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Fluoride Ion Sensing by an Anion−π Interaction

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Abstract: We report the discovery of a supramolecular interaction (anion−π and charge/electron transfer, CT/ET) involving fluoride ion and π-electron deficient colorless naphthalene diimide (NDI) receptors. Strong electronic interactions between lone-pair electrons of F^- ion and π^*-orbitals of the NDI unit lead to an unprecedented $F^-\rightarrow$NDI ET event, which produces an orange colored $NDI^{\bullet-}$ radical anion. Further reduction of $NDI^{\bullet-}$ by another F^- ion produces a pink colored NDI^{2-} dianion, rendering NDI a colorimetric F^- sensor. Preorganization of two NDI units in overlapping positions using folded linkers improves their selectivity and sensitivity for the F^- ion significantly, allowing F^- detection at nM concentration in 85:15 DMSO/H_2O solutions.

The recent discovery of anion−π interaction[1] — a noncovalent interaction between an anion and an electron deficient organic π-system with a strong positive quadrupole moment — has added new dimensions to recognition, sensing,[2] and transmembrane passage[3] of anions. Myriads of anions play critical roles in chemical and biological processes, demanding continuous research in the field of anion recognition.[4] Dunbar et al.[2b] recently reported chromogenic anion−π and charge transfer interactions involving halides ($Cl^- > Br^- > I^-$) and electron deficient aromatic rings in organic solvents.

Herein, we present an unprecedented example of chromogenic anion−π and CT interactions involving the F^- ion and π-electron deficient colorless NDI receptors.[3,5] A plethora of experimental evidence, supported by computational models, indicate that (Figure 1) NDI/F^- interactions facilitate an unprecedented $F^-\rightarrow$NDI electron transfer (ET) event, which generates an orange $NDI^{\bullet-}$ radical anion. Excess amounts of F^- chemically reduces $NDI^{\bullet-}$ further to a pink NDI^{2-} dianion. Thus, NDI/F^- interactions and ET events produce a two-step optical response, offering a new strategy for toxic F^- ion sensing.

A fluoride deficiency causes osteoporosis and poor dental health.[6] Overexposure to F^- is blamed for fluorosis and osteosarcoma.[7] The EPA-recommended F^- level in drinking water is 1 ppm, and over 2 ppm is considered a health-risk.[8] The low level of F^- tolerance demands for a selective and sensitive F^- sensor. Gabbaï and others developed borane, lanthanide, and other Lewis acid based efficient, albeit disposable, F^- sensors.[9] Conventional hydrogen bonded F^- receptors have also been reported.[10] Because of the nonchromogenic nature of most Y−H···X^- interactions, H-bonded receptors[10] rely on either adjacent chromophore units or deprotonation followed by electron delocalization to display a colorimetric response. Therefore, they cannot differentiate F^- from other strongly basic anions, such as AcO^- and $H_2PO_4^-$.[10e] In contrast, the selectivity and reusability of NDI-based F^- sensors that exploit reversible anion−π and CT/ET interactions distinguish them from the existing F^- sensors.

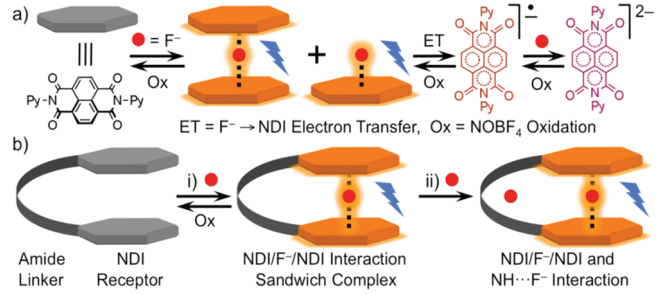

Figure 1. Graphical illustrations of (a) anion−π and CT interactions between F^- and NDI receptor, generating fluorochromogenic response via $F^-\rightarrow$NDI ET event, (b) stepwise F^- recognition by preorganized receptors (PR) through (i) π−anion−π and (ii) H-bonding interactions.

Iverson and others demonstrated that CT and π−π-stacking interactions between a colorless NDI unit and electron rich aromatic rings produce colored donor−acceptor CT complexes.[5] We envisioned that NDI units could also bind with appropriate anions through anion−π interactions and report the binding event by generating optical signals on account of anion→NDI CT interactions (Figure 1). To test our hypothesis, we surveyed interactions of NDI receptors with F^-, Cl^-, Br^-, I^-, NO_2^-, NO_3^-, N_3^-, PF_6^-, AcO^-, and $H_2PO_4^-$ anions as tetra-*n*-butylammonium (TBA) salts.

