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Convergent Ditopic Receptors Enhance Anion Binding upon Alkali Metal Complexation for Catalyzing the Ritter Reaction

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Abstract

A supramolecular approach to catalyzing the Ritter reaction by utilizing enhanced anion-binding affinity in the presence of alkali metal cations was developed with ditopic hydrogen-bonded amide macrocycles. With prebound cations in the macrocycle, particularly Li⁺ ion, their metal complexes exhibit greatly enhanced catalytic activities. The catalysis is switchable by removal or addition of the bound cation. The method described in this work may be generalized for use in other anion-triggered organic reactions involving heteroditopic receptors capable of ion pairing.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03778. Experimental procedures, characterization of compounds **1a** and **1b**, and additional NMR, IR, and ESI-MS spectra (PDF)

The authors declare no competing financial interest.

The past decade has witnessed a growing wealth of ditopic receptors that are capable of cooperatively binding pairs of cations and anions.¹ Compared to a monotopic molecular receptor² that only recognizes a single ion, these receptors show enhanced binding affinity and selectivity, leading to interesting applications which include salt solubilization,³ extraction,⁴ ion-sensing, and transmembrane ion transport.⁵ So far, ion-pair binding has been explored in a variety of scaffolds including crown ethers,⁶ calix[4]pyrroles,⁷ and urea derivatives.⁸ In particular, hosts that utilize convergent binding sites have shown a significant increase in anion affinity and selectivity in the presence of alkali metal cations.⁹ While direct complexation of inorganic salts requires both ionic species to be bound to two specific sites, a cation-enhanced anion binding process involves addition of a metal cation first, followed by introduction of an external anionic guest to the core of the receptor system. This would be useful in catalyzing a reaction when the mechanism calls for anion sequestration. Despite many reports on research into enhanced anion binding in the presence of alkali metal ions with ditopic receptors,¹⁰ none of these have been developed for catalytic reactions.

Recently, anion-binding receptors have attracted particular interest in supramolecular catalysis.¹¹ Catalysts that require anion sequestration generally employ hydrogen-bonding interactions based on strongly polarized N–H,¹² O–H,¹³ aryl C–H¹⁴ and halogen bonds.¹⁵ Our previous work with hydrogen-bonded (H-bonded) amide macrocycles¹⁶ (Figure 1) showed that convergent heteroditopic cyclo[6]aramides¹⁷ were able to coordinate organic ion pairs. This is ascribed to a convergent binding site composed of two amide N–Hs and an aryl C–H serving as H-bond donors for anions and four amide carbonyl oxygens for cations. However, use of H-bonded aromatic amide macrocycles¹⁸ for binding anionic guests to achieve catalytic reactions has remained unknown.

Herein, we present a supramolecular strategy for catalysis of the Ritter reaction by using convergent H-bonded amide macrocycles as receptors with prebound alkali metal to enhance

anion affinity. Importantly, the catalytic process was found to be switchable in an on-and-off manner triggered by external addition of inorganic salts. To this end, two new ditopic receptors (**1a** and **1b**), bearing $-\text{NO}_2$ and $-\text{OMe}$ groups with contrasting electronic properties, were synthesized (Figures S1–S9). The anion-binding effect with the presence of alkali metal ions was probed first, followed by employing the cation complex of the heteroditopic receptors as anion-binding catalysts for promoting the Ritter reaction.

Anion affinity for halide guests (Cl^- , Br^- , and I^-) was initially determined (Figure 2) in the absence of alkali metal cations via ^1H NMR spectroscopy studies in a 1:1 solution of CDCl_3 and CD_3CN using tetrabutylammonium (TBA) salts, since TBA is too large to fit in the ditopic receptor binding pocket (Figure S11). Downfield shifting of amide NH (H_j) and aromatic ArH resonances (H_k) in receptor **1a** was observed only for Cl^- , while H-bond donor resonances remained unmoved upon addition of Br^- and I^- , indicating receptor selectivity toward Cl^- . As expected, receptor **1b** containing the electron-donating group (OMe) shows a relatively smaller chemical shift upon anion addition owing to the decreased acidity of amide protons (Figure S12). The receptors were also assessed for alkali metal ions Li^+ , Na^+ , and K^+ in the form of their perchlorate (ClO_4^-) and hexafluorophosphate (PF_6^-) salts (Figures S10 and S15–S17). The response to either anions or cations indicates site-specific binding by these convergent heteroditopic receptors.

