Differential Recognition of Various Anions Utilizing Aromatic C—H Hydrogen Bonding

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Dihydrogen phosphate selective anion receptors **1**, **2,** and **3** that utilize amide N—H, and C—H for anion recognition have been designed and synthesized. For **1** and **2**, aromatic C—H hydrogen bonding element is present on naphthyl rings ($\mathbf{H_a}$). In addition, for receptor **1**, this aromatic hydrogen bonding element is further polarized by the nitro groups, which would enhance the hydrogen bonding ability. Partial charges derived from Natural Population Analysis also supported the existence of this polarization. That is, positive partial charge of $\mathbf{H_a}$ in receptor **1** was more positive than that in receptor **2**. As expected from the partial charge values, receptor **1** consistently showed highest affinity among three receptors, followed by receptor **2** regardless of the anions tested in this study. Therefore, we have shown that affinity modulation of a receptor was possible by changing the nature of the aromatic C—H hydrogen. In addition, the receptors showed selectivity toward dihydrogen phosphate among various anions including acetate and chloride.

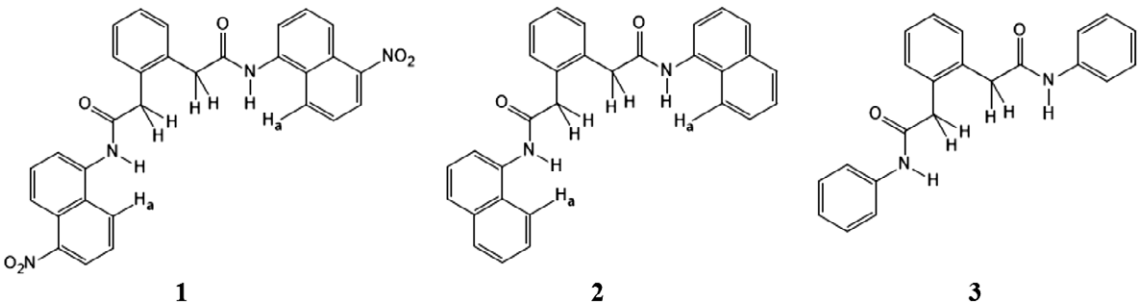
Keywords: Dihydrogen phosphate selective anion receptor, C—H hydrogen bonds, Polarization of C—H bond

Introduction

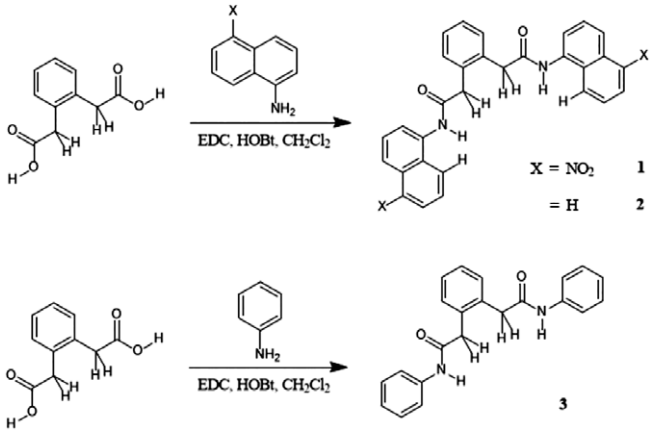
There have been still a few examples of anion receptors utilizing C—H hydrogen bonds.[1]

although C — H hydrogen bonds plays crucial roles in nature.[2] In many artificial anion receptors utilizing C—H hydrogen bonds, anion binding is assisted by additional weaker interactions of the C—H hydrogen bonds with anions.[3] As an attempt to develop new anion receptors that have C—H hydrogen bonds as an important binding factor, new receptors **1**, **2,** and **3** have been designed and synthesized. The receptors **1** and **2** have 1,2-phenylenediamide scaffold and have amide N — H, α-C — H (aliphatic) to carbonyl group and naphthyl C–H (aromatic) as hydrogen bond donors. In relation to anion recognition, the main difference among these receptors is the aromatic C—H hydrogen bonding. For example, receptor **1** has nitro groups, which induce higher polarity of C-H_a bonds compared to receptor **2**. Receptor **3** does not have naphthyl C–H_a bond. Therefore, by comparing the associations of these receptors with anions, the contribution and importance of aromatic C–H hydrogen bonding would be studied. The binding phenomena of receptors **1**, **2,** and **3** were studied by UV–Vis and ^{1}H NMR spectra. Using these results the binding poses were constructed by modeling studies.