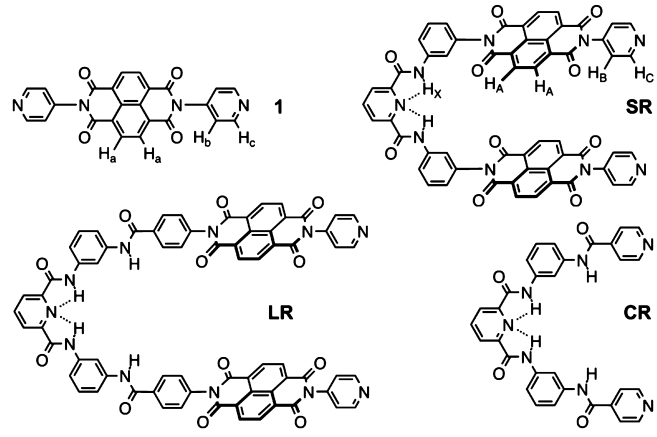

Figure 2. Molecular structures of receptors **1**, **SR**, **LR**, and **CR**.

We further postulated that preorganization of two overlapping NDI units by connecting them with folded linkers[11] should improve the anion binding affinity, selectivity, and sensitivity. To investigate the effect of preorganization we designed and synthesized (Supporting Information (SI), Scheme S1) NDI receptor **1**, a short receptor (**SR**) containing a bisamide linker connecting two NDI units, a long receptor (**LR**) containing a tetraamide linker between two NDI units, and a control tetraamide receptor (**CR**) carrying no NDI unit (Figure 2). Bifurcated intramolecular H-bonds involving

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the pivotal pyridine N atom and adjacent amide protons should render the bis- and tetraamide linkers folded conformations that bring two ends of receptor molecules into close proximity.[11] Hartree−Fock global energy minimization shows that while the short linker in **SR** brings two NDI units into a parallel overlapping orientation, the longer linker in **LR** projects two NDI units at an angle (SI, Figure S1). In addition to properly orienting NDI units, amide linkers of **SR** and **LR** provide additional anion binding sites in their cavities via H-bonding interaction.

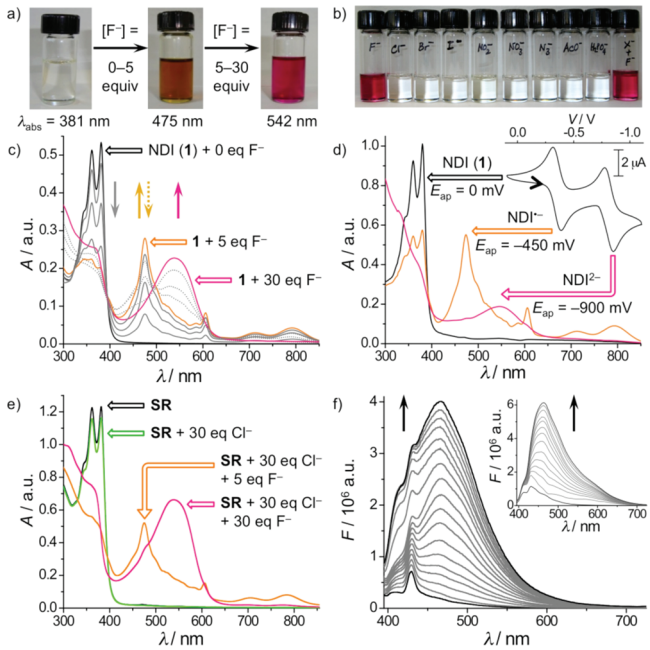

Figure 3. Colorimetric changes of **1** (a) from colorless (no F^-) to orange (0−5 equiv of F^-) to pink (5−30 equiv of F^-) and (b) by other anions (30 equiv) in DMSO. (c) UV/Vis titration of **1** (10 μM/DMSO) with F^- and (d) spectroscopic changes of **1** (0.5 mM in 0.1 M $TBAPF_6$/DMF) upon direct electrochemical reduction in the absence of F^-. Black trace: neutral NDI **1** (E_{ap} = 0 mV); orange trace: $NDI^{\bullet-}$ (E_{ap} = −450 mV); and pink trace: NDI^{2-} (E_{ap} = −900 mV). Inset: cyclic voltammogram of **1** (vs Ag/AgCl in 0.1 M $TBAPF_6$/DMF) in the absence of F^-. (e) Optical response of **SR** to F^- (orange and pink) in the presence of excess Cl^- but no change only with Cl^- (green vs black). (f) Fluorescence amplifications of **SR** (1 nM/DMSO); inset: **1** (10 μM/DMSO) by F^- ion (0−30 equiv F^-, $\lambda_{excitation}$ = 381 nm).

