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Cation-Assisted Reversible Folding and Anion Binding by a Naphthalenediimide-Based Ditopic Ion-Pair Receptor

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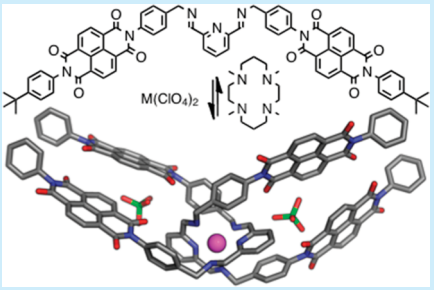
Supporting Information

ABSTRACT: A novel heteroditopic ion-pair receptor was synthesized by tethering two π-acidic naphthalenediimide units with a tridentate bisimine linker. Upon chelating a Zn^{II} or Cd^{II} ion with the linker, it adopts a U-conformation allowing the parallel NDI arms to sandwich charge-diffuse anions, and two such folded receptor molecules interlock with each other forming an $[\mathbf{R3}\cdot M^{II}\cdot\mathbf{R3}\cdot X^{-}]$ ion-pair complex. Extraction of the guest cation with a tetraazacrown ether returns the receptor to its original unfolded form.



Biomimetic dual guest recognition under allosteric regulation,[1−3] where the binding of one guest changes the receptor conformation and regulates the subsequent binding of another guest at a different location, is one of the most fascinating, potentially rewarding, and yet, rather underexplored aspects of supramolecular chemistry. One of the areas that could particularly benefit from cooperative dual guest binding is ion-pair recognition,[4−11] which entails simultaneous binding of cation and anion with heteroditopic receptors having disparate binding sites. Unlike monotopic anion and cation receptors,[12−16] which encounter competitions from the unbound counterions, heteroditopic ion-pair receptors not only circumvent such an ion-pairing effect but also actually benefit from the electrostatic attraction between the cobound guest ions, which enhances the affinities of both. In addition, many ion-pair receptors also experience guest-induced conformational changes, rendering quantification of overall cooperativity and deconvolution of the factors extremely difficult, especially when one guest binds significantly more strongly than the other. As a result, phenomenological evidence of cation-induced anion binding and *vice versa* is far more common than actual quantification.

While myriads of anion receptors have been developed over the past decades to capture hard anions through H-bonding interaction, the manipulation of charge-diffuse ions is only beginning to draw attention, as their diverse biological, environmental, and industrial relevance are being exposed.[17,18] Unlike hard anions, they have low enthalpy of H-bond formation and favor soft binding sites having complementary size and shape.[11,19−21] Although soft CH···anion[11,21] and anion−π interactions[22−24] meet these criteria, they have been seldom exploited in ion-pair receptors.[11,25,26] The most notable among them are (i) Flood's aryl-triazole-ether macrocycles that cooperatively bind $NaClO_4$ via CH···anion interaction with the triazole units[11] and (ii) Wang's calix[4]arene containing two π-acidic triazine units that binds Zn^{II} and Cl^{-} via anion−π interaction.[25] Expanding the scope and boundary of anion/π-acid interactions, we demonstrated that naphthalenediimide (NDI) and perylene diimide (PDI) compounds can discriminate anions on the basis of their electronic properties by engaging the charge-diffuse anions in anion−π[27] and CH···anion interactions[28] and Lewis basic anions in formal electron transfer and charge transfer events.[29,30] While the different modes of anion−π-acid interactions have been exploited for anion sensing and sequestration,[27−30] membrane transport,[26] and light-harvesting[31] applications, to our knowledge, there exists no NDI-based ion-pair receptor.

Herein, we report the design and synthesis of novel NDI-based heteroditopic ion-pair receptors and demonstrate their cation-induced conformational changes and anion recognition capabilities through ^{1}H NMR titration, ROESY NMR, MALDI-TOF, and computational studies. While simple NDI compounds, such as **1**, lack cation binding sites, receptors **R2** and **R3** having two NDI units tethered by bisimine linkers (Figure 1) can potentially chelate transition metal ions with the linkers and anions with the NDI units. These receptors were synthesized via imine coupling reactions (Supporting Information (SI), Figure S1). Succinctly, the coupling of isophthaladehyde and amine-functionalized NDI **4** yielded bidentate receptor **R2** having a central benzene ring flanked by two imine groups, and 2,6-pyridinedicarboxaldehyde and **4** coupled to form a tridentate receptor **R3** having a central pyridine ring flanked by two imine groups. Two control receptors, **R2′** and **R3′** having the same linkers but lacking the NDI units, were also synthesized to decipher the cation-induced changes and the anion recognition capability of **R2** and **R3**. The tridentate linker used in **R3** and **R3′** is known to chelate transition metal ions and form interlocked 2:1 host−guest complexes.[32,33]