Synthesis. For the synthesis of receptor **1**, 1,2-phenylenediacetic acid and 5-nitro-1-naphtylamine[4] were reacted to give receptor **1** in 64% yield. For the synthesis of receptor **2**, 1,2-phenylenediacetic acid and naphtylamine were reacted to give receptor **2** in 82% yield. For the synthesis of receptor **3**, 1,2-phenylenediacetic acid and aniline were reacted to give receptor **3** in 75% yield (Scheme 1).



1 **2** **3**



Scheme 1. Synthesis of receptors **1**, **2,** and **3.**

Results and Discussions

The binding ability of receptor **1** for dihydrogen phosphate was studied in 60 μM DMSO solution using UV–Vis titration spectra. Receptor **1** showed strong absorption bands at 260 and 367 nm. On addition of increasing amounts of tetrabutylammonium dihydrogen phosphate, the absorption band showed slight bathochromic shift with multiple isosbestic point at 267, 305, and 378 nm, which suggested the generation of a hydrogen bonding complex between receptor **1** and dihydrogen phosphate (Figure 1(a)). In addition, standard ^{1}H NMR titration experiments in DMSO-d_6 showed the complexation ability of receptor **1** to dihydrogen phosphate. During the experiments, the concentration of host was 2 mM and the concentration of tetrabutylammonium dihydrogen phosphate was increased. With the addition of tetrabutylammonium dihydrogen phosphate to the solution of receptor **1** in DMSO-d_6, downfield shifts of amide N─H, aromatic C─H (H_a) and aliphatic CH_2 (alpha to the carbonyl group) peaks were observed. For example, amide N─H peak moved from 10.39 to 12.00 ppm, aromatic C─H (H_a) moved from 8.43 to 8.69 ppm and aliphatic CH_2 peak moved from 4.07 to 4.22 ppm (Figure 1(b)). This result indicates that the added dihydrogen phosphate is complexed by receptor **1** through amide N─H, aromatic C─H (H_a), and aliphatic C─H.

The stoichiometry of receptor **1** to dihydrogen phosphate was turned out to be 1:1 using ^{1}H NMR Job plot in DMSO-d_6 (Figure 2).

The change of 367 nm in the UV–Vis spectra was utilized in plotting a Benesi–Hildebrand plot[5] and hydrogen chemical shifts in ^{1}H NMR was utilized in EQNMR[6] analysis to give association constant. From the experiments, the association constant for dihydrogen phosphate turned out to be 1.5×10^3 (M^{-1}) from UV–Vis titration and 1.3×10^3 (M^{-1}) from ^{1}H NMR titration respectively.

Receptor **2** and receptor **1** have similar structures except that receptor **2** does not have nitro group that polarizes aromatic C-H_a group. Receptor **2** showed absorption bands at 297 nm in DMSO. On addition of increasing amounts of