The first indication of selective F^- ion sensing by **1**, **SR**, and **LR** came from visible color changes (Figure 3). While Cl^-, Br^-, I^-, NO_2^-, NO_3^-, N_3^-, AcO^-, and $H_2PO_4^-$ even at 30 equiv did not affect the colorless solutions of NDI-based receptors, titrations with F^- in aqueous DMSO, DMF, DMAc, MeCN, Me_2CO, and THF, containing up to 15% of H_2O, immediately changed the color in two steps (Figure 3a,b). At first, the colorless NDI solutions turned orange at lower F^- equivalents (≤5 equiv) and then turned pink at higher F^- equivalents (>5 equiv). NDI-free **CR** did not change color in response to any anion.

ESI-MS confirmed (SI, Figure S2) the formation of [**1**·F^-], [**1**·F^-·**1**], [**SR**·F^-], and [**LR**·F^-] complexes by revealing the corresponding peaks at *m*/*z* 439.06, 859.15, 1018.28, and 1256.27, respectively, as well as signals associated with **1**, **1**·**1** dimer, **SR**, and **LR** at *m*/*z* 420.23, 840.23, 999.25, and 1237.29, respectively, at F^- ion concentrations up to 1 equiv. At 2 equiv of F^- [**SR**·2F^-] and [**LR**·2F^-] complexes were found at *m*/*z* 518.40 and 637.70, respectively.

UV/Vis titration experiments were conducted to quantify F^--induced colorimetric transitions of NDI receptors. Receptors **1**, **SR**, and **LR** display characteristic NDI absorption peaks at 343, 361, and 381 nm. Titration of **1** with 0−5 equiv of F^- gradually bleached NDI absorption peaks and concurrently produced new peaks at 475, 605, 711, and 791 nm, establishing a clear isosbestic point at 394 nm (Figure 3c), as the solution turned orange. The absorption spectrum of orange species generated by F^- (Figure 3c) matches exactly with that of an electrochemically generated $NDI^{\bullet-}$ radical anion (−450 mV vs Ag/AgCl in DMF) produced in the absence of F^- (Figure 3d: orange trace). Manifestations of identical spectroscopic changes with the same isosbestic point (394 nm) during F^- titration (Figure 3c) and during spectroelectrochemical (SEC) analysis of **1** in the absence of F^- (SI, Figure S3a) strongly suggest that the F^-→NDI ET event takes place in the NDI/F^- complex. A nucleophilic attack of F^- on NDI forming a covalent C−F bond should have produced spectroscopic transitions different from SEC. The EPR spectrum (SI, Figure S4) of the F^--induced orange solution of **1** further confirms the formation of a delocalized $NDI^{\bullet-}$ radical anion (g = 2.0030). These results indicate that at first F^- binds with NDI through anion−π and CT interactions that facilitate F^-→NDI electron transfer and generate $NDI^{\bullet-}$ (Figure 1a).

As the solution of **1** turned from orange to pink during the titration with 5−30 equiv of the F^- ion, $NDI^{\bullet-}$ absorption peaks gradually disappeared concomitantly with the emergence of a broad absorption band at 542 nm. This transition at higher F^- equivalents can be attributed to one of the following possibilities: (a) $NDI^{\bullet-}$ is further reduced to NDI^{2-} dianion by another F^- ($E_{1/2}$ = −2.87 V) or (b) $NDI^{\bullet-}$ is attacked by the F^- ion forming a C−F bond, which would be an extremely high-energy process because of electrostatic repulsions. Strong similarities between absorption spectra of the pink solution of **1** produced by excess F^- (Figure 3c) and electrochemically generated NDI^{2-} at −900 mV vs Ag/AgCl, DMF in the absence of F^- (Figure 3d, SEC, pink trace) strongly support the first scenario. A higher relative intensity of the 542 nm band of the F^--induced quickly generated pink solution than that of slowly (diffusion controlled) electrochemically reduced NDI^{2-} may be attributed to degradation of reduced NDI species under the UV/Vis light during prolonged SEC experiments. Consistent with the formation of NDI^{2-} by excess F^-, the pink solution of **1** became EPR silent (SI, Figure S4).

