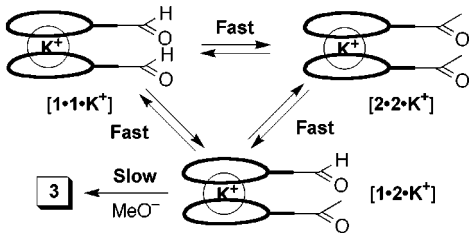
ABSTRACT



Curtin–Hammett–Winstein–Holness kinetics are exploited in the acceleration of the aldol reaction between formylbenzo-15-crown-5 and acetylbenzo-15-crown-5. Potassium cations facilitate this acceleration through the fast, reversible formation of a 1:1:1 sandwich complex between the crown ethers and the metal cation.

The emulation of some of the catalytic efficiency and selectivity of enzymes[1] remains a long-term goal for the supramolecular chemist. Over the past 20 years, a wide range of enzyme mimics[2] have appeared in the literature, many of which are based on the ability of crown ethers to bind cations strongly and selectively. We have become interested in exploiting recognition processes to accelerate and direct the outcome of chemical reactions. Our previous work[3] has focused on the use of recognition sites located on the two reactive partners that allow the formation of a reactive complex in which the reaction becomes pseudointramolecular. Recently, we identified an alternative approach (Figure 1) to the question of recognition-mediated acceleration of chemical reactions. Rather than locating complementary recognition sites on the reactive partners **A** and **B**, we can rely on a cofactor **C**, which is capable of forming the 1:1:1 complex [**A**·**B**·**C**], to assemble the reagents in a reactive complex. The formation of this complex renders the reaction between **A** and **B** pseudointramolecular, and hence, we might expect significant rate acceleration[4] through its formation.

The approach shown in Figure 1 relies on the ability of the cofactor **C** to form the 1:1:1 complex [**A**·**B**·**C**]. This requirement places constraints on the recognition motifs that can be used in this approach. The formation of 2:1 sandwich complexes[5] between benzo-15-crown-5 derivatives and potassium cations is well established. Therefore, we identified the base-catalyzed aldol reaction between formylbenzo-15-

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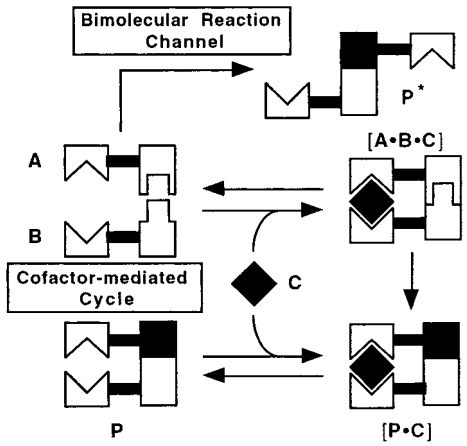
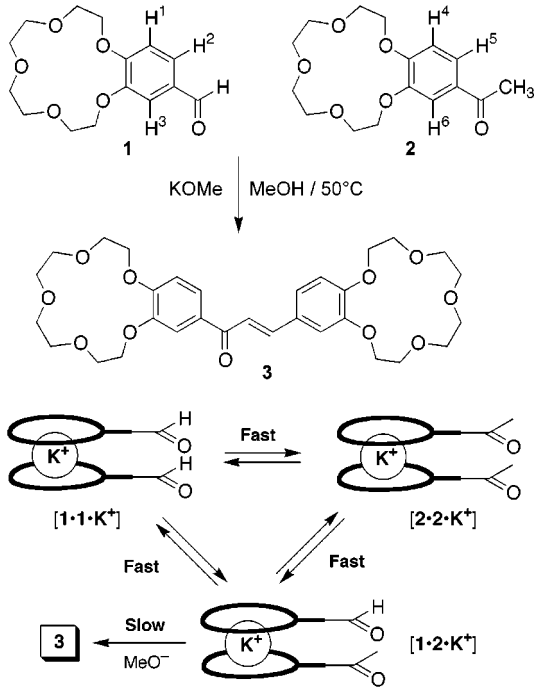


Figure 1. The reaction of **A** and **B** occurs either via the bimolecular reaction channel or by a cofactor-mediated cycle. In principle, these two pathways can lead to products **P** and **P*** with different regio- and/or stereochemistry.

crown-5 **1** and acetylbenzo-15-crown-5 **2** (Scheme 1) as being suitable for investigating the effectiveness of rate acceleration through the mechanism shown in Figure 1.