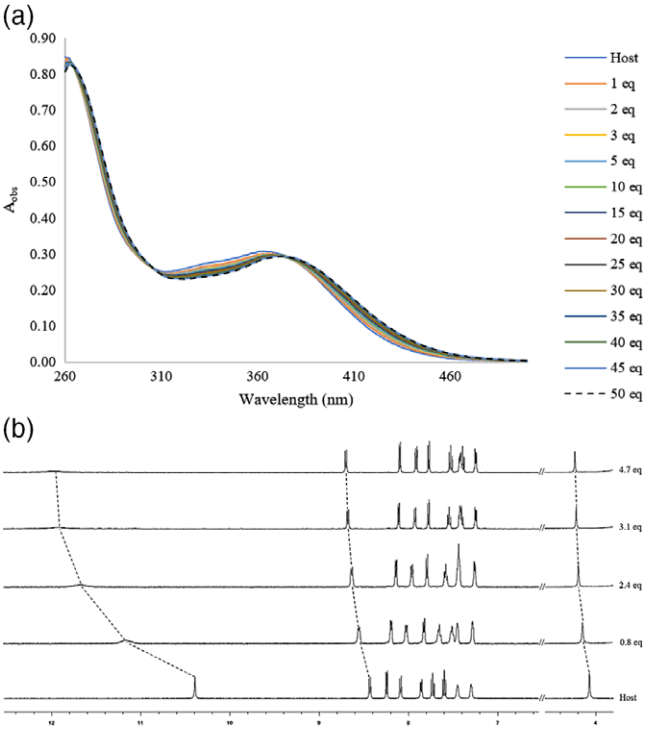


Figure 1. (a) Family of UV–Vis spectra recorded over the course of titration of in DMSO solution of the receptor **1** with the standard solution tetrabutylammonium dihydrogen phosphate (b) ^{1}H NMR spectra of **1** with increased amounts of tetrabutylammonium dihydrogen phosphate (0–4.7 equiv) in DMSO-d_6.

dihydrogen phosphate, the formation of a hydrogen bonding complex was also observed with an isosbestic point at 336 nm (Figure 3(a)). Receptor **2** showed the hydrogen bonded complex again in ^{1}H NMR titration. Until 8.2 equiv of dihydrogen phosphate were added, the amide N─H peak moved from 10.20 to 10.99 ppm, aromatic C─H (H_a) moved from 8.06 to 8.15 ppm and aliphatic CH_2 peak moved from 4.06 to 4.12 ppm (Figure 3(b)). These results indicate that these hydrogens are also major hydrogens involved in hydrogen bonding with anions during titration and added dihydrogen phosphate is complexed by receptor

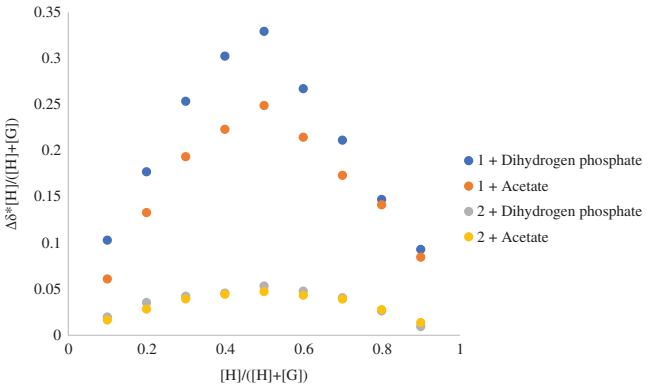


Figure 2. Job plot analysis of receptor **1** and **2** with dihydrogen phosphate and acetate.

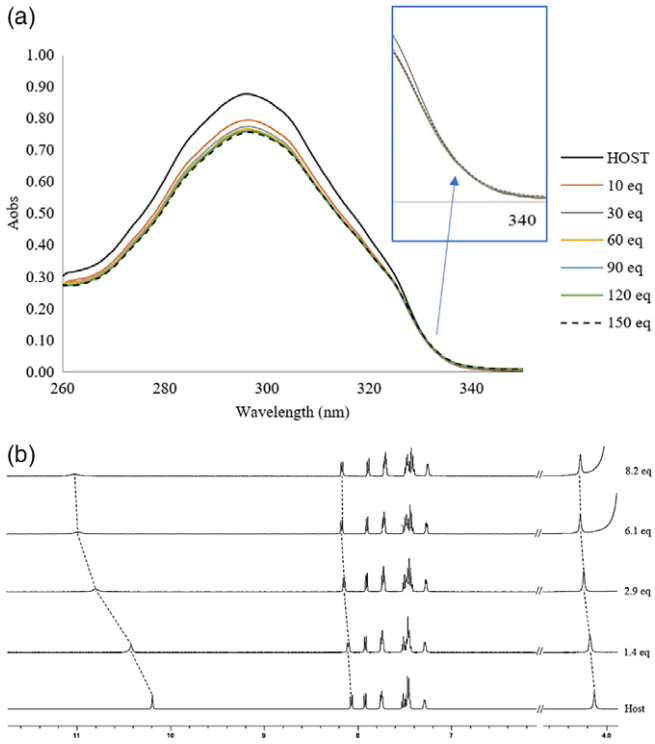


Figure 3. (a) Family of UV–Vis spectra recorded over the course of titration of in DMSO solution of the receptor **2** with the standard solution tetrabutylammonium dihydrogen phosphate (b) ^{1}H NMR spectra of **2** with increased amounts of tetrabutylammonium dihydrogen phosphate (0–8.2 equiv) in DMSO-d_6.

