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Preference of intra- and intermolecular cation–π interaction: *cis–trans* geometrical effects of amide bond on the interaction mode

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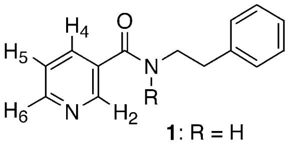
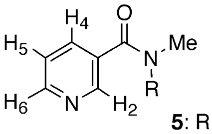
Abstract—An intermolecular cation–π interaction is observed in *trans*-amide **3**, whereas an intramolecular interaction is observed in *cis*-amide **4**, suggesting that *cis–trans* conformational difference plays a critical role in the preference of the interaction modes.

Cation–π interaction[1] between a pyridinium cation and an aromatic ring plays an important role in the formation of intramolecular complexes,[2,3] inclusion complexes[4] and supramolecules,[5] because of its larger interaction energy than that of related π–π and CH–π interactions.[6] Since the structure of molecules is responsible for the formation of complexes, elucidation of the relationship between the molecular structure and the interaction mode will provide insight into the design of various new complexes and supramolecules. In our previous studies, we have clarified a considerable substituent effect on the formation of the desired intramolecular pyridinium–π complex in *N*-methylnicotinium amides.[2] Tanaka and his co-workers reported that the steric bulkiness of the substituent in bis(pyridiniopropyl)benzene derivatives has a significant effect on the preference of the intra- and intermolecular interaction mode in crystal.[7]

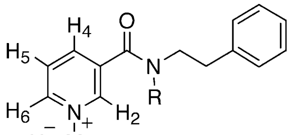
To clarify further the factors governing the interaction mode, we focused on very simple nicotinic amides **1** and **2** and the corresponding *N*-methyl salts **3** and **4**, the structures of which were investigated by ^{1}H NMR measurements and X-ray structural analyses. In this letter, we describe that *cis* and *trans* geometrical differences in the amide linkage significantly affect the interaction modes.



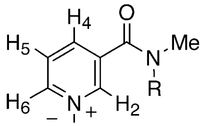
1: R = H
2: R = t-Bu



5: R = H
6: R = t-Bu



3a: R = H, X = Br
3b: R = H, X = I
4a: R = t-Bu, X =Br
4b: R = t-Bu, X = I



7: R = H
8: R = t-Bu

Table 1. δ Values for **1**–**8** and $\Delta\delta$ values for **1**–**4**[a]

	δ**1**	δ**5**	$\Delta\delta$**1**	δ**2**	δ**6**	$\Delta\delta$**2**	δ**3a**	δ**7**	$\Delta\delta$**3a**	δ**4a**	δ**8**	$\Delta\delta$**4a**
H2	8.85	8.96	−0.11	8.55	8.67	−0.12	10.37	9.70	0.67	8.02	9.07	−1.05
H4	8.05	8.12	−0.07	7.55	7.77	−0.22	9.04	9.07	−0.03	7.56	8.41	−0.85
H5	7.37	7.39	−0.02	7.30	7.33	−0.03	8.00	8.20	−0.20	7.87	8.12	−0.25
H6	8.69	8.73	−0.04	8.62	8.63	−0.01	8.84	9.13	−0.29	9.45	9.36	0.09
Me	—	—	—	—	—	—	4.62	4.62	0.00	4.57	4.74	−0.17

[a] Measured at 400 MHz in 10 mM solution of $CDCl_3$.

Keywords: Cation–π interaction; Pyridinium–π interaction; *cis–trans* effect; Amide bond.

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Table 2. Concentration dependence of the δ values of **3a** and **4a** in $CDCl_3$[a]

	δ**3a**			δ**4a**		
	2 mM	10 mM[b]	50 mM	2 mM	10 mM[b]	50 mM
H2	10.56	10.37 (9.92)	10.09	7.92	8.02 (7.92)	8.18
H4	9.03	9.04 (8.94)	9.05	7.49	7.56 (7.54)	7.64
H5	8.00	8.00 (8.05)	8.03	7.80	7.87 (7.84)	7.94
H6	8.65	8.84 (8.81)	9.12	9.45	9.35 (9.12)	9.26
Me	4.63	4.62 (4.57)	4.62	4.55	4.57 (4.44)	4.58

[a] Measured at 400 MHz.

[b] δ Values in the presence of 2 vol % of CD_3OD were indicated in the parentheses.

