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A Molecular Seesaw Balance: Evaluation of Solvent and Counteranion Effects on Pyridinium−π Interactions

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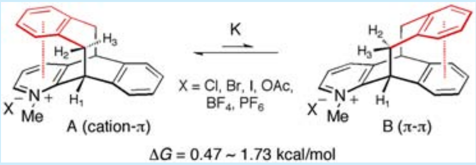
Supporting Information



ABSTRACT: A molecular seesaw balance **1**·MeI has been developed to measure pyridinium−π interactions. This balance adopts two distinct conformers, **A** and **B**, which are stabilized by a cation−π interaction and a π−π interaction, respectively. The conformer ratio was determined on the basis of the averaged ^3J coupling constants for H1−C−C−H2 and the corresponding boundary J values for conformers **A** and **B**. The effects of the solvent and the counteranion on the ΔG values were investigated using this molecular balance. Thermodynamic parameters obtained from a van't Hoff plot helped us to better understand the solvent and counteranion effects.

It has been well documented that cation−π interactions[1] play an important role in protein structure and molecular recognition in biological[2] and supramolecular systems.[3] Moreover, the interactions are used for crystal engineering[4] and stereoselective transformation[5] through the control of molecular assembly and conformation. As the strength of the cation−π interaction energy is larger than those of other aromatic interactions,[6] elucidation of the nature of cation−π interactions is of great importance in understanding its role in such systems as well as in the further development of its utility. While there have been a number of theoretical studies on the characterization of cation−π interactions, there have been relatively few experimental approaches although they are expected to provide valuable information regarding the behavior of molecules in solution.

To measure the strength of the noncovalent interactions experimentally, various molecular balances have been synthesized,[7] such as conformationally restricted cyclophanes,[8] Tröger's base derivatives,[9] *N*-arylsuccinimides,[10] propargylic amides,[11] triptycenes,[12] biarylimines,[13] dibenzobicyclic [3.2.2]-nonanes,[14] and *N*-benzylpyridinium systems.[15] While most of these are used for the characterization of π−π and CH−π interactions, there remain only a few molecular balances for assessing cation−π interactions.[10d,15b]

We designed a bidirectional molecular balance, a seesaw balance,[14b,26] for the comparative study of interaction energies between pyridinium−π and π−π interactions. This balance consists of azaanthracene- and quinodimethane-derived fragments as shown in Figure 1; the azaanthracene-derived fragment possessing both aryl and pyridine rings forms the base unit of the balance, and the quinodimethane-derived fragment with a benzene ring is the mobile unit. The mobile unit is connected to the base unit at C9 and C10, the benzene ring of which can move back and forth like a seesaw through its attraction to the benzene and pyridinium rings of the base. This balance is in equilibrium between two conformers, **A** and **B**, which are stabilized by a cation−π interaction and a π−π interaction, respectively (Figure 1). Motherwell and Aliev have reported this type of molecular balance for the investigation of π−heteroatom interactions.[14a]

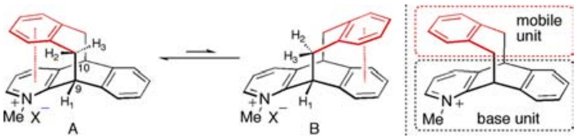


Figure 1. A seesaw balance for the quantification of pyridinium−π interactions.

This molecule has several advantages as a molecular balance as follows: (1) The molecular balance adopts only two distinct conformers, excluding undesirable conformational flexibility; (2) the benzene ring of the mobile unit is restricted to a parallel orientation in approaching the pyridine and benzene rings of the base, thus limiting face-to-face interactions; and (3) the two conformers show a high degree of symmetry, enabling direct comparison of the conformers without the need for any reference compounds. In this letter, we report the synthesis of a new molecular balance together with the characterization of pyridinium−π interactions achieved through its application.

A new molecular balance **1** was prepared by the reaction of 1-azaanthracene[16] and *o*-quinodimethane,[17] which is produced from the corresponding sulfone *in situ*, as shown in Scheme 1. The quarternization of the pyridine ring of **1** with methyl iodide gave the corresponding *N*-methylpyridinium iodide (**1**·MeI) in 77% yield. The iodide ion was replaced with other anions to give various salts with a different counteranion.