Subsequently, anion-binding properties for halide guests were evaluated (Figure 2) in the presence of alkali metal cations. Addition of Br^- to a solution of **1a**· Li^+ in a 1:1 solution of CDCl_3 and CD_3CN leads to 0.66 and 0.61 ppm downfield shifts of H_j and H_k (Figure 2). Tests of **1b**· Li^+ with Br^- followed the same trend (Figure S14). Typically, shifting observed in the presence of Li^+ increases by over 6-fold compared to the shifting in the absence of these metal ions (Figure S13). This indicates that prebound metal cations can enhance the complexation of anions by these ditopic receptors. Recently, the Johnson and Haley groups also revealed a similar phenomenon with a phosphine oxide based ditopic receptor.¹⁹

To quantify the anion-binding ability of receptors **1a** and **1b** in the absence or presence of alkali metal cations, ^1H NMR spectroscopy titration experiments were performed in a 1:1 solution of CDCl_3 and CD_3CN and the downfield shifts of the amide resonances (H_j) were tracked after addition of TBA salts of the halides. The binding constants (Table 1 and Table S2) were determined by fitting to a 1:1 binding model for all experiments except for **1a**· Li^+ and **1b**· Li^+ binding with Br^- , which was fit to a 2:1 binding model²⁰ (Figures S18–S55).

The anions affinities for **1a**· Li^+ were determined using lithium perchlorate as a Li^+ source and yielded a noticeable increase in K_a for all of the halide anions in comparison to the metal-free system. The enhanced affinity afforded by the presence of Li^+ allowed for an accurate determination of the K_a of Cl^- ($K_a = 2300 \text{ M}^{-1}$), Br^- ($K_1 = 1100 \text{ M}^{-1}$, $K_2 = 55000 \text{ M}^{-1}$), and I^- ($K_a = 9800 \text{ M}^{-1}$), which are otherwise not observed in the absence of Li^+ salt. A 1:1 binding stoichiometry for Cl^- and Br^- in the presence of Na^+ and K^+ was derived from the ^1H NMR titration curves for **1a** and **1b** (Figures S24–S53). Furthermore, job plot experiments suggested a 2:1 stoichiometry between the complex of **1a**· Li^+ and Br^- (Figure S32).

While significant increases in K_a for Cl^- and Br^- persisted in the presence of Na^+ and K^+ cations, I^- remained unbound. The inability to effectively bind I^- is attributed to the confined cavity restricting the size of the halide guest after the coordination of larger metal ions. With no metal ion present, **1a** was unable to engulf I^- ; however, after the addition of smaller-sized Li^+ , I^- was strongly bound with a K_a as high as 9800 M^{-1} . Therefore, I^- could only be accommodated alongside a smaller cation (Li^+) where sufficient space was still available for the larger anionic guest. These findings were echoed by a similar ion-size trend that was observed for **1b** (Table S2). The enhanced anion affinity is attributed to cooperative action from hydrogen bonding of amide NH with the anion and electrostatic attraction from the metal cation within the cavity, the later of which is corroborated by the loss of binding of Br^- and I^- with the receptor **1a** alone, and the inability of **1b** to bind any halides in the absence of alkali metals. The affinity increases between **1a** and **1a** cation complexes are further supported by the results from the Gibbs free energies (ΔG) (Table S2).

The strong halide binding exhibited by macrocycles **1a** and **1b** in the presence of alkali metals makes them attractive as supramolecular catalysts. The catalytic potential of the hosts was investigated by using the Ritter reaction of bromodiphenyl-methane (**2a**) and acetonitrile as a benchmark reaction. The receptors are expected to promote cleavage of the carbon–bromide bond, wherein the Ritter product, benzhydryl acetamide (**2b**), is formed. Reactions were run in the presence of stoichiometric amounts of catalyst (20 mol %) at room temperature for 5 days (Figures S58–S60). The resulting yields of benzhydryl acetamide are reported in Table 2.

A control reaction composed solely of **2a** in a 1:1 solution of CH_2Cl_2 and CH_3CN was performed and failed to effectively afford Ritter product **2b** in the absence of catalyst (Table 2, entry 1). The addition of metal-free **1a** also failed to catalyze the reaction (Table 2, entry 2) due to its weak affinity for Br^- . Subsequently, a series of experiments involving the alkali metal (Li^+ , Na^+ , and K^+) complexes of **1a** and **1b** as the catalysts were carried out under the same conditions as the control experiments (Table 2, entries 3–12). In the presence of 1 equiv of alkali cations, the reaction proceeded to a significant extent as indicated by the yields of 42% (**1a**· Li^+), 18% (**1a**· Na^+), and 16% (**1a**· K^+), with Li^+ exhibiting the highest yield (Table 2, entry 3). Furthermore, increasing the amount of Li^+ to 10 equiv led to an even higher yield of 64% (Table 2, entry 7). Excess Li^+ can increase the amount of **1a**· Li^+ owing to the equilibrium between the receptor and Li^+ . Low solubility of the Na^+ and K^+ salts prevented any catalytic reactions at higher concentrations of the cations. These results indicate that **1a** can effectively catalyze the reaction in the presence of Li^+ compared to other metal ions. Under the same conditions, the contrasted receptor **1b** catalyzed the reaction less effectively (Table 2, entries 9–12). Obviously, the difference in catalytic activity between **1a** and **1b** can be ascribed to the electronic effect of substituents in the macrocycles: an electron-withdrawing group ($\text{X} = \text{NO}_2$) enhances the acidity of NH protons, which in turn, assists binding of the Br^- . In the presence of Na^+ and K^+ salts, they give very similar results (Table 2, entries 11 and 12), possibly as a result of relatively loose binding of the anion compared to the use of Li^+ (Table 1).

