Molecular Recognition

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F···H–N Hydrogen Bonding Driven Foldamers: Efficient Receptors for Dialkylammonium Ions**

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An essential attribute of biomacromolecules such as proteins and nucleic acids is their accurate control over the noncovalent forces that govern folding and self-assembly processes.[1] In recent years, chemists have been engaged in the development of foldamers,[2] artificial molecules that utilize noncovalent forces to modulate folding or helical structures. Among other noncovalent forces, the O···H–N hydrogen bonding motif has been widely utilized for this purpose,[3,4] a number of pyridine-N···H–N hydrogen-bonded folding architectures have also been developed.[5] Although it has been well established that the fluoride ion acts as a very strong proton acceptor,[6,7] it has been reported that covalently bound fluorine is a very weak intermolecular hydrogen-bonding acceptor.[8,9] We recently found that intramolecular F···H–N hydrogen bonding could be used to promote the stability of hydrazide-based quadruply hydrogen-bonded heterodimers.[10] We envisioned that rationally designed, intramolecular F···H–N hydrogen bonding might provide a novel approach for the formation of new rigid, well-established conformations. Herein, we demonstrate how intramolecular F···H–N hydrogen bonding controls the crescent and helical conformations of aromatic amides to such an

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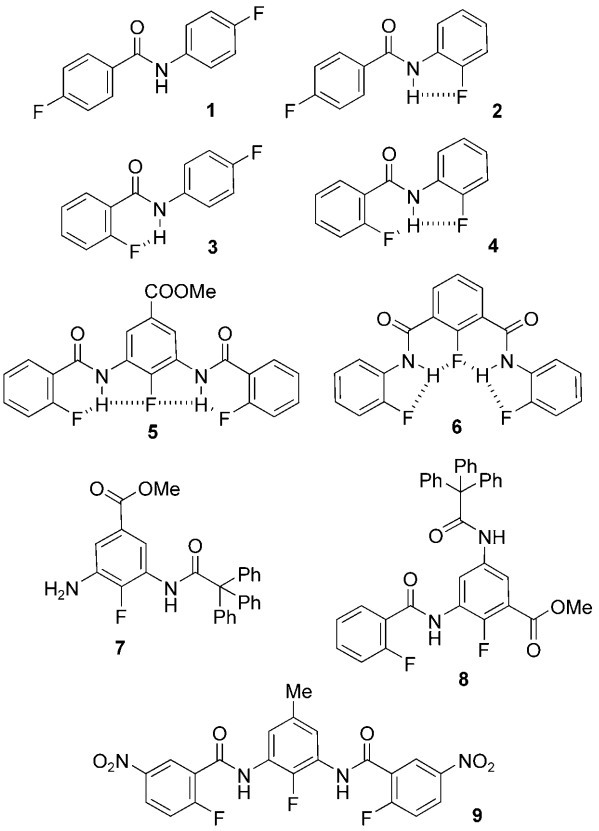
extent that the new foldamers can strongly bind dialkylammonium ions.

The molecular design was based on the recently established three-centered O···H–N hydrogen-bond motif.[11,12] Compounds **1**–**6** were prepared and a comparison of the



chemical shift of the amide proton in **2**–**6** with that in **1**, which cannot form intramolecular hydrogen bonds (Table 1), reveals a significant downfield shift of their NH signals, suggesting the formation of an intramolecular hydrogen bond in **2**–**6**. Larger changes with respect to **1** are exhibited for **4**–**6** than for **2** and **3**, indicating that the NH protons in **4**–**6** are involved in two hydrogen bonds simultaneously, as observed in the RO-related systems.[11–13]

Numerous attempts to crystallize **2**–**6** were unsuccessful. Given the well-known crystallinity of triphenylmethyl and nitro compounds,[14,15] compounds **7**–**9** were prepared. Crystals of **7**–**9** suitable for X-ray analysis were grown by slow evaporation of a dichloromethane/ethyl acetate solution of **7**–**9**. All three compounds adopt a well-defined planar conformation, which is rigidified by intramolecular F···H–N hydrogen bonds (Figure 1). For **7**, the F···H (amide) distance

Table 1: Chemical shifts (ppm) of the NH signals of **1**–**8**, **10**, and **11a** in $CDCl_3$ (1.0 mM) at 25 °C.[a]

Compound	Chemical shift	Compound	Chemical shift
1	7.78	**6**	8.57 (0.79)
2	8.00 (0.22)	**7**	8.43 (0.65)
3	8.47 (0.69)	**8**	8.88 (1.10)
4	8.83 (1.05)	**10**	8.91 (1.13)
5	8.92 (1.14)	**11a**	9.04 (1.26)

[a] The value in parentheses is the downfield change of the chemical shift relative to that of **1**.