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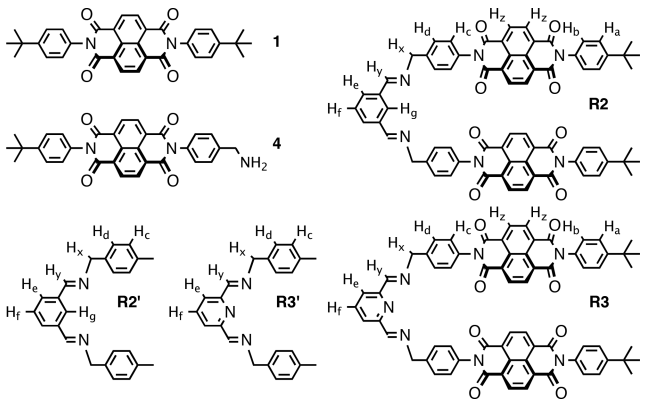

Figure 1. Ion-pair and control receptors.

The first indication of simultaneous cation and anion binding by **R3** came from MALDI-TOF analysis, which revealed [**R3**·M^{II}·**R3**] complexes at m/z = 2275.41 and 2325.56 with Zn^{II} and Cd^{II}, respectively, as well as the corresponding [**R3**·M^{II}·**R3**·ClO_4^-] ion-pair complexes at 2374.83 and 2424.45 (Figure S2) and [**R3**·Zn^{II}·**R3**·TfO^-] at 2425.47.[34] No such complex was formed with the corresponding Bu_4N^+ salts. These results not only revealed 2:1 stoichiometry of **R3** and M^{II} in the complexes, but also suggested that M^{II} coordination by the tridentate linker enabled **R3** to capture a guest anion at a different location.

To determine the structures of these complexes, we conducted ^{1}H NMR titration experiments with Zn^{II} and Cd^{II} salts having charge-diffuse BF_4^-, ClO_4^-, and TfO^- anions. Since bidentate **R2** and tridendate **R3** have different cation binding sites, their recognition behaviors also differ significantly. During the ^{1}H NMR titration experiments (Figures 2, S3, and S4) of **R3** with these M^{II} salts (0−0.5 equiv, no further changes was observed after that), the signals corresponding to the H_y proton of the imine group and H_f proton of the central pyridine ring shifted noticeably downfield ($\Delta\delta \approx 0.2-0.4$ ppm) due to M^{II} chelation. At the same time, the H_x protons of CH_2 groups and H_c and H_d protons of the adjacent phenyl rings shifted upfield ($\Delta\delta \approx 0.4-0.5$ ppm) suggesting that, upon M^{II} chelation, **R3** adopted a 'U'-shape, and two U-shaped **R3** molecules became interlocked with each other forming 2:1 [**R3**·M^{II}·**R3**] complexes, in which the central pyridine ring of one molecule was intercalated between the two parallel phenyl rings of the other, causing an upfield shift of the corresponding protons due to shielding effect.[35,36] The cation-induced folding and interlocking of two **R3** molecules was further confirmed by ROESY NMR spectroscopy (*vide infra*). The downfield shift of H_y signal and the upfield shift of H_c and H_d signals were both more pronounced with Cd^{II} than Zn^{II} (Figures 2, S3, and S4), possibly due to more facile octahedral complex formation involving all six N atoms of two interlocked **R3** molecules by the larger Cd^{II} ion, as opposed to a distorted octahedral or trigonal bipyramidal complex formation by the smaller Zn^{II} ion.