The structures of **1** and **1**·MeI were confirmed by X-ray structural analyses. As shown in Figure 2, the structure of **1** adopted the geometry of conformer **A**, the benzene ring of which overlaps with the pyridine ring. The distance between the centroids is 3.883 Å. Contrary to our expectations, the structure of **1**·MeI adopts the geometry of conformer **B**, and the benzene

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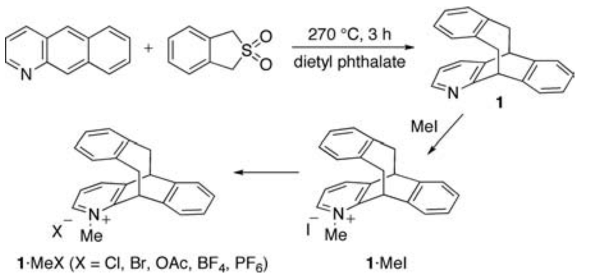
Scheme 1. Synthesis of the Molecular Balances 1 and 1·MeX



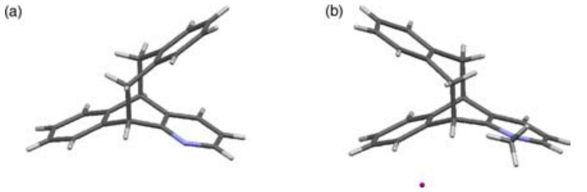


Figure 2. X-ray structures of (a) **1** and (b) **1**·MeI.

ring of the mobile unit is close to the benzene ring of the base with a distance of 3.844 Å between the centroids. However, intermolecular cation−π interactions were observed between the pyridinium and benzene rings as shown in Figure S11. The molecules form a columnar motif, which is stabilized by $Py^{+}\cdots Ar$ interactions with a distance of 3.673 Å. This may be due to the formation of more stable crystals through intermolecular cation−π interactions. Similar intermolecular cation−π interactions were also observed in the X-ray structure of **1**·$MeBF_4$ (Figure S12). The interplanar angles of the two rings in the base and mobile units are 49°−52°, which are the result of the restricted motion of the aromatic ring due to the rigid framework structure. It is well-known that the parallel stacking of aromatic rings gives rise to repulsive forces between them.[18] In this case, the larger interplanar angle significantly reduces the repulsive force.

To assess the population of conformers **A** and **B** shown in Figure 1, we first attempted to measure the population of conformers using dynamic ^1H NMR spectroscopy in CD_2Cl_2 (Figure S6). The methylene protons coalesced at 181 K, but the two conformers were not separated at temperatures above the freezing point of this solvent, suggesting that the interconversion energy of this balance is much smaller than that required to separate the two conformers. Therefore, an alternative approach was examined on the basis of the coupling constant of a bridgehead methine proton. Figure 3 shows the ^1H NMR spectra for **1** and **1**·MeI in $CDCl_3$. The methine proton H_1 of **1** appeared at δ 4.51, which coupled differently to vicinal protons H_2 and H_3 with coupling constants of 7.66 and 6.02 Hz, respectively. In the case of **1**·MeI, H_1 appeared at δ 5.23 as a doublet of doublets with coupling constants of 9.83 and 3.95 Hz for $J_{H1,H2}$ and $J_{H1,H3}$, respectively. The differences in the $J_{H1,H2}$ values between **1** and **1**·MeI indicate that the changes in the population of conformers **A** and **B** is the result of the quarternization of the pyridine ring. These observed averaged coupling constants are a function of the population of the conformers, N_A and N_B, and are defined by following equation: $J_{obs} = N_AJ_A + N_BJ_B$, where J_A and J_B are the boundary values of the corresponding coupling constants for conformers **A** and **B**, respectively.