In order for this approach to be successful, it is essential that the various complexes formed between the crown ether and the potassium cation are in fast exchange. If this condition is met, then Curtin−Hammett type kinetics[6] will operate and the reaction will occur through the $[\mathbf{1}\cdot\mathbf{2}\cdot\mathbf{K}]^+$ complex only. This behavior obviates any requirement that the reactive complex, in this case $[\mathbf{1}\cdot\mathbf{2}\cdot\mathbf{K}]^+$, should be the dominant species in solution.

Scheme 1



To test this hypothesis, we synthesized **1** and **2** using standard procedures[7] and examined their reaction with each other in the presence of KOMe in methanol solution. First, however, we planned to establish (a) the existence of 2:1 complexes between the crown ethers **1** and **2** and potassium and (b) that these complexes were in fast exchange under the proposed reaction conditions.

Accordingly, we prepared solutions of **1**, **2**, and KBF_4 in methanol at varying stoichiometries. When the crown-to-metal ratio was 2:1, i.e., for $[\mathbf{1}_2\cdot K^+]$ and $[\mathbf{2}_2\cdot K^+]$, analysis of the samples by fast atom bombardment mass spectrometry[8] (FABMS) demonstrated the presence of species corresponding to $[\mathbf{1}_2\cdot K^+]$ and $[\mathbf{2}_2\cdot K^+]$. When a sample was prepared with a stoichiometry of 1:1:1 in respect of **1**, **2**, and KBF_4, FABMS analysis demonstrated that, in addition to the $[\mathbf{1}_2\cdot K^+]$ and $[\mathbf{2}_2\cdot K^+]$ complexes, the 1:1:1 complex $[\mathbf{1}\cdot\mathbf{2}\cdot K^+]$ was present in the sample.

In order for the Curtin−Hammett principle to be effective in this system, the existence of the complex is not sufficient. We must also demonstrate that the three complexes shown in Scheme 1, $[\mathbf{1}_2\cdot K^+]$, $[\mathbf{2}_2\cdot K^+]$, and $[\mathbf{1}\cdot\mathbf{2}\cdot K^+]$, have the desired sandwich-type structures and that they are in fast exchange. Therefore, 300 MHz ^{1}H NMR spectroscopy was employed to assess these factors. The addition of 0.25, 0.50, and 1.00 molar equiv of KBF_4 to a solution of **1** and **2** in d_4-MeOH resulted in significant changes in the chemical shifts of the six aromatic proton resonances (H^1 through H^6, Scheme 1). Significantly, at all concentrations of K^+, the observed chemical shift changes (Figure 2) were *upfield* shifts. This

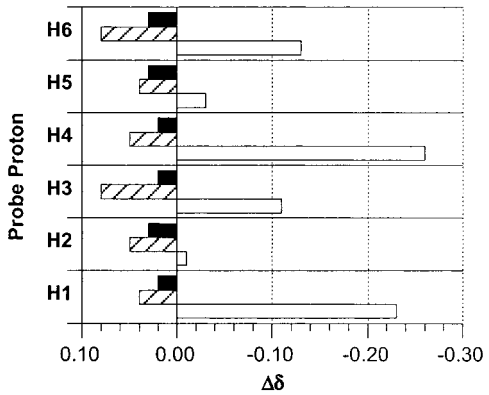


Figure 2. Chemical shift changes observed on addition of 1.00 equiv of KBF_4 (unfilled bars), $LiBF_4$ (hatched bars), or $NaBF_4$ (filled bars) to solutions containing equimolar quantities of **1** and **2** in d_4-MeOH at room temperature. Values of $\Delta\delta$ that are *negative* indicate that the resonance is shifted *upfield* on addition of the salt. Probe proton labels are given in Scheme 1.

pattern of chemical shift changes suggests strongly that the aromatic rings present in **1** and **2** are stacked in a parallel fashion with respect to one another in a sandwich-type arrangement.