2 through amide N─H, aromatic C–H_a and aliphatic CH_2. The association constants calculated between receptor **2** and dihydrogen phosphate were found to be 8.8×10^2 from UV–Vis titration and 8.7×10^2 from ^{1}H NMR titration.

Receptor **3** has structure which does not have aromatic C–H_a group to bind anions. Therefore, it has only amide N─H and aliphatic CH_2 for anion binding. Interestingly, receptor **3** did not show any changes in the spectrum in UV–Vis titration. Probably, these hydrogens bonds are not strong enough to make a complex with dihydrogen phosphate in UV–Vis titration condition (60 μM), which indicates the importance of polarization of C–H_a in receptors **1** and **2**. However, complex formation between receptor **3** and dihydrogen phosphate was observed in ^{1}H NMR titration experiments in DMSO-d_6 using a constant host concentration (2 mM). The addition of tetrabutylammonium dihydrogen phosphate to the solution of receptor **3** in DMSO-d_6 resulted in a downfield shift of amide N─H, and aliphatic CH_2 peaks. For example, amide N─H peak moved from 10.19 to 11.66 ppm and aliphatic CH_2 peak moved from 3.81 to 3.89 ppm (Figure 4). The stoichiometry of receptor **1** to dihydrogen phosphate turned out to be 1:1 using ^{1}H NMR Job plot in DMSO-d_6 (Figure S11, Supporting information). Although isosbestic point was not observed in UV–Vis titration, we were able to observe 1:1 binding in ^{1}H NMR

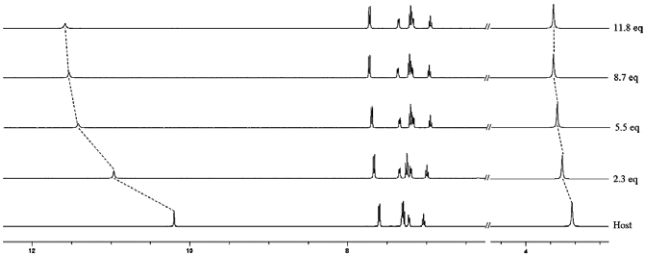


Figure 4. ^{1}H NMR spectra of **3** with increased amounts of tetrabutylammonium dihydrogen phosphate (0–11.8 equiv) in DMSO-d_6.

condition. Therefore, we were able to calculate association constant between receptor **3** and dihydrogen phosphate. It turned out to be 4.4×10^2 from ^{1}H NMR titration.

The recognition of acetate with receptor **1** were also studied in DMSO using UV–Vis titration spectra. Like dihydrogen phosphate, the complex formation between receptor **1** and acetate was observed from the slight bathochromic shift of absorption band and multiple isosbestic point at 260 and 367 nm upon addition of tetrabutylammonium acetate (Figure 5(a)). ^{1}H NMR titration experiments also showed complex formation between receptor **1** and acetate. The addition of tetrabutylammonium acetate to the solution of receptor **1** in DMSO-d_6 resulted in a downfield shift of amide N─H, aromatic C─H (H_a), and aliphatic CH_2 (alpha to the carbonyl group) peaks. For example, amide N─H peak moved from 10.39 to 11.76 ppm, aromatic C─H (H_a) moved from 8.43 to 8.56 ppm and aliphatic CH_2 peak moved from 4.07 to 4.15 ppm (Figure 5(b)).

From the experiments, the association constant for acetate was found to be 4.8×10^2 (M^{-1}) from UV–Vis titration and 4.5×10^2 (M^{-1}) from ^{1}H NMR titration, respectively. Similar behavior was observed when receptor **2** and **3** were titrated with acetate. Receptor **2** and **3** showed relatively low association constants for acetate in both UV–Vis titration and ^{1}H NMR titration (Table 1), which also indicate the importance of polarization of C–H_a in these receptors. Halides showed weak association constants with these receptors although their association trend is same with dihydrogen phosphate and acetate. Iodide, nitrate, hydrogen sulfate did not show any affinities for these receptors. Cyanide and Fluoride showed only deprotonation of amide N─H. The binding constants calculated for all the anions investigated are summarized in Table 1.

