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Importance of Open Structure of Nonmetal Based Catalyst in Hydrogen Bond Promoted Methanolysis of Activated Amide: Structure Dynamics between Monomer and Dimer Enabling Recombinant Covalent, Dative, and Hydrogen Bonds

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The importance of an *opened structure* such as an open dimer or monomer in organometallic reactions is now gaining recognition among chemists.[1] Formation of open dimers from the more stable closed dimers (Figure 1, left) or releasing the monomers from those species is believed to be a key step to push forward chemical entities into a favorable transition state. However, the significance of such an open structure in metal-free catalysis, namely in hydrogen bond promoted catalysis, remains totally obscured.[2] We report here that the open structure is important for catalysis involving subtle interplay of multiple hydrogen bonds. Open structures were elaborated by controlling novel structural dynamics of aminoorganoboron (AOB) compounds[3] undergoing the monomer−recombinant dimer equilibrium (Figure 1, right).

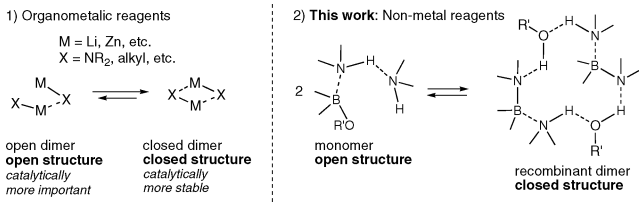
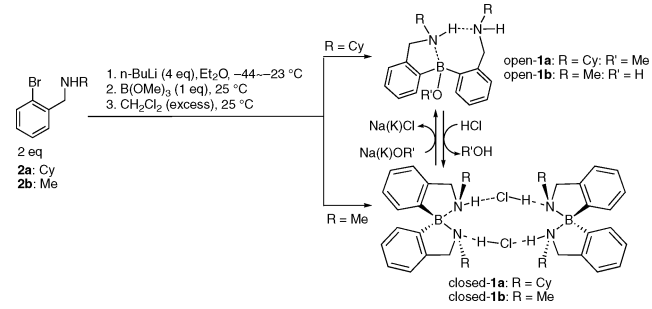


Figure 1. Open and closed structures of organometallic and non-metal reagents.

The AOB alkoxide open-**1a** was readily prepared by dilithiation of **2a** (2 equiv) with *n*-BuLi (4 equiv) in Et_2O at −44 °C for 1 h, followed by exposure to $B(OMe)_3$ (1 equiv). The resulting mixture was stirred at 25 °C for 12 h, during which time the mixture became a white suspension. Making a clear solution by adding excess CH_2Cl_2, followed by treatment with hexane, immediately produced a white precipitate in ∼40% yield (Scheme 1), which was filtrated and recrystallized from $CHCl_3$/MeOH cosolvents. The obtained single crystal was subjected to XRD analysis, showing a novel structure of open-**1a**,[4] in which the multiple elements were arranged linearly within the structure (opened array) delineated as $O(\delta^-)-B(\delta^+)$--$N(\delta^-)-H(\delta^+)$--$N(\delta^-)-H(\delta^+)$ (−: covalent bond; --: noncovalent bond, in a canonical structure). The alternating array of two different bonds, namely covalent and noncovalent bonds, was another characteristic feature. This structure recalls, for example, the open dimer of lithium diisopropylamide (LDA) that should assume a transition structure during deprotonation of the α-proton of carbonyl compounds, in which the interacting elements make a similar alignment of different bonds alternating as $(\alpha\text{-C})(\delta^-)-H(\delta^+)$--$N(\delta^-)-Li(\delta^+)$--$N(\delta^-)-Li(\delta^+)$.[1c] Of note is that alternations of acid(δ^+)/base(δ^-) elements and covalent/noncovalent bonds were both embedded into the structure of a single molecule open-**1a**, being isolated as a monomer.

In contrast, if we followed the experimental procedure[5] upon reaction of **2b** with $B(OMe)_3$ (Scheme 1), closed-**1b** was obtained in ∼20% yield representing an entirely different structure, disclosed by the XRD analysis.[4] The 12-membered heterocycle comprises multiple hydrogen bonds, in which two N−B--N−H residues make linkages with two HCl molecules, forming a dimer, closed-**1b**. The dimer adopts two boron-centered spiro structures, interacting in a manner to make a mirror image. The heterochiral *R* and *S* interaction has been commonly observed in chiral organometallic compounds.[6]

Scheme 1



What we envisaged from these two different structures, open- and closed-**1a** (or **1b**), was that these two would be interchangeable by altering acidic or basic environments in their solution state (Scheme 1). Indeed, by adding NaOMe (1 equiv) to a CH_3OH solution of closed-**1a**, the structure immediately returned to open-**1a** accommodating >99% conversion of closed-**1a**. In contrast, when open-**1a** was treated with 1 equiv of HCl in CD_3Cl at 25 °C, structural change completed within a few seconds, forming the structure closed-**1a**, ascertained by ^1H and ^{13}C NMR analysis.[4] Reversible change was controllable by merely supplying either acid or base! Analogously, addition of KOH to a H_2O solution of closed-**1b** afforded open-**1b** as the sole product. Going back and forth among these structural changes, covalent, dative, and hydrogen bonds were cleaved and/or reorganized.[7]