The ^1H NMR spectra of **1**–**4** showed that each compound exists as a single conformer on the amide linkage in $CDCl_3$ at 25 °C, and the NOE experiments clarified that the amide moiety of **1** and **3** is *trans* and that of **2** and **4** is *cis*. Table 1 shows the δ and $\Delta\delta$ values of the pyridine or pyridinium moiety for **1**–**8**. The $\Delta\delta$ values are the chemical shift differences of **1**–**4** with **5**–**8**. The $\Delta\delta$**1** and $\Delta\delta$**2** values are very small, indicating the phenyl groups are apart from the pyridine rings in **1** and **2**. In contrast, the absolute values of $\Delta\delta$**3a** and $\Delta\delta$**4a** for pyridinium salts **3a** and **4a** are much larger than those of $\Delta\delta$**1** and $\Delta\delta$**2**. The $\Delta\delta$**3a** and $\Delta\delta$**4a** lie in the range of -0.29 to 0.67 and -1.05 to 0.09, respectively, suggesting the existence of cation–π interactions in **3a** and **4a**. These results are in agreement with the observations that pyridinium–π interaction is stronger than the corresponding pyridine–π (π–π) interaction.[3,6] Remarkable is the significantly different trends between the $\Delta\delta$**3a** and $\Delta\delta$**4a** are significantly different from each other. While the $\Delta\delta_{H2}$ and $\Delta\delta_{H4}$ of **4a** are negatively very large, $\Delta\delta_{H2}$ of **3a** is positively very large. In addition, $\Delta\delta_{H6}$ of **4a** is positive whereas that of **3a** is negative.

Table 2 shows concentration dependence of the δ values of **3a** and **4a** in $CDCl_3$. The chemical shifts of **3a** significantly depend on the concentration; H2 is shifted to upfield and H6 is shifted to downfield with increase in concentration. On the other hand, the concentration dependence of **4a** is much smaller than that of **3a**, suggesting the difference in the interaction modes between them. Addition of 2 vol % of CD_3OD remarkably affects the δ_{H2} of **3a** and δ_{H6} of **4a**. This supports the complex formation of **3a** and **4a** in $CDCl_3$, since it is known that addition of polar solvent accelerates the dissociation of a cation–π complex.[8]

NOE experiments of **4a** clarified that the two rings are very close to each other; NOEs were observed between *N*-methyl, H2 and H4 protons and *m*- and *p*-protons of the phenyl group.[9] On the other hand, no such NOE was observed for **3a** as well as for **2**. These differences in the $\Delta\delta$ values, concentration effects and NOEs between **3a** and **4a** suggest that **3a** and **4a** prefer inter- and intramolecular cation–π interactions, respectively.

Preparation of single crystals of **3a** suitable for X-ray structural analyses was unsuccessful. However, recrystallization of the corresponding iodides **3b** from $CHCl_3$ gave good crystals suitable for X-ray analysis. The ORTEP diagram and the packing structure are shown in Figures 1 and 2, respectively.[10] It is clear that the amide linkage in **3b** is *trans* and the pyridinium and the phenyl rings are apart from each other as expected. As can be seen from Figure 2, every two molecules of **3b** make a dimeric complex, and are arranged in face-to-face and

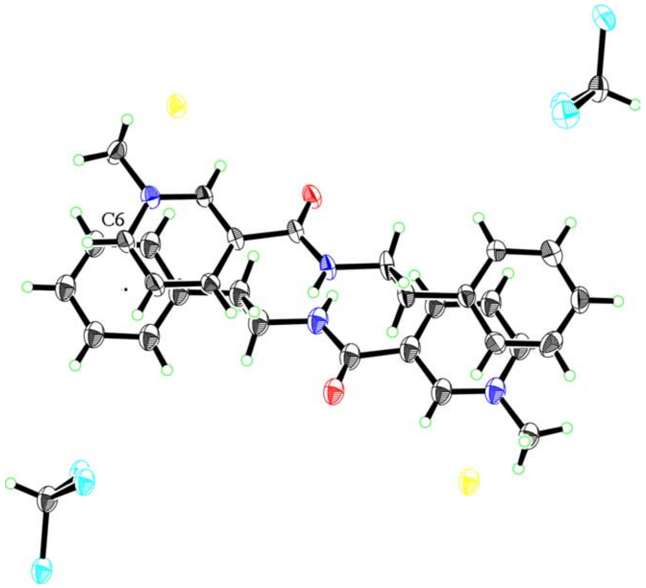

Figure 1. ORTEP drawing for **3b**·$CHCl_3$ at the 30% probability level. Two molecules are displayed to show their relative positions.