The presence of the [**1**·F^-] complex at ≤1 equiv of F^- suggests that $NDI^{\bullet-}$ may exist in the electron delocalized NDI/F^- ↔ $NDI^{\bullet-}$/$F^\bullet$ anion−π and CT complex. In contrast, ESI-MS in the presence of excess F^- reveals only the $[\mathbf{1}]^{2-}$ dianion at *m*/*z* 210.40 but does not show any signal representing $[\mathbf{1}/F_n]^{n-}$ ($n \geq 1$) complexes (SI, Figure S2c). Therefore, only the first F^-→NDI ET event that produces $NDI^{\bullet-}$ is facilitated by NDI/F^- anion−π binding, whereas the formation of NDI^{2-} with an additional F^- ion takes place through the direct chemical reduction of $NDI^{\bullet-}$ and not via a physical binding of F^- with $NDI^{\bullet-}$ due to electrostatic repulsions (Figure 1a). ESI-MS also confirms that once the NDI^{2-} dianion is formed it does not associate with F^- anymore.

Oxidation of orange ($\mathbf{1}^{\bullet-}$) and pink ($\mathbf{1}^{2-}$) solutions with $NOBF_4$ decolorized them. Because of strong absorptions of $NOBF_4$ in 350−400 nm regions, regeneration of **1** could not be confirmed by UV/Vis spectroscopy. However, ^{1}H NMR spectroscopy confirmed complete recovery of **1** after $NOBF_4$ oxidation (*vide infra*). The reversibility of NDI/F^- interactions further proves that these are noncovalent interactions.

Preorganized NDI receptor **SR** displayed (SI, Figure S5a) similar two-step spectroscopic changes with F^-. In addition to binding a F^- ion between two terminal NDI units, forming an NDI/F^-/NDI sandwich complex, **SR** and **LR** can potentially bind a second F^- ion in the amide cavities via H-bonding interaction (Figure 1b).

This interaction, however, did not produce an additional optical signal. NDI-free **CR** showed (SI, Figure S5b) a modest change in the UV region owing to NH···F^- interaction and possible deprotonation of amide protons.

Interestingly, NDI receptors did not show any significant spectroscopic change with other anions (SI, Figure S5c), although the [**1**·Cl^-] complex was found in ESI-MS (*m/z* 455.07).[3] To investigate the selectivity and sensitivity of **SR** toward F^-, it was titrated with F^- in the presence of 30 equiv of Cl^- (Figure 3e). While **SR** did not optically respond to Cl^-, it showed the characteristic two-step color change with F^- even in the presence of Cl^-, demonstrating the desired selectivity for the F^- ion. The selective colorimetric response of NDI receptors for F^- recognition compared to nonchromogenic binding of more polarized anions may be attributed to the smaller ionic radius (1.33 Å) and 2*p* orbital of the F^- ion.[1d] These factors allow F^- to come into closer proximity of the NDI π-surface and engage in efficient anion$-\pi$ and CT interactions through better orbital interactions with NDI π*-orbitals.[2b] Such interactions facilitate an electron transfer from F^- to the NDI π-system that produces the orange $NDI^{\bullet-}$ radical anion. Larger size, orbital mismatch,[1d,2b] and weaker binding of Cl^- and other anions[3b] with NDI π-systems could rationalize why they do not induce visible color change.

Effects of preorganization on the sensitivity of NDI receptors were probed by monitoring the F^--induced fluorescence changes at the minimum receptor concentrations. The titration of **SR** (1 nM in DMSO) with F^- (30 nM), probed by 381 nm excitation, displayed a 4.5-fold amplification of the original 430 nm emission peak of the NDI unit and a 20-fold amplification of a new peak at 465 nm (Figure 3f). NDI **1** (10 μM in DMSO) showed a similar fluorescence profile and 5.5-fold increase of the 465 nm emission peak (Figure 3f, inset), albeit at 10^4 times higher concentrations than **SR**. The excellent nM sensitivity of **SR** vs weaker μM sensitivity of **1** supports our hypothesis that preorganization of two NDI units should improve the F^- affinity and sensitivity through stronger NDI/F^- interactions. The high F^- ion sensitivity of preorganized receptors (**PR**) bode well for their potential applications as F^- ion sensors.