(6) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (c) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.

In contrast, when an identical experiment was performed with either $LiBF_4$ or $NaBF_4$, the pattern of chemical shift change was entirely different (Figure 2). In this case, all six aromatic resonances are shifted *downfield*, consistent with the deshielding effect of the electrophilic cation.

It was also apparent that the addition of KBF_4 did not result in the observation of separate resonances corresponding to the bound and the unbound species, although they must both be present in solution. This strongly suggests that all of the complexes present in solution must be exchanging at a rate faster than the ^1H NMR time scale, and hence, a time-averaged spectrum is observed. These observations demonstrate that the exploitation of Curtin−Hammett−Winstein−Holness kinetics in this system will be possible if the rate of the aldol reaction is much slower than the rate of exchange between the complexes shown in Scheme 1.

4 **5**

A series of experiments was performed to assess the effect that the recognition process has on the rate of the base-catalyzed reaction between **1** and **2**. Optimum reaction conditions were determined to be at a concentration of 25 mM with respect to **1**, **2**, and KOMe, at a temperature of 50 °C in d_4-methanol. The course of the reaction was followed by 400 MHz ^1H NMR spectroscopy, and the product concentration ((a), Figure 3) calculated by the comparison of the deconvoluted area of the aldehyde resonance arising from **1**, centered on δ 9.76, with respect to a resonance arising from the product centered on δ 7.81. Additionally, control experiments were performed involving aldehyde **4** and acetophenone **5** ((c) and (d), Figure 3) and where the base used was LiOMe ((b) and (c), Figure 3) instead of KOMe.

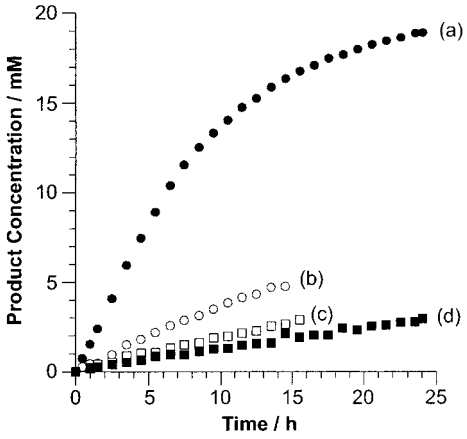


Figure 3. Concentration−time profiles for the reaction between (a) **1** and **2** in the presence of 1 equiv of KOMe, (b) the reaction between **1** and **2** in the presence of 1 equiv of LiOMe, (c) the reaction between **4** and **5** in the presence of 1 equiv of LiOMe, and (d) the reaction between **4** and **5** in the presence of 1 equiv of KOMe. All reactions were carried out in d_4-methanol at 50 °C at individual reagent concentrations of 25 mM.

It is clear that the reaction involving **1** and **2** proceeds at a far higher rate than any of the control reactions. However, it is also apparent that the reaction between **1** and **2** in the presence of LiOMe also displays a significant rate enhancement. We attributed this enhancement to an increase in basicity of the methoxide anion as a result of cation complexation by the crown ethers and to an enhancement of the electrophilicity of the aldehyde as a result of cation complexation. To test these hypotheses, additional cross control experiments were performed **(**Figure 4) under identical conditions to those employed previously.

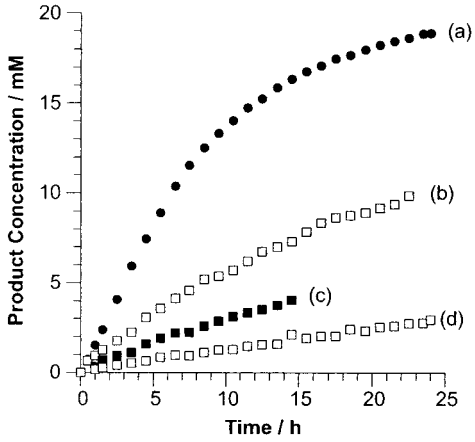


Figure 4. Concentration−time profiles for (a) the reaction between **1** and **2**, (b) the reaction between **1** and **4,** (c) the reaction between **2** and **5**, and (d) the reaction between **4** and **5**. All reactions were carried out in d_4-methanol at 50 °C in the presence of KOMe at individual reagent concentrations of 25 mM.