Furthermore, in the presence of different Zn^{II} and Cd^{II} salts, the NDI core protons (H_z), which appeared as a singlet in free **R3**, split into two doublets and shifted slightly downfield (Figures 2, S3, and S4). While all M^{II} salts caused similar splitting of the H_z signal, its net downfield shift varied with different anions (i.e., BF_4^-, ClO_4^-, and TfO^-) depending on the anion's ability to interact with the NDI units and the strength of these interactions (Figure 3a). These changes can be attributed to two counter-balancing factors: M^{II} coordination at the tridentate linker makes the NDI units more π-acidic (causing a downfield shift) and less

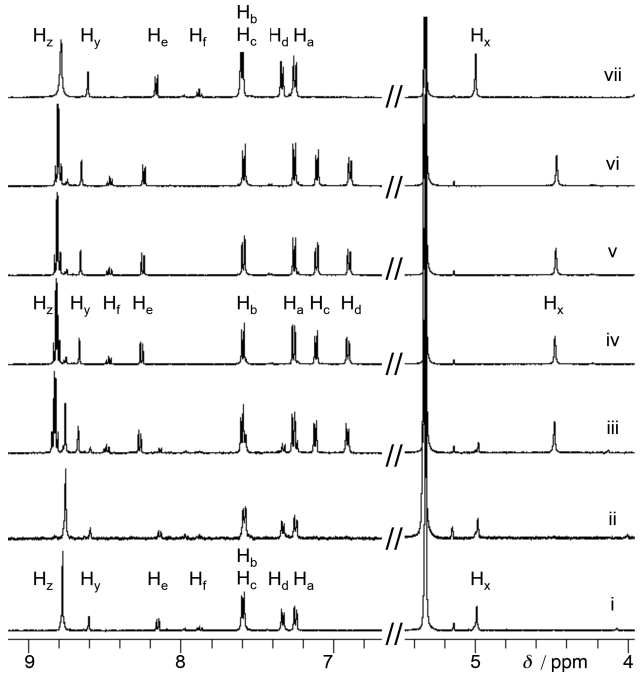

Figure 2. The ^{1}H NMR titration data of **R3** (4:1 CD_2Cl_2/CD_3CN, 500 MHz) with $Zn(ClO_4)_2$ (0−1 equiv) show 2:1 [**R3**·Zn^{II}·**R3**] complex formation, anion/NDI interaction, and, finally, the regeneration of **R3** with 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (TACT): (i) free **R3**; (ii) **R3** with $Bu_4N^+ClO_4^-$ (1 equiv); (iii−vi) (**R3** + $Bu_4N^+ClO_4^-$) with 0.25, 0.5, 0.75, and 1.0 equiv of $Zn(ClO_4)_2$ salts; and (vii) upon addition of TACT (1.1 equiv) to [**R3**·Zn^{II}·**R3**].

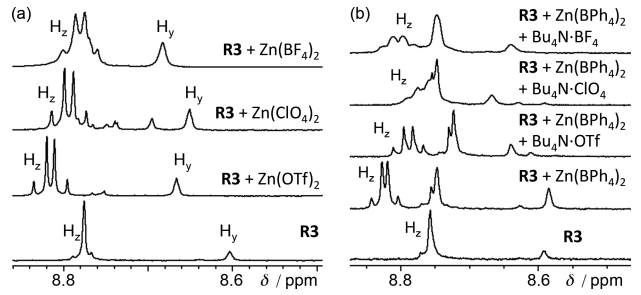

Figure 3. Partial ^{1}H NMR spectra of **R3** (4:1 CD_2Cl_2/CD_3CN, 500 MHz) recorded in the presence of different ZnX_2 salts show the impact of different anions on the NDI's H_z signal revealing the distinct NDI/anion interactions.

symmetric (causing splitting), whereas the anion−π interaction increases the electron density of NDI units,causing a slight upfield shift that partially offsets the downfield shift caused by M^{II} coordination with the linker. All NMR shifts of **R3** were complete in the presence of 0.5 equiv of M^{II} salts, and the spectra did not change further upon addition of more salts, confirming the formation of stable 2:1 [**R3**·M^{II}·**R3**] complexes, which did not transform into 1:1 complexes in the presence of excess M^{II} ions or over time.