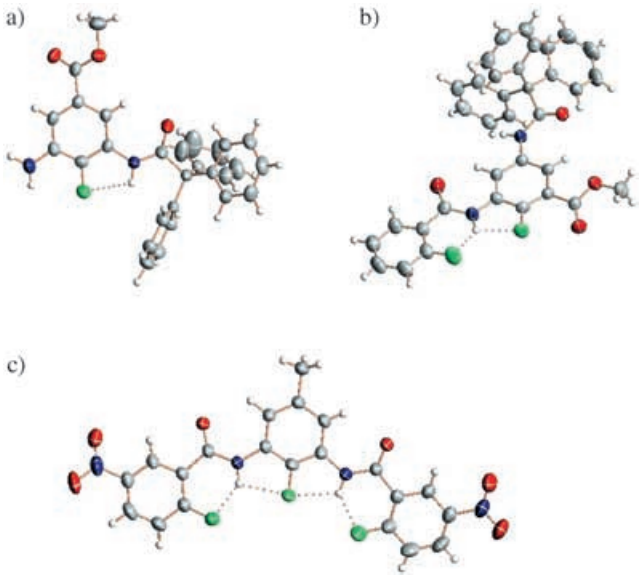
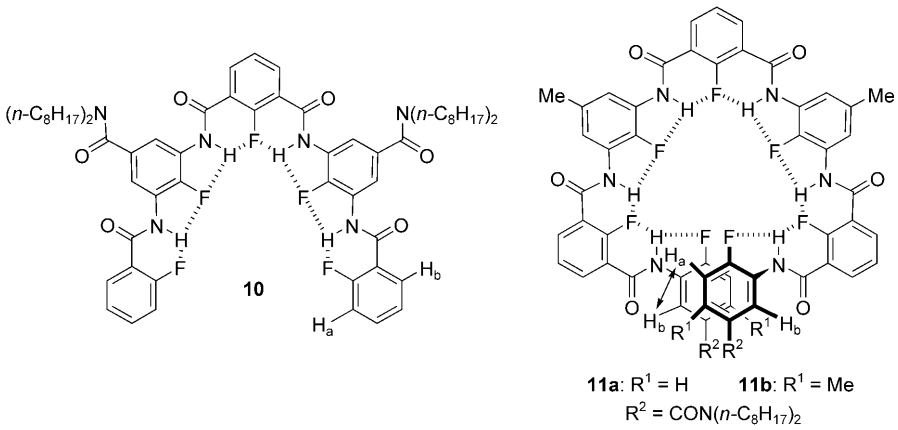


Figure 1. The crystal structures of a) **7**, b) **8**, and c) **9**.

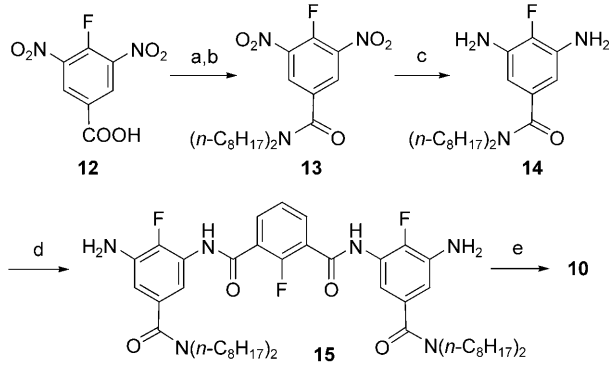
is 2.227 Å, and the F···H–N angle is 106.37°. The fluorine atoms of both **8** and **9** are located in the proximity of the amide hydrogen atom due to the formation of the three-centered hydrogen bonds. The F···H (amide) distance in the six- and five-membered hydrogen bonds is 1.935 and 2.184 Å for **8**, and 1.968 and 2.183 Å for **9**, respectively, and the corresponding F···H–N angles are 135.72 and 107.59° for **8** and 135.98 and 111.21° for **9**. All these values fall in the range considered acceptable for F···H–N hydrogen bonds, namely, the F···HN distance is less than 2.3 Å and the F···H–N angle is greater than 90°.[9a] In contrast, the F···HN distance for the amine group in **7** is 2.385 Å, which is outside the acceptable range given above. In addition, the skeleton of 3-mer **9** adopts a folding conformation.