Computational Procedure. All the calculations have been performed with Gaussian 09 suite of programs.[7] We have used popular hybrid B3LYP functional[8] with extensive basis sets of 6-311G(d,p). All the geometries were fully optimized without any constraints and later confirmed to be at the local minima in energy hypersurface by second derivative calculations with respect to coordinate. Solvation effects were handled with polarizable continuum model (PCM)[9] using dielectric constant of DMSO. Partial charges

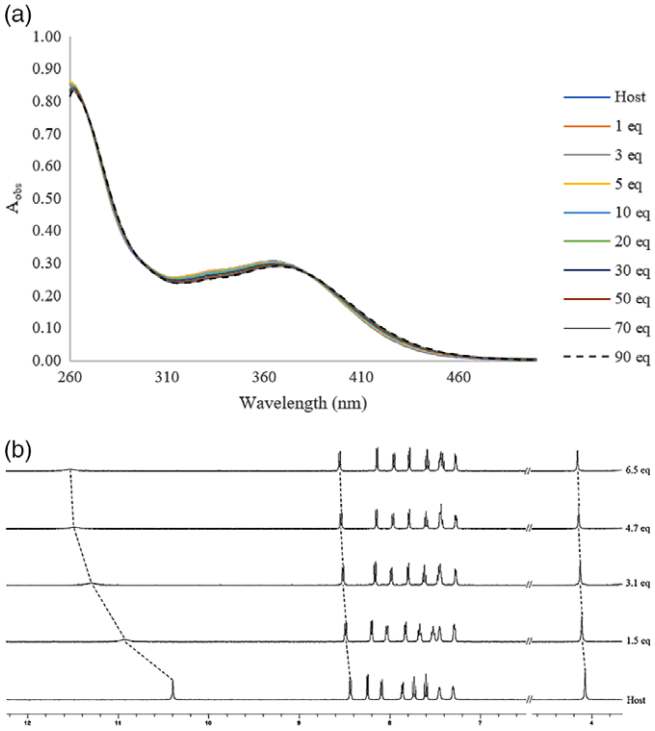


Figure 5. (a) Family of UV–Vis spectra recorded over the course of titration of in DMSO solution of the receptor **1** with the standard solution tetrabutylammonium acetate (b) ^{1}H NMR spectra of **1** with increased amounts of tetrabutylammonium acetate (0–6.5 equiv) in DMSO-d_6.

Table 1. Association constants (M^{-1}) of receptors **1**, **2,** and **3** with various anions in DMSO.

	1		**2**		**3**
Anion	NMR	UV–Vis	NMR	UV–Vis	NMR
$H_2PO_4^-$	1.3×10^3	1.5×10^3	8.7×10^2	8.8×10^2	4.4×10^2
CH_3COO^-	4.5×10^2	4.8×10^2	3.8×10^2	4.0×10^2	2.1×10^2
Cl^-	8.0×10^1	8.3×10^1	7.6×10^1	7.7×10^1	4.6×10^1
Br^-	3.9×10^1	3.9×10^1	3.1×10^1	3.2×10^1	1.2×10^1

were evaluated using natural population analysis scheme. For visual geometry inspection, GaussView5.0 was used (Figure 6).

Modeling Results. Receptor geometries were optimized and NPA partial charges are depicted as shown in Figure 6. Here, only hydrogens which have shown to interact with anions by NMR experiments are depicted. The biggest difference is the charge of $\mathbf{H_a}$, which is positive for both receptors **1** and **2**. For receptor **1**, the charge of $\mathbf{H_a}$ is significantly more positive via electron withdrawing effect of NO_2 functional groups. The partial charges of $\mathbf{H_a}$ nicely explains why the affinity order of these hosts toward various anions is **1** > **2** > **3**.