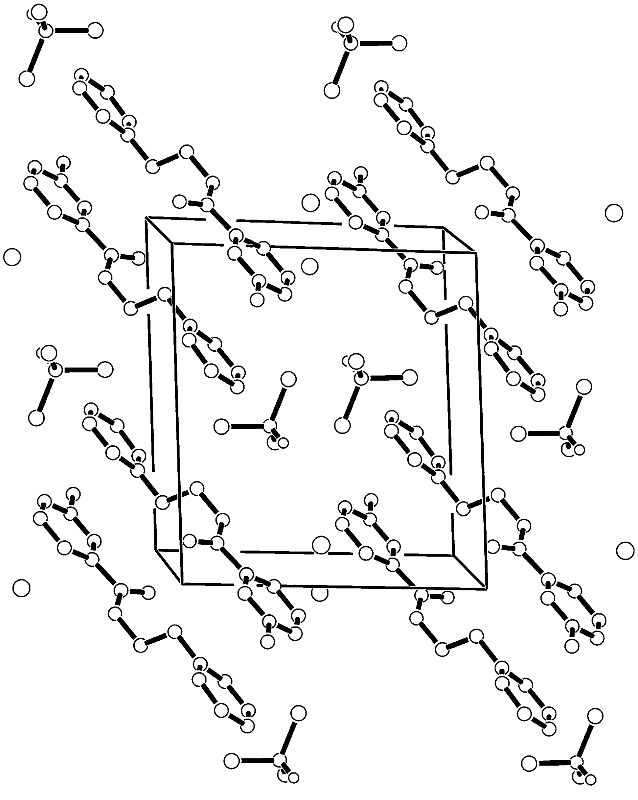

Figure 2. Packing structure of **3b**·$CHCl_3$. Hydrogen atoms are omitted for clarity.

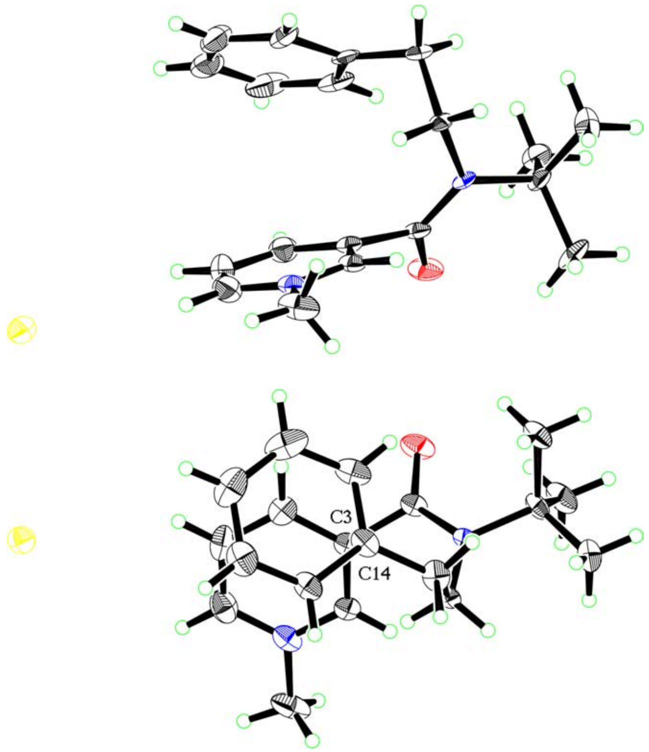

Figure 3. ORTEP drawing for **4b** (side view (up) and top view (down)) at the 30% probability level.

head-to-tail manner. The dimeric units are surrounded by anions and solvent, which may prevent the formation of infinite stacks. The centroid–centroid distance between the phenyl and the pyridnium rings is 3.700 Å and the distance of 3.504 Å between C6 and the centroid of the phenyl group is close to the sum of van der Waals radii of aromatic carbons.[11] It is important to note that no intermolecular hydrogen bonding in the N–H moiety is observed in this complex. These observations strongly suggest the existence of an intermolecular cation–π interaction in **3b**. This X-ray structure can explain the larger $\Delta\delta_{H2}$ and negatively larger $\Delta\delta_{H5}$ and $\Delta\delta_{H6}$ for **3a** in the ^{1}H NMR studies, suggesting a similar intermolecular interaction even in $CDCl_3$.