Further experiments demonstrated that either an open or a closed structure was formed preferentially when a subtle modification of the basicity of phenoxides (thus pK_a of phenol) was adjusted upon reaction with closed-**1b** (Scheme 2). For example, predominant formation of open-**4a** was detected by ^1H NMR analysis using Na-**3a** (closed/open = 4:96; [**4a**] = ca. 40 mM), whereas closed-**4g**[8] was formed preferentially with Na-**3g** (closed/open = ca. 60:40). More precise switching of phenoxides through Na-**3b** to Na-**3f**, which were derived from the parent phenols of an inherent pK_a in

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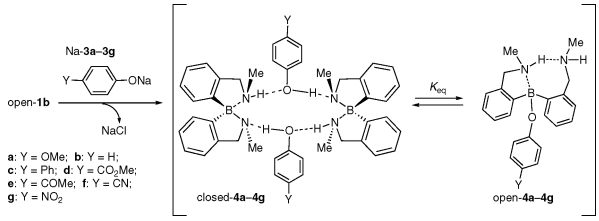
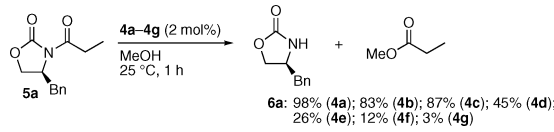
H_2O ranging from 7.15 to 10.21,[9] affected the dynamic behavior yielding a mixture of two structures open- and closed-**4** in a different ratio.[4] A Hammett plot of the logarithm of equilibrium constant K_{eq} ([open-**4**]/[closed-**4**]) vs the σ_p^- parameters for the substituents of phenols was approximately linear and yielded a negative ρ-value of -1.12 (Figure 2a). It is obvious that the ratio of the dynamic structures is proportional to the pK_a of phenols. The more basic the phenoxide, the more stable the open structure. We next attempted the methanolysis of Evans's *N*-acyl oxazolidinone **5a**[10] as a model reaction to see any differences in catalytic activity among a series of AOB phenoxides **4a**−**4g** (Scheme 3). Plotting the logarithm of the relative apparent rate ([**6a**(%)]/[**6a**(%) with **4b**] calculated from isolated yields of **6a** after reacting **5a** for 1 h at 25 °C in MeOH; [**4a**] = ca. 10 mM) vs log K_{eq} conformed again to a linear free-energy relationship, suggesting that open-**4** should be more responsible for a higher reaction rate (Figure 2b).

Scheme 2



Scheme 3



Methanolysis of aldol product **5b**[10] proceeded as well in the presence of 5 mol % of open-**1a** at −25 °C (pH = 7−8 in MeOH; [cat] = 25 mM) to give methyl ester **6b** in 90% yield without racemization (Scheme 4).[4] The cyclic structure and the chirality of oxazolidinone **6a** remained intact,[4] which was recovered in 91% yield. The cleavage

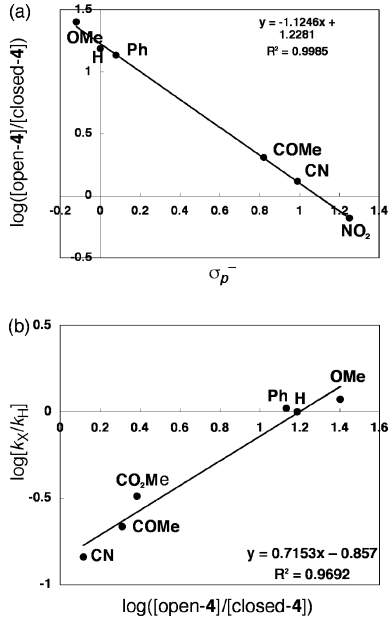
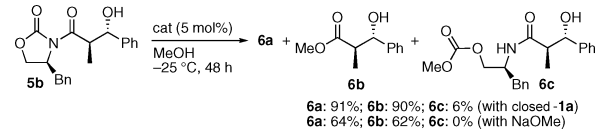


Figure 2. Linear free-energy relationships: (a) log K_{eq} vs σ_p^-; (b) log(relative apparent rate) vs log K_{eq}.

of the alternative amide bond of **5b** giving **6c** was reasonably prevented. This could be ascribed to the almost neutral pH conditions, and/or to some molecular recognition events, in which a specific functional group such as a β-dicarbonyl unit was favorably discriminated by very active species. In fact, more neutral catalyst open-**1a** gave a selectivity superior to NaOMe (5 mol %, pH = 9−10 in MeOH), which facilitated further fragmentation.

Scheme 4



In summary, we disclosed structural dynamics hidden behind a series of AOB compounds that involved a recombinant of covalent, dative, and hydrogen bonds. A combination process occurred via reorganizing elements and bonds between the two major structures open- and closed-**1** (or **4**), which were chemically switchable through precise adjustment of either acidic or basic conditions. The structural dynamics favoring an open structure seem to be more important for catalysis, as represented by the methanolysis of activated amides. Within the open structures, a linear alignment of alternating covalent and noncovalent bonds should be well organized in such a way that relatively acidic (δ^+) and basic (δ^-) elements can cooperate effectively in a transition state.

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Supporting Information Available: Full experimental details and ^1H, ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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