A mechanistic pathway would be the catalyst-assisted cleavage of the carbon–bromide bond of **2a** followed by the rapid attack of acetonitrile (Scheme 1a). To gain a better

understanding of the *in situ* capture of the Br⁻ by the **1a**·Li⁺ complex in the course of Ritter reaction, we performed NMR titration studies of **1a**·Li⁺ and **1b**·Li⁺ with the substrate **2a** in CDCl₃/CD₃CN (1/1) (Figures S56 and S57). The amide protons H_j were found to shift downfield upon addition of **2a**. The noticeable change in chemical shifts is a consequence of binding of the Br⁻ as the reaction progresses. This strongly supports the proposition in the first step that **1a**·Li⁺ activates the brominated substrate **2a** via hydrogen bonding to promote the formation of carbocation. This is followed by nucleophilic attack by a molecule of acetonitrile to generate the nitrilium cation.²¹ To evidence the possibility in the next step that the adduct formed by addition of a molecule of water from the wet solvent acts as a proton source to facilitate removal of bound Br⁻ from the cavity, CF₃CO₂H (20 mol %) was added to the reaction system. Indeed, a significant increase in yield up to 57% was observed with **1a**·Li⁺ as the catalyst (Table 2, entry 8) compared to the case with **1a** alone (Table 2, entry 6) where only the starting material is recovered. This suggests that the presence of proton source favors the departure of bromide trapped in the macrocyclic complex to generate the catalyst again for use in the next catalytic cycle.

The reversible switching of the catalytic process between ON and OFF was also tested (Scheme 1b). Upon addition of excess HSO₄⁻ (10 equiv) as its tetrabutylammonium salt to the reaction system, no conversion to product **2b** was observed. The Ritter reaction was turned “off” as a result of precipitation of LiHSO₄ (Figure S61). Increasing the concentration of Li⁺ by *in situ* adding its salt switched “on” the reaction, resulting in a yield of 49% comparable to the case with **1a**·Li⁺ as the catalyst (Table 2, entry 3). This result proves possible to control the progress of the Ritter reaction by removal or addition of Li⁺ cation.

In conclusion, we have demonstrated that convergent ditopic H-bonded amide macrocycles can effectively enhance the binding affinity for anions in the presence of alkali metal cations. In particular, a greater increase in the binding of Br⁻ is observed in the presence of lithium ion. With this as a starting point, a practical approach to catalyzing the Ritter reaction by exploiting enhanced anion-binding affinity was developed. The catalytic process can be switched in an on-and-off fashion. Our work provides an alternative way to catalyze anion-promoted catalytic reactions by utilizing cation-dependent anion affinity effects, which may find applications in other anion-promoted reaction systems using various heteroditopic receptors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Molecular structures of hydrogen-bonded receptors with protons labeled and their cartoon representation and alkali metal ions/anions involved in the catalytic reaction.

Figure 2. Partial ^1H NMR spectra (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, $v/v = 1/1$, 298 K) of receptor **1a** and $1\text{a}\cdot\text{Li}^+$ with 2 equiv of halide ions. (●) = H_J , (Δ) = H_K .

Scheme 1.
Proposed Catalytic Cycle and Switchable Catalyzed Reaction

Table 1.Association Constants K_a (M^{-1}) of Complexes in $CDCl_3/CD_3CN$ (1:1, v/v) at 298 K

receptor	Cl^-	Br^-	I^-
1a	110	<i>a</i>	<i>a</i>
1a ·Li ⁺	2300	1100, ^{<i>b</i>} 55000	9800
1a ·Na ⁺	4000	4200	<i>a</i>
1a ·K ⁺	4900	3800	<i>a</i>

^{*a*} $K_a < 10 M^{-1}$ and could not be accurately determined.^{*b*} Stoichiometry was 2:1.

Table 2.Investigation of the Anion-Binding-Catalyzed Ritter Reaction with Various Potential Catalysts^a

entry	catalyst	yield ^c (%)
1	<i>b</i>	<5
2	1a	<5
3	1a ·Li ⁺	42
4	1a ·Na ⁺	18
5	1a ·K ⁺	16
6	1a + CF ₃ CO ₂ H (20%) ^d	<5
7	1a ·(10 equiv of Li ⁺)	64
8	1a ·Li ⁺ + CF ₃ CO ₂ H (20%) ^d	57
9	1b ·Li ⁺	22
10	1b ·(10 equiv of Li ⁺)	36
11	1b ·Na ⁺	18
12	1b ·K ⁺	20

^aReaction conditions: 20 μmol of **2a** and 4 μmol of catalyst (20 mol%) in 2.0 mL of 1:1 solution of CH₂Cl₂ and CH₃CN at room temperature.^bIn the absence of any macrocycle or catalyst.^cYields determined after 5 days by ¹H NMR.^d20 mol % of CF₃CO₂H was added.