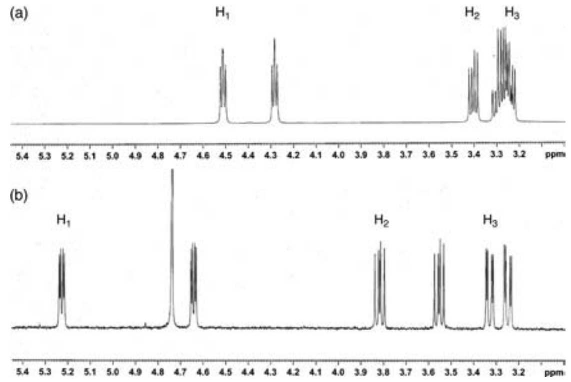


Figure 3. ^1H NMR spectra for (a) **1** and (b) **1**·MeI in $CDCl_3$.

The boundary J_A and J_B values of the corresponding conformers **A** and **B** can be obtained from H_1−C−C−H_2 torsion angles, $\phi_{A(H1,H2)}$ and $\phi_{B(H1,H2)}$, using the Karplus−Altona equation.[19] The $\phi_{A(H1,H2)}$ and $\phi_{B(H1,H2)}$ for **1** and **1**·Me^+ were obtained from the optimized geometries of the corresponding conformers **A** and **B** by MP2 calculations at the 6-311G* level, and the X-ray structures of **1** and **1**·MeI also provided corresponding torsion angles as shown in Table 1. As the J values obtained from the calculated and observed dihedral angles are very close, it appears reasonable to use the dihedral angles obtained from the optimized geometries for the quantification of the interaction energies.

Table 1. Φ_A and Φ_B Values Obtained from the Optimized Geometries and X-ray Structures, and the Calculated Boundary J_A and J_B Values

compd	source	Φ_A (deg)	Φ_B (deg)	J_A (Hz)	J_B (Hz)
1	MP2/6-311G*	4.69	106.27	10.49	2.07
1·Me+	MP2/6-311G*	4.71	110.33	10.49	2.60
1	X-ray	6.63	–[a]	10.43	–[a]
1·MeI	X-ray	–[b]	109.55	–[b]	2.49

[a] The X-ray structure for conformer **B** is not obtained. [b] The X-ray structure for conformer **A** is not obtained.

Table 2 shows the observed coupling constants $J_{H1,H2}$ and the population of conformers N_A and N_B as well as the ΔG values for **1** and **1**·MeI. From these results, the population of the conformer **A** of **1** is 66.4% in $CDCl_3$. This is in agreement with the reported observations that the interaction energies of $Py\cdots Ar$ are larger than those of $Ar\cdots Ar$.[6b,10d] On the other hand, the population of conformer **A** of **1**·MeI is 91.7% in the same solvent. This clearly shows a significant contribution of the cation−π interaction to

Table 2. ΔG Values for 1 and 1·MeI Obtained from J Values in Various Solvents[a]

compd	solv	J_{obs} (Hz)[b]	N_A (%)	N_B (%)	ΔG (kcal/mol)[c]	ε
1	$CDCl_3$	7.66	66.4	33.6	−0.40	4.8
1·MeI	$CDCl_3$	9.83	91.7	8.30	−1.42	4.8
1·MeI	CD_2Cl_2	9.40	86.2	13.8	−1.09	8.9
1·MeI	$(CD_3)_2CO$	8.66	76.9	23.1	−0.71	20.6
1·MeI	CD_3CN	8.00	68.5	31.5	−0.46	35.9
1·MeI	$(CD_3)_2SO$	8.24	71.5	28.5	−0.55	46.4
1·MeI	D_2O	8.04	69.0	31.0	−0.47	78.4

[a] A 1.0 mM solution was used for the measurement of ^1H NMR at 298 K. [b] Determined by ^1H NMR. The coupling constants were measured within an error range of ±0.01 Hz using the expanded spectra. [c] The error in the ΔG values is estimated to be within ±0.01 kcal/mol.

the determination of the conformer ratio for **1**·Me$^+$. The major conformer was assigned on the basis of NOESY measurement, where a correlation was observed between N−CH$_3$ and the aromatic proton of the mobile unit, and no correlation was observed between the two aromatic ring protons (Figure S5). The calculated energy differences between the optimized conformers **A** and **B** support the contribution of cation−π interactions (Table S16).