Based on the NMR titration data, we have modeled binding poses those are listed in Table 1. Since all three

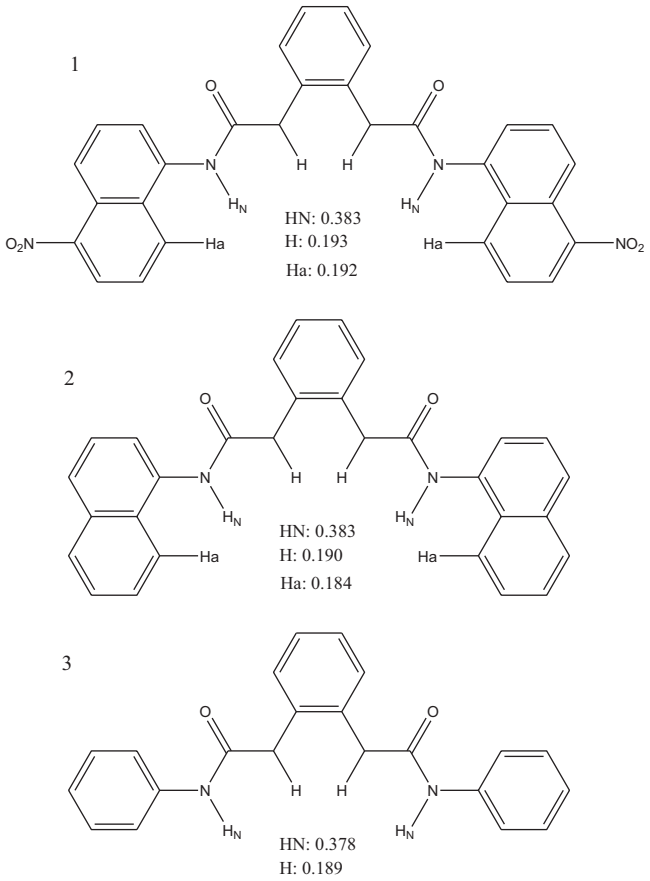


Figure 6. The partial charges of hydrogens involving anion recognition, $\mathbf{H_N}$: Amide hydrogen, **H**: Aliphatic hydrogen, $\mathbf{H_a}$: Aromatic hydrogen.

receptors showed selectivity toward dihydrogen phosphate, the binding poses three receptors with dihydrogen phosphate are depicted in Figure 7. All the coordinates for optimized anion and receptor complex structures were listed in Supporting information.

As shown in Figure 7, all the complex structures possess the hydrogen bonding interactions from NMR titration experiments. It is very likely that these modeled structures can be regarded as reasonable structures, although they are only snap shots of dynamic molecular recognition processes. However, the relative binding energies obtained

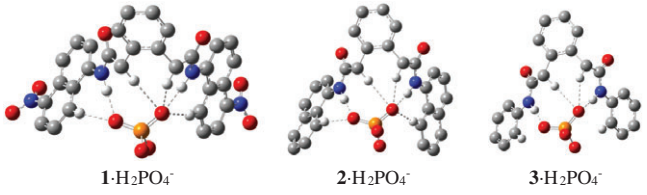


Figure 7. Dihydrogen phosphate complexes with three receptors **1**, **2,** and **3**; hydrogen bonding interactions which are responsible to anion recognition are denoted by dotted lines. All the hydrogens except the ones involving anion recognition are omitted for visual convenience.

from these structures are not consistent with experimental data. For example, in calculated relative binding energy, it is predicted that acetate is the strongest binder among various guests tested in this study. We believe that the modeled structures could be reasonably accurate. But the energetic values obtained from various DFT calculations were not accurate enough to simulate DMSO solution phase. Therefore, we only reported structural features, and the detailed energy calculation values are reported in supplementary material for further reference. (Tables of S1–S4).

Conclusion

In conclusion, we have designed and synthesized anion receptor **1**, **2,** and **3** based on 1,2-phenylenediamide scaffold. For any anions tested, receptor **1** and **2** have higher binding affinity than receptor **3**, indicating positive involvement to anion recognition of aromatic hydrogens which are present only in receptor **1** and **2**. Between receptor **1** and **2**, receptor **1** always showed higher binding affinity regardless of the anions tested in this study. This notion was further supported by the partial charge analyses using NPA (natural population analysis) scheme based on the electron density (B3LYP/6-311G**). More positive charges of $\mathbf{H_a}$ in receptor **1** by electron withdrawing effect of NO_2 group should be responsible for higher anion affinity of receptor **1**. Therefore, the contribution of aromatic C─H hydrogen bond was demonstrated. And we could modulate anion affinity via an aromatic C─H hydrogen bonding element. In addition, all the receptors (**1**, **2,** and **3**) are selective for dihydrogen phosphate and acetate.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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