The three-centered F···H–N hydrogen-bonding motif, which is present both in solution and in the solid state, is an ideal candidate for the construction of foldamers. To explore this possibility, 5-mer **10** and 7-mers **11a** and **11b** (Scheme 1) were synthesized, as shown in Scheme 2 and Scheme 3. Thus, acid **12** was first transformed to amide **13**, which was then reduced to diamine **14**. Treatment of **14** with 2-fluoroisophthaloyl chloride afforded **15**. Finally, reaction of **15** with 2-fluorobenzoyl chloride yielded **10**. For the preparation of **11a**, **16** was first reduced to amine **17**, which was acylated to yield **18**. The latter was then hydrolyzed to acid **19**, followed by a coupling reaction to give **20**. Treatment of **20** with 2-fluoroisophthaloyl chloride afforded **11a** (Scheme 3). Compound **11b** was prepared according to the similar route.

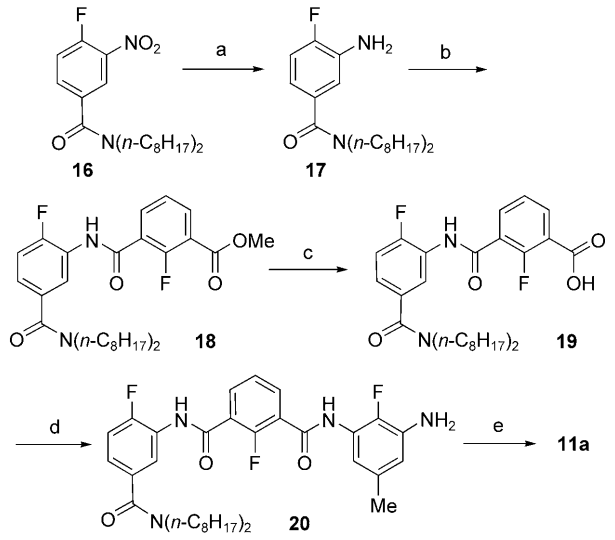
The peaks in the ^{1}H NMR spectrum of **10**, **11a**, and **11b** in $CDCl_3$ are sharp. Their signals have been assigned based on 2D-NOESY and COSY experiments. As expected, their NH signals are also shifted downfield substantially (Table 1) and



Scheme 1. The structure of crescent **10** and helical **11a** and **11b**. Compound **11b** displayed intramolecular end-to-end NOE values (500 MHz, 2.5 mM in $CDCl_3$ at 25 °C), which support a helical conformation for **11**.



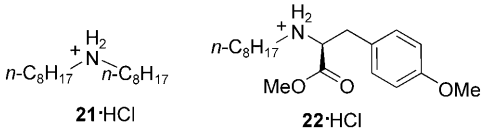
Scheme 2. The synthesis of **10**: a) oxalyl chloride, DMF (cat.), THF, RT, 0.5 h; b) $NH(n\text{-}C_8H_{17})_2$, NEt_3, THF, −10 °C, 1 h, 59%; c) H_2, Pd/C, MeOH/THF, RT, 48 h, 92%; d) 2-fluoroisophthaloyl chloride, NEt_3, CH_2Cl_2, RT, 0.5 h, 33%; e) 2-fluorobenzoyl chloride, NEt_3, CH_2Cl_2, RT, 1 h, 47%.