^{1}H and ^{19}F NMR titration experiments were conducted to gain a better insight into NDI/F^- interaction (Figure 4). The ^{1}H NMR spectrum of receptor **1** reveals a singlet at 8.75 ppm corresponding to four identical NDI core protons (H_a) and two doublets at 7.58 and 8.81 ppm corresponding to H_b and H_c of the pyridine ring, respectively (Figure 4a). During the titration of **1** with F^- all signals became broad but none shifted at all, virtually ruling out the possibility of a CH···F^- H-bond formation. Consistent with UV/Vis results, only the H_a signal gradually disappeared as F^- reached 1 equiv, indicating the formation of the $NDI^{\bullet-}$ radical anion. The EPR spectrum of this species (SI, Figure S4) confirmed the presence of the $NDI^{\bullet-}$ radical anion. $NOBF_4$ oxidation of the $\mathbf{1}^{\bullet-}$ radical anion completely regenerated **1**, as the original NMR spectrum reappeared, showing the H_a signal at 8.75 ppm (SI, Figure S6). The fact that the H_a signal never splits as a result of NDI/F^- interactions, a sign that would have indicated a loss of symmetry of the NDI core had a covalent C$-$F bond formed, rule out this possibility. These results support our hypothesis that NDI/F^- interactions facilitate the $F^-\rightarrow$NDI ET event that generates the $NDI^{\bullet-}$ radical anion (Figure 1a).

In **SR**, NDI core protons (H_A) and the bisamide linker (H_X) appeared at 8.73 and 11.25 ppm, respectively (Figure 4b). During the titration of **SR** with F^- the H_A signal gradually disappeared as the F^- ion concentration reached 1 equiv, while the H_X signal shifted slightly downfield, indicating that at first F^- binds with NDI units.

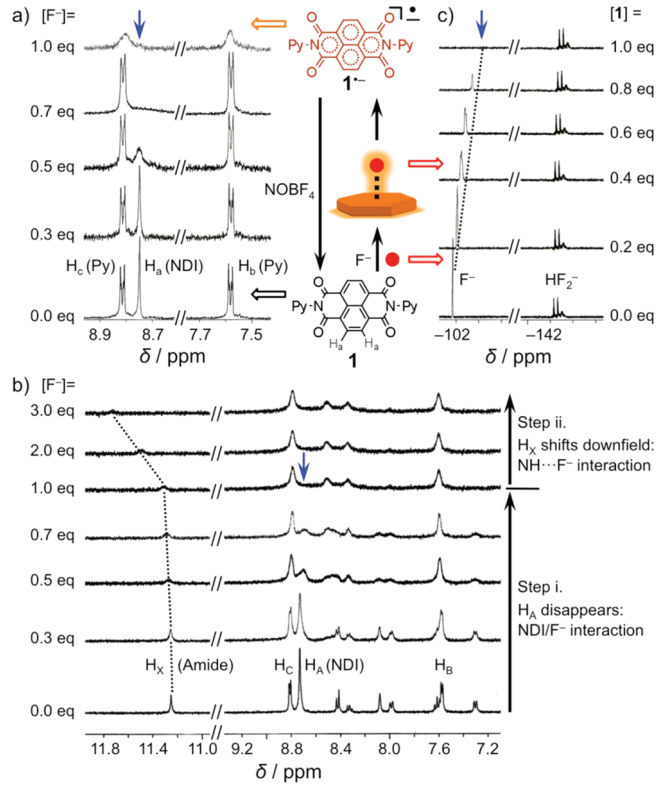

Figure 4. ^{1}H NMR titration of (a) **1** and (b) **SR** with F^-, and (c) ^{19}F NMR titration of **1** with F^- showing NDI/F^- interaction (DMSO-d_6, 298 K). Blue arrows: signal disappearance; dotted lines: signal shift.

NDI core protons in **SR** (Figure 4b) and **LR** (SI, Figure S7a) did not split before disappearing, potentially indicating the formation of NDI/F^-/NDI sandwich complexes in which both NDI units interact evenly with the F^- ion. A significant downfield shift of the H_X signal at 1$-$2 equiv of F^- indicates subsequent NH···F^- H-bonding interaction with amide protons. These NMR results are consistent with ESI-MS data. In addition to showing [**SR**·F^-] and [**LR**·F^-] complexes at $\leq$1 equiv of F^-, ESI-MS of **SR** and **LR** in the presence of 2 equiv of F^- revealed signals that represent [**SR**·2F^-] and [**LR**·2F^-] complexes, respectively (SI, Figure S2d$-$g). These results confirm that **PR**s can bind up to two F^- ions. The binding of two F^- ions within one receptor molecule possessing two recognition sites has been reported previously.[10a]