The effect of anion/NDI interaction was verified by comparing the net shift of H_z signal observed in the presence of a completely noninteracting spectator anion BPh_4^- and others that are capable of forming weak anion−π interactions. Among different Zn^{II} salts, the largest downfield shift of H_z signal was observed in the presence of a non-interacting anion, BPh_4^- (Figure 3b), as Zn^{II} coordination with the tridentate linker rendered the NDI units more π-acidic and less symmetric.[37] Upon addition of Bu_4NX salts

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(X^- = TfO^-, ClO_4^-, and BF_4^-) into the medium, the H_z signal shifted upfield from the previous position indicating that anion/NDI interaction increased the electron density of NDI (Figure 3b). In comparison, in the presence of only Bu_4N^+ cation, the H_z signal of **R3** shifted slightly upfield and all other signals remained unaffected, confirming that the M^{II}-induced folding, the 2:1 interlocked complex formation, and anion/NDI interactions all contributed to the distinct NMR changes observed in the presence of MX_2 salts. Furthermore, the M^{II} cation-assisted BF_4^- anion binding by **R3** was also evident from the ^{19}F NMR experiments, which revealed an upfield shift of the BF_4^- signal when it bound with **R3** in the presence of Zn^{II}, but not with Bu_4N^+ (Figure S5).

The fact that free **R3** molecules and [**R3**·M^{II}·**R3**] complexes displayed two distinct sets of NMR signals, and no intermediate signals corresponding to a weighted average of initial and final signals appeared at any point during the titration experiments, indicated an extremely strong M^{II} binding affinity ($K > 10^8$ M^{-2}) with the equilibrium heavily favored toward the 2:1 complex formation.[35] Furthermore, in the absence of charge transfer and electron transfer events, the weak anion/NDI interactions ($K <$ 10 M^{-1})[38] do not induce any discernible UV/vis absorption and/or fluorescence changes.[39]

Further evidence of M^{II}-induced folding and interlocking of two U-shaped **R3** molecules emerged from ROESY NMR experiments (Figure 4a). In the absence of M^{II} ions, **R3** is free to

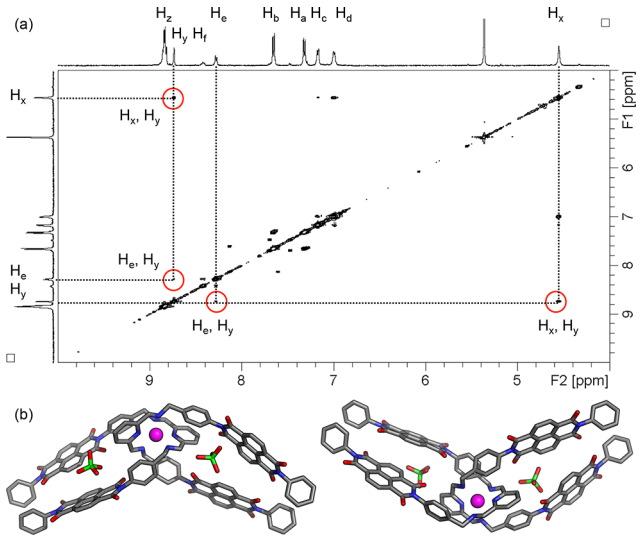

Figure 4. Partial ROESY NMR spectrum of [**R3**·M^{II}·**R3**] complex shows NOE coupling of H_y with H_e and H_x protons when **R3** adopts a cation-induced U-shape. (b) The energy minimized structures of the complex show that two interlocked U-shaped **R3** molecules chelate an M^{II} ion with their tridentate linkers and charge diffuse anions with the NDI units.

adopt any random conformations, and therefore, H_y and H_e protons, which are not directly coupled, do not display any NOE correlation. In the presence of M^{II} ions, the ROESY spectrum of **R3** revealed NOE correlation between these two remote protons, confirming that once **R3** adopted the 'U' conformation, they came within close proximity activating through-space interaction. The cation-induced folding also enabled two U-shaped tridentate **R3** molecules to interlock with each other and chelate a transition metal ion with their linkers and sandwich charge diffuse anions between the overlapping NDI arms. The energy minimized quantum chemical computational model based on MO6 functionals and 6-311-G(D,P) basis sets also corroborated this interlocked 2:1 complex structure as well as anion binding with the NDI arms (Figure 4b).

The entire process, i.e., the cation-induced folding of **R3**, 2:1 complex formation, and anion binding with the NDI units, was fully reversible. Upon addition of a stronger M^{II} chelator, such as TACT, all signals corresponding to the ion-pair complexes disappeared and the original free **R3** signals reappeared indicating regeneration of guest-free receptor that could be used again for ion-pair recognition (Figure 5).