From Table 2, it is clear that the solvents have an effect on the conformer ratio of **1**·MeI. The ΔG values are in the range of −0.47 to −1.42 kcal/mol. These ΔG values are related to the polarity of the solvent: as the dielectric constant ε increases, the ΔG decreases. Based on computational studies, Dougherty and co-workers[20] reported a similar trend in the solvent effect on the cation−π interaction between methylammonium and benzene, where a linear relationship was observed between ΔG and $1/\varepsilon$. A plot of the dielectric dependence of the binding energies is shown in Figure 4; a good linear relationship was observed between ΔG and $1/\varepsilon$ with the exclusion of the ΔG value in CD$_3$CN. This solvent effect is speculated to result from the fact that the solvation of the pyridinium ion weakens the interaction between the pyridinium and benzene rings. Although the reason for the lower ΔG value for CD$_3$CN is not clear, an interaction between the iodide ion and CH$_3$CN[21] would affect the strength of the pyridinium−π interaction energy. It should be noted that as the ΔG values are the differences in the interaction energies between cation−π and π−π, the strength of the original cation−π interaction energy will be larger than the ΔG by the π−π interaction energy.

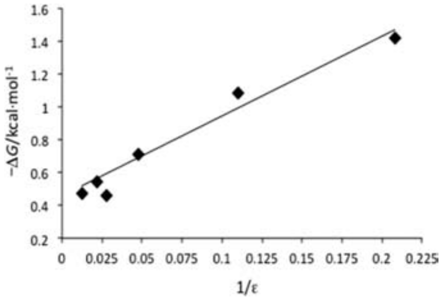


Figure 4. Plots of ΔG vs $1/\varepsilon$ for **1**·MeI (r^2 = 0.964 and 0.978 before and after exclusion of the ΔG value in CD$_3$CN, respectively).

Next, the counteranion effect on the ΔG values was investigated. With regard to the complexation of cations by the aromatic receptors in organic solvents, it has been reported that the association constant is correlated to the cation−anion attraction of the ion pair.[22,23] Hunter and colleagues applied chemical double mutant cycles to such three-component systems and confirmed that the intermolecular Py$^+$···Ar interaction energy is independent of the counteranions.[24] On the other hand, the effect on the intramolecular interaction has not yet been evaluated. We presumed that our molecular balance could be used to evaluate the counteranion effect on intramolecular cation−π interactions.

To clarify the counteranion effect on the intramolecular Py$^+$···Ar interactions, ΔG values of **1**·MeX possessing various counteranions were measured in CDCl$_3$ and (CD$_3$)$_2$CO. Table S1 shows the ΔG values for **1**·MeX as well as the ion radius r_{ci}.[25] It is clear that the counteranion had a significant effect on the ΔG values in CDCl$_3$, the values of which are in the range of −1.16 to −1.73 kcal/mol. Figure 5 shows plots of ΔG vs r_{ci}. A good linear relationship was observed between them after the exclusion of an acetate ion, with the ΔG decreasing as the ion size was increased. In contrast, in (CD$_3$)$_2$CO, the ion size had little effect on the ΔG value. These results can be explained by the fact that the anion binds with a cation to form an ion pair in nonpolar solvents (Figure 6a and 6b), and therefore, the steric bulkiness of the counteranion hinders intramolecular attraction. A hydrogen bond of the acetate ion with a pyridinium proton may be a reason for its failure to fit the linear relationship. In (CD$_3$)$_2$CO, both the cation and the counteranion are solvated and they are apart from each other (Figure 6c and 6d); as a result, the ΔG values are independent of the counteranions.

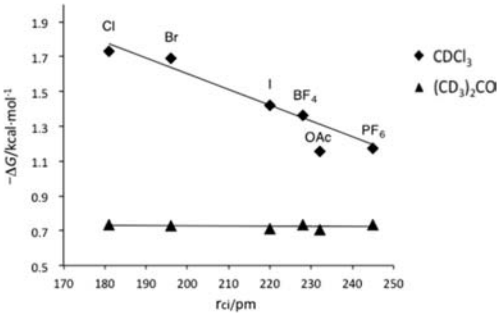


Figure 5. Plots of ΔG vs r_{ci} for **1**·MeI in CDCl$_3$ (r^2 = 0.921 and 0.974 before and after exclusion of the ΔG value for an acetate ion, respectively) and (CD$_3$)$_2$CO.