Figure 3 shows the crystal structure of **4b**.[10] The amide linkage is *cis*, and the pyridinium ring and the phenyl ring lie parallel to each other with a face-to-face arrangement. The 3.556 Å of the C3 and C14 distance is close to those of reported intramolecular pyridinium–π interaction. This clearly suggests the existence of an intramolecular cation–π interaction in **4b**. This stacking structure can satisfactorily explain the observed larger upfield shifts of H2 and H4 and NOEs in ^{1}H NMR studies. Therefore, it is concluded that the geometry in solution is very close to that in crystal.

Structural optimization of the pyridinium cation of **4** by DFT calculations at B3LYP/6-31G* level predicted a stable conformer with a stacked geometry as shown in Figure 4.[12] This geometry is very close to that obtained by X-ray analysis, though the interaction face is opposite. This result also supports the preference of intramolecular cation–π interaction in **4b**.

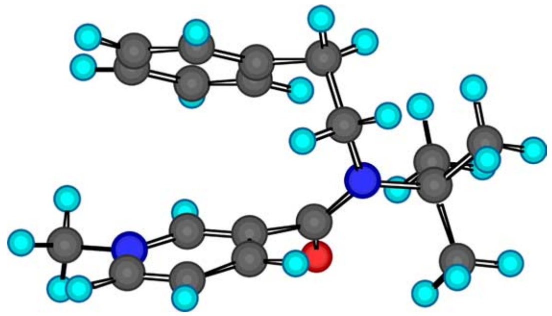

Figure 4. Optimized structure of a pyridinium cation of **4** predicted by DFT calculations.

In conclusion, ^{1}H NMR studies, X-ray structural analyses and DFT calculations of a series of nicotinic amides elucidated that compounds **3** and **4** prefer inter- and intramolecular cation–π complex formation both in solution and in crystal, respectively. This means that the *cis*–*trans* geometrical change of the amide linkage serves as a switch of the preference between intra- and intermolecular cation–π interaction modes.

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irradiation of *m*- and *p*-protons of the phenyl group resulted in 2.8%, 3.6% and 3.1% NOEs for the 2, 4 and 5-protons of the pyridinium ring, respectively.

10. Crystal data and structure refinement for **3b** and **4b**: Data were collected on a Rigaku AFC7R diffractometer with Cu-Kα radiation ($\lambda = 1.54178$ Å). The structures were solved by direct methods with SHELXS-86 and refined by full-matrix least-squares on F^2 using SHELXL-93. Compound **3b**: $C_{16}H_{18}Cl_3IN_2O$, $M = 487.59$, triclinic, P-1, $\mu = 14.090$ mm^{-1}, $a = 11.525(3)$, $b = 11.885(3)$, $c = 7.5846(9)$ Å, $\alpha = 102.963(14)$, $\beta = 104.153(13)$, $\gamma = 91.14(2)$, $V = 978.7(3)$ Å^3, $T = 230$ K, $Z = 2$, $D_c = 1.654$ g cm^{-1}. A total of 4776 reflections were collected and 3529 are unique ($R_{int} = 0.1775$). $R1$ and $wR2$ are 0.0972 [$I > 2\sigma(I)$] and 0.2785 (all data), respectively. Compound **4b**: $C_{19}H_{25}IN_2O$, $M = 424.31$, triclinic, P-1, $\mu = 13.067$ mm^{-1}, $a = 10.0397(11)$, $b = 13.718(2)$, $c = 7.5821(8)$Å, $\alpha = 100.226(10)$, $\beta = 102.344(10)$, $\gamma = 103.047(10)$, $V = 965.4(2)$ Å^3, $T = 296$ K, $Z = 2$, $D_c = 1.460$ g cm^{-1}. A total of 4790 reflections were collected and 3470 are unique ($R_{int} = 0.1223$). $R1$ and $wR2$ are 0.0502 [$I > 2\sigma(I)$] and 0.1898 (all data), respectively. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 267263 and 267264. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.jp].
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