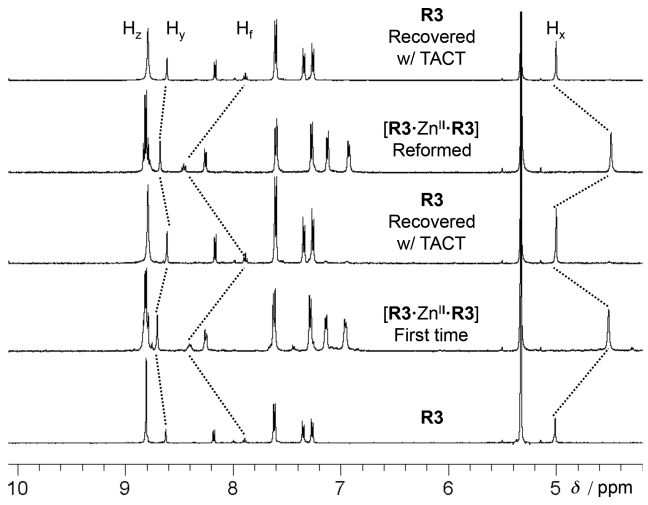

Figure 5. Partial ^1H NMR spectra (4:1 CD_2Cl_2/CD_3CN, 500 MHz) show M^{II}-induced folding and ion-pair recognition by **R3** and TACT-mediated release of ions and regeneration of **R3**.

The cation-induced folding and 2:1 interlocked complex formation by **R3** was further supported by similar NMR changes shown by control receptor **R3′** having the same M^{II} binding site (Figure S5). Although we were not able to obtain diffractable crystals of [**R3**·M^{II}·**R3**] complexes due to the amorphous nature of NDI compounds, the crystal structures of analogous [**R3′**·M^{II}·**R3′**] complexes revealed[33] that two U-shaped **R3′** molecules are interlocked with each other around a central M^{II}-binding pocket. However, lacking the π-acidic NDI units, **R3′** does not function as an ion-pair receptor.

In contrast, bidentate **R2** displayed NMR chemical shifts only in the presence of Zn^{II} but not with Cd^{II} (Figures S6), because it could not satisfy the octahedral coordination of Cd^{II} even after 2:1 complex formation. In the presence of Zn^{II}, however, the imine H_y peak of **R2** disappeared while a characteristic aldehyde peak appeared at ca. 10 ppm and the H_x signal shifted significantly upfield (δ = 4.22 ppm), indicating hydrolysis of the imine bonds into isophthaladehyde and amine **4** instead of a stable complex formation. Unlike **R3**, **R2** did not display any ^1H NMR and ROESY signals indicative of cation-induced folding and interlocking of two molecules. Moreover, the Zn^{II}-induced NMR changes of **R2** could not be reversed with TACT, further confirming irreversible imine hydrolysis. Similarly, control receptor **R2′** also displayed Zn^{II}-induced irreversible NMR changes consistent with imine hydrolysis (Figure S7). The drastically different responses of **R2** and **R3** to M^{II} ions are attributed to different compositions of the linker units. While tridentate **R3** was able to chelate an M^{II} ion with the help of the central pyridine ring and two imine groups forming stable interlocked 2:1 complexes, lacking the pyridine group, bidentate

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R2 was more vulnerable to Lewis acid (M^{II}) assisted imine hydrolysis. NDI **1** did not display any NMR changes indicative of anion/NDI interaction (Figure S8), confirming that the anion/NDI interaction in **R3** was indeed facilitated by the cation-induced folding and electrostatic interaction.

In summary, we have designed and synthesized two NDI-based ditopic receptors and demonstrated how a key structural difference led to dramatically different cation, anion, and ion-pair recognition behaviors. The tridentate receptor **R3** undergoes M^{II}-induced folding into a 'U' conformation, leading to the formation of ion-pair complexes, in which two interlocked **R3** molecules bind a metal ion with their linkers and anions with the NDI units. The entire process can be reversed with a strong chelator, making **R3** a reusable ion-pair receptor. By contrast, bidentate **R2** undergoes Zn^{II} mediated imine hydrolysis, revealing the importance of the central pyridine ring on the entire ion-pair recognition process. To our knowledge, **R3** represents the first NDI-based ion-pair receptor, which captures guest cation and anion simultaneously under allosteric regulation, as the cation-induced folding and dimerization enabled anion binding at a different location. In future, the cation-induced folding of bis-NDI receptors could also be exploited for neutral guest recognition,[40] sensing, and electron transfer processes. These prospects are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03861.

Experimental details, synthesis of receptors, additional NMR and MALDI-MS data (PDF)

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Notes

The authors declare no competing financial interest.

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