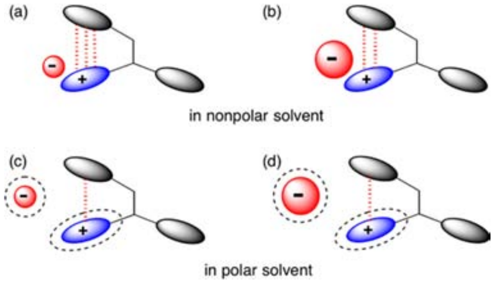


Figure 6. Schematic representation of **1**·MeX with (a) smaller and (b) larger counteranions in a nonpolar solvent, and **1**·MeX with (c) smaller and (d) larger counteranions in a polar solvent, the dotted lines of which show the solvation by a polar solvent.

To gain further insights into the details of the solvent and counteranion effects on the ΔG values, the thermodynamic data were obtained for **1**·MeI and **1**·MeCl in CDCl$_3$ and **1**·MeI in (CD$_3$)$_2$CO using the van't Hoff plot. Figure S10 shows a good linear relationship for $\ln(N_{\text{A}}/N_{\text{B}})$ vs $1/T$. The solvent had a significant effect on the slope, with the slope observed for (CD$_3$)$_2$CO being less steep than that for CDCl$_3$. The ΔH and ΔS values obtained from the plots are summarized in Table 3. The data show that all enthalpies are negative, but the value in (CD$_3$)$_2$CO is much smaller than the others. On the other hand, the entropies are negative in CDCl$_3$ and positive in (CD$_3$)$_2$CO. The smaller ΔH value and positive ΔS value in (CD$_3$)$_2$CO suggest the solvation of **1**·MeI by a polar solvent, thereby lowering the ΔG values. The larger ΔH value for **1**·MeCl than for **1**·MeI supports the notion of a counteranion effect in which a smaller chloride ion exerts less steric hindrance than an iodide ion on the intramolecular attraction.

In summary, we have synthesized a new molecular balance having two distinct conformers, **A** and **B**, which are stabilized by pyridinium−π and π−π interactions, respectively. The quantifi-

Table 3. ΔH° and ΔS° Values for 1·MeI and 1·MeCl Obtained from a van't Hoff Plot[a,b]

compd	solv	ΔH° (kcal/mol)	ΔS° (cal/mol·K)	$T\Delta S^\circ$ (kcal/mol)
1·MeI	$CDCl_3$	−2.75 ± 0.04	−4.4 ± 0.1	−1.31 ± 0.03
1·MeCl	$CDCl_3$	−3.72 ± 0.07	−6.6 ± 0.2	−1.97 ± 0.06
1·MeI	$(CD_3)_2CO$	−0.20 ± 0.02	1.82 ± 0.08	0.54 ± 0.02

[a] A 1.0 mM solution was used for the measurement of ^1H NMR. [b] Details of the calculations of ΔH° and ΔS° are shown in Tables S2−S7.

cation of the ΔG values for this molecular balance indicated that the solvation of the cation and anion by a polar solvent reduces the ΔG values, while the formation of an ion pair with a larger counteranion in the nonpolar solvent reduces the ΔG values due to steric hindrance to the intramolecular attraction. Further studies of the substituent effects and their application to a molecular switch are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02420.

Experimental and computational details; ^1H and ^{13}C NMR spectra of new compounds (PDF)
X-ray structural data for **1** (CIF)
X-ray structural data for **1**·MeI (CIF)
X-ray structural data for **1**·$MeBF_4$ (CIF)

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Notes

The authors declare no competing financial interest.

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(26) A part of this research has been reported in the 25th Symposium on Physical Organic Chemistry held at Sendai, Japan (a book of Abstract, 2P057, 2014). The term of "seesaw balance" has been used in there.