It is clear from the results presented in Figure 4 that the reactions in which one crown ether is present proceed at rates significantly higher than the reaction between **4** and **5**. The reaction between **1** and **5** proceeds at a faster rate than that between **2** and **4** as a result of the enhanced electrophilicity of **1** when bound to K^+. Although it is clear from these experiments that the reaction is fastest when a crown ether ring is present on both nucleophile and electrophile, thus facilitating the formation of the reactive [**1**·**2**·K^+] complex, it is not possible from these data to decide whether the rate enhancement observed is simply the sum of the increase in basicity and electrophilicity.

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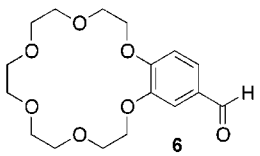
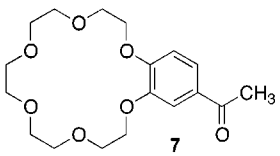
(8) FABMS analysis has been used previously in the study of bis(crown) complexes; see: Yamada, K.; Matsutani, S.; Uchiyama, A.; Takahashi, T. *J. Inclusion Phenom.* **1991**, *11*, 49.





To determine whether the observed rate enhancement is, in fact, simply an additive effect, we performed reactions involving aldehyde **6** and acetophenone **7**. It is well-known[9] that benzo-18-crown-6 derivatives form 1:1 complexes with potassium cations. Therefore, if the rate enhancement observed in the reaction between **1** and **2** is simply an additive result of increased basicity and electrophilicity arising from cation complexation, then the reaction involving **6** and **7** should, in principle, exhibit the same rate enhancement. The reaction between **6** and **7** was performed at a concentration of 25 mM in d_4-methanol at 50 °C. Two equivalents of potassium cations are required to complex both crown ether rings. Hence, the reaction was performed in the presence of 25 mM KOMe and 25 mM KBF_4. The course of the reaction was followed by 400 MHz ^{1}H NMR spectroscopy, and the product concentration was determined as before. Although this reaction does proceed at an enhanced rate with respect to the control (Figure 5), the reaction proceeds at a much lower rate than that between **1** and **2** under identical conditions.

Hence, we can conclude that the majority of the rate enhancement observed in the reaction between **1** and **2** is the result of the formation of the reactive complex [**1**·**2**·K^+] within the rapidly equilibrating manifold of bis(crown) complexes shown in Scheme 1.

In summary, we have demonstrated the exploitation of the Curtin−Hammett principle, as applied to supramolecular assemblies, to achieve significant rate enhancement of chemical reactions. This work represents a proof of principle, and current developments in our laboratories focus on the development of other cofactor-based systems capable of generating stereo- and regiocontrol mediated by the cofactor and the immobilization of appropriate cofactors on solid supports.

(9) Bradshaw, J. S.; Izatt, R. M.; Yan, Z. *Chem. Rev.* **1994**, *94*, 939.

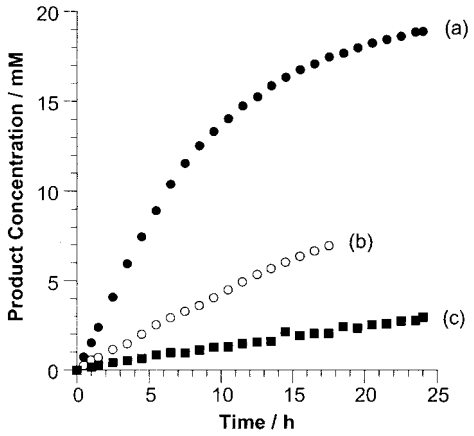


Figure 5. Concentration−time profiles for (a) the reaction between **1** and **2** in the presence of KOMe, (b) the reaction between **6** and **7** in the presence of 1 equiv of KOMe and 1 equiv of KBF_4, and (c) the reaction between **4** and **5** in the presence of 1 equiv of KOMe. All reactions were carried out in d_4-methanol at 50 °C at individual reagent concentrations of 25 mM.

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Supporting Information Available: FABMS data for the crown ether/K^+ sandwich complexes and spectroscopic data for compounds **1**, **2**, **3**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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