Scheme 3. The synthesis of **11a**: a) H_2, Pd/C, MeOH/THF, RT, 24 h, 98%; b) 2-fluoro-3-(methoxycarbonyl)benzoyl chloride, NEt_3, CH_2Cl_2, 0.5 h, 91%; c) LiOH, THF/H_2O, RT, 5 h, 98%; d) 2-fluoro-5-methylbenzene-1,3-diamine, EDCI, DMAP (cat.), CH_2Cl_2, RT, 12 h, 45%; e) 2-fluoroisophthaloyl chloride, NEt_3, CH_2Cl_2, RT, 1 h, 55%.

the values are comparable to those of the shorter oligomers **4**, **5**, and **8**. The results indicate that three-centered F···H–N hydrogen bonding also occurs in these oligomers. Moderate NOE values between H_a and H_b of the terminal benzene rings was observed for **11b** (Scheme 1). Because similar NOE values were not revealed for **10** even at the higher concentration of 10 mM, the observed NOE between H_a and H_b in **11b** can only be ascribed to that produced by an end-to-end arrangement, as shown in Scheme 1. This cross-ring NOE strongly supports a rigidified helical conformation of **11b** in chloroform.[4a,b] In contrast, 5-mer **10** is not long enough for its two end benzene units to stack or even to be in close proximity. In principle, a similar NOE might also be displayed in **11a**, but this could not be assigned due to signal overlap for the terminal benzene groups.

Molecular modeling revealed a crescent planar conformation for **10** and a helical conformation for **11a** and **11b**, in which the fluorine atoms converge towards the center of their skeletons creating a polar internal cavity of 6.5 and 6.6 Å diameter, respectively. Such a cavity appears well suited to complex secondary $R_2NH_2^+$ ions in a manner similar to that of dibenzo[24]crown-8.[16] The interactions of **10** and **11a** with symmetrical **21**·HCl were first investigated by means of ESI-MS analysis of their 1:1 solutions (1.0 mM) in chloroform.



Strong peaks for the complexes **10**·**21**·HCl and **11a**·**21**·HCl were observed (Figure 2). The ^{1}H NMR NOESY spectrum also revealed intermolecular a NOE of modest strength for the 1:1 solution of **10** and **21**·HCl as well as **11a** and **21**·HCl in $CDCl_3$ (Scheme 4). These results clearly indicate that strong intermolecular F···H electrostatic interactions or hydrogen bonding also exist between the new F···H–N hydrogen-bonded foldamers and **21**·HCl.[17]

Addition of **21**·HCl to the solution of **10** and **11a** in chloroform remarkably decreased the intensity of the emission for the folding oligomers in the fluorescent spectrum. Similar quenching was not observed when **21**·HCl was replaced with $n\text{Bu}_4\text{N}^+\text{Cl}^-$ under identical conditions. This result rules out the possibility of a salt effect at a higher concentration of ammonium and indicates that the reduction of the emission intensity was caused by the complexation of the folding molecules around the ammonium ion. As an example, the titration spectra of **11a** with **21**·HCl are provided in Figure 3. By fitting the data to a 1:1 binding mode, the association constant K_{assoc} of complexes **10**·**21**·HCl and