Thus, ^{1}H NMR titrations of **SR** and **LR** showing the disappearance of NDI signals before the onset of significant downfield shifts of amide signals, as well as ESI-MS showing the presence of [**PR**·2F^-] species, suggest that the first F^- ion binds through NDI/F^-/NDI interaction and then a second F^- binds within the amide cavities (Figure 1b). The first **PR**/F^- interaction is fully reversible by $NOBF_4$ oxidation (SI, Figure S6b), indicating that it involves NDI/F^- interaction. In the presence of excess F^-, amide protons may be deprotonated, as their NMR signals became broad and finally disappeared and NDI units were further reduced to NDI^{2-} as the solutions turned pink. No F^- ion should be bound with the receptors at this stage because of strong electrostatic repulsions.

^{1}H NMR titrations of receptor **1** with Cl^- and other anions did not display any change (SI, Figure S8a), confirming that NDI/Cl^- anion$-\pi$ interaction is weak.[3b] It can be attributed to weaker electronic interactions of the NDI unit with larger anions compared to a stronger electronic interaction with F^-. Titrations of receptor **1**, **SR**, and **LR** with Cl^-, Br^-, and I^- did not affect NDI protons. Only the ^{1}H NMR signals of amide protons in **SR** and **LR** shifted

downfield in the presence of Cl^-, showing that Cl^- preferentially binds inside the cavities of amide linkers via stronger N−H···Cl^- H-bonding interaction (SI, Figure S8b−c).

Fluoride ion recognition by NDI receptors was also observed from ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum of TBAF·$3H_2O$ in DMSO-d_6 shows (Figure 4c) a strong singlet at −102 ppm corresponding to the F^- ion and a weak doublet at −142.5 ppm for HF_2^-.[12] Titrations of TBAF with **1** caused an upfield shift of the −102 ppm signal (Figure 4c), which indicates shielding of F^- by the NDI receptor. The disappearance of the F^- signal at 1:1 TBAF/**1** may be attributed to an oxidation of F^- to $F^•$ as a result of the F^-→NDI ET process that produces the $NDI^{•-}$ radical anion. Although we previously considered a possibility of C−F bond formation as one of the modes of NDI/F^- interaction, it was not supported by any evidence, including ^{19}F NMR, as no new signal corresponding to a covalent C−F bond was observed.

The fact that F^- induced reductions of NDI to $NDI^{•-}$ and NDI^{2-} can be fully reversed by oxidizing them back to neutral NDI with $NOBF_4$ and that the process can be repeated (SI, Figure S6a) confirm that F^- or the resulting $F^•$ never reacts with any NDI species covalently. Whether the transient $F^•$ reacts ultimately with solvent molecules, TBA counterions, homocouples to emanate F_2 gas, or generates HF acid remains unclear after extensive analyses of NDI/F^- mixtures. Nevertheless, $F^•$ is produced as a result of NDI/F^- interaction and ET events. Therefore, the lack of precise information on the fate of $F^•$ is inconsequential, as it does not impede the clear understanding of NDI/F^- anion−π interaction that leads to an unprecedented F^-→NDI ET event.

To demonstrate a potential application of NDI/F^- interaction, **SR** was treated individually with aqueous DMSO extracts of an anticavity toothpaste containing 0.24% (w/v) NaF and F^--free toothpaste. To our delight, colorless **SR** turned light orange and displayed the absorption spectrum of the $NDI^{•-}$ radical anion with the F^- containing toothpaste but did not show any optical changes with the F^--free one (SI, Figure S9).

For the first time, a strong NDI/F^- interaction was identified and fully characterized by experimental results, as well as validated by computational models (SI, B3LYP/6-31+G**). Supramolecular NDI/F^- (anion−π and CT) interactions promote an unprecedented electron transfer process from the F^- ion to electron deficient NDI receptors. NDI receptors are highly selective toward F^- over other anions because of better orbital interactions. They display nM range F^- sensitivity in preorganized systems, in which two NDI units perfectly overlap with each other. The reversibility of the colorimetric response and reproducibility of NDI receptors render them excellent reusable F^- ion sensors. Therefore, NDI derivatives may be exploited for the detection of various levels of F^- ion concentrations in drinking water, consumer products, as well as bone and muscle tissues for the early detection and prevention of F^- ion related diseases.

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Supporting Information Available: Energy minimized structures; synthesis and characterizations; additional NMR, EPR, SEC, and ESI-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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