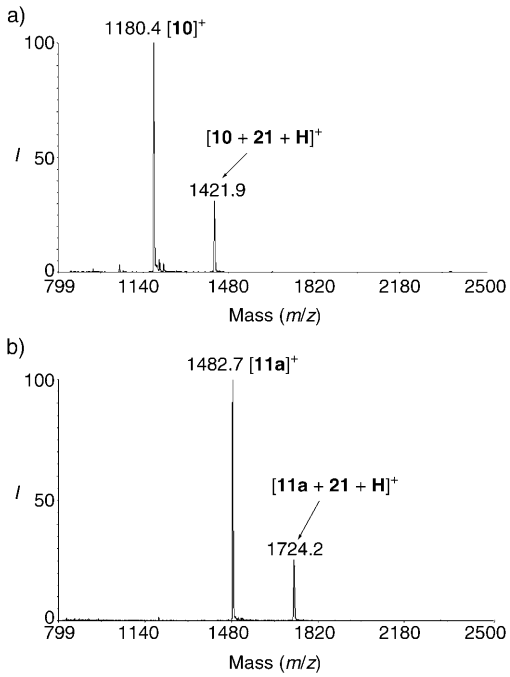
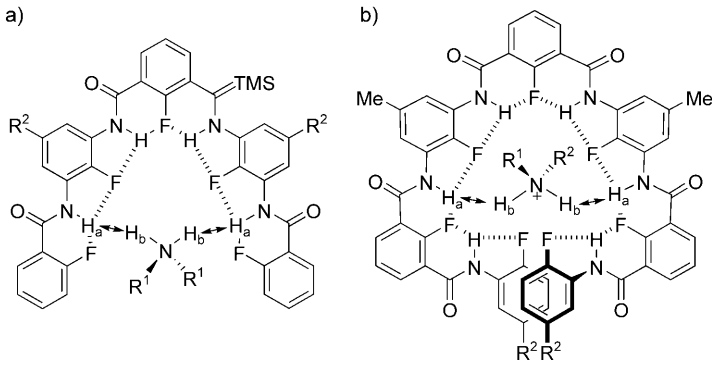


Figure 2. ESI mass spectrum obtained from the 1:1 solution (1.0 mM) of a) **10** and **21**·HCl and b) **11a** and **21**·HCl in chloroform.



Scheme 4. Intermolecular NOE connections revealed by the NOESY spectrum (500 MHz) of the 1:1 solution of a) **10** and **21**·HCl and b) **11a** and **21**·HCl in $CDCl_3$ (4.0 mM) at 23 °C (mixing time: 0.5 s).

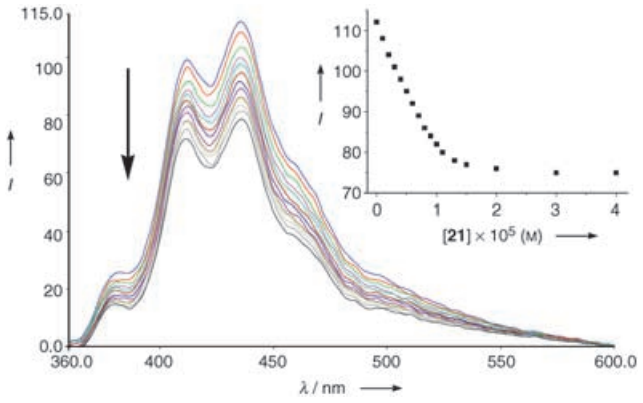


Figure 3. Fluorescent spectra of **11a** (1.5×10^{-5} M, excitation wavelength = 330 nm) in $CHCl_3$ at 25 °C, decreased gradually on addition of **21**·HCl (0 to 4.0×10^{-5} M).

11a·**21**·HCl was determined to be $4.9(\pm0.6)\times10^6$ and $8.1(\pm0.9)\times10^6\,M^{-1}$, respectively.[4b] The 1:1 stoichiometry of the complexes was estimated based on Job plots. The binding constants are considerably larger than that of the complex between dibenzo[24]crown-8 and dialkylammonium ions (ca. $2.7\times10^4\,M^{-1}$ in chloroform),[18] suggesting that highly efficient electrostatic interactions or hydrogen bonding could occur intermolecularly between fluorine and ammonium protons due to the rigidified conformation of the oligomers. By using the same method, the K_{assoc} values for the complexes of **10** with chiral **22**·HCl as well as **11a** with chiral **22**·HCl were determined to be $2.4(\pm0.2)\times10^5$ and $7.3(\pm0.8)\times10^5\,M^{-1}$, respectively. The values are notably lower than those of the respective complexes with **21**·HCl, but still larger than that of the complex between dibenzo[24]crown-8 and dialkylammonium ions.

Given the above strong binding features, chirality induction through complexation of **10** and **11a** with chiral L-tyrosine-derived ammonium **22**·HCl was investigated.[4b,19] The guest molecule itself (**22**·HCl) exhibits a CD signal at about 277 nm. Therefore, induced CD spectra generated from the interaction of **22**·HCl with **10** and **11a** were obtained by subtracting the spectrum of **22**·HCl from that of the complex. Figure 4 shows the typical CD curves of the complexes. Both

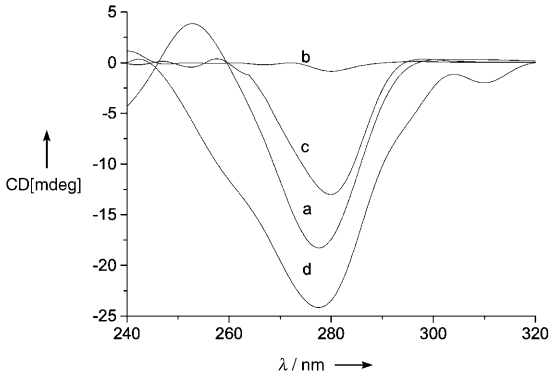


Figure 4. Induced CD spectra of complexes of **22**·HCl (1.0 mM) with a) **10** (1.0 mM), b) **11a** (0.01 mM), c) **11a** (0.05 mM), and **11a** (0.2 mM) in chloroform at 25 °C.

complexes gave rise to negative CD signals, which increased with the increase of the concentration of the foldamers. The intensity of the CD signals decreased on addition of polar methanol in the solvent and vanished in a mixture of methanol and chloroform (1:3 (v/v)), indicating that the signals were generated through intermolecular electrostatic interactions or hydrogen bonding. The different shape of the signals of the two complexes presumably reflects the different binding environments for both complexes.

In conclusion, we have demonstrated that intramolecular F···H–N hydrogen bonds can be utilized to construct a new generation of folding architectures. The new foldamers strongly bind dialkylammonium ions by means of intermolecular electrostatic interactions or F···H–N hydrogen bonding, which can give rise to chiral induction or amplification through complexation with chiral L-tyrosine-derived ammonium ions. It has been proposed that organic fluorine hardly ever accepts hydrogen bonds, the present work reveals that

relatively stable F···H–N hydrogen bonds can be formed, at least, in elaborately designed aromatic amides. This opens new possibilities in supramolecular chemistry. Future work will be aimed at the construction of helical and tubular systems with deeper and larger cavities. It also remains to be shown whether intra- or intermolecular F···H–O hydrogen bonds can be formed in organofluorine molecules.

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[1] D. S. Lawrence, T. Jiang, M. Levett, *Chem. Rev.* **1995**, *95*, 2229.
[2] a) D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015; b) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; c) K. D. Stigers, M. J. Soth, J. S. Nowick, *Curr. Opin. Chem. Biol.* **1999**, *3*, 714; d) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893; e) M. S. Cubberley, B. L. Iverson, *Curr. Opin. Chem. Biol.* **2001**, *5*, 650; f) A. R. Sanford, B. Gong, *Curr. Org. Chem.* **2003**, *7*, 1649; g) C. Schmuck, *Angew. Chem.* **2003**, *115*, 2552; *Angew. Chem. Int. Ed.* **2003**, *42*, 2448; h) I. Huc, Ivan, *Eur. J. Org. Chem.* **2004**, 17.
[3] a) P. S. Corbin, S. C. Zimmerman, P. A. Thiessen, N. A. Hawryluk, T. J. Murray, *J. Am. Chem. Soc.* **2001**, *123*, 10475; b) K. Gademann, A. Hane, M. Rueping, B. Jaun, D. Seebach, *Angew. Chem.* **2003**, *115*, 1573; *Angew. Chem. Int. Ed.* **2003**, *42*, 1534; c) J. S. Nowick, J. O. Brower, *J. Am. Chem. Soc.* **2003**, *125*, 876; d) J. S. Park, H. S. Lee, J. R. Lai, B. M. Kim, S. H. Gellman, *J. Am. Chem. Soc.* **2003**, *125*, 8539.
[4] a) B. Gong, H. Zeng, J. Zhu, L. Yuan, Y. Han, S. Cheng, M. Furukawa, R. D. Parra, A. Y. Kovalevsky, J. L. Mills, E. Skrzypczak-Jankun, S. Martinovic, R. D. Smith, C. Zheng, T. Szyperski, X. C. Zeng, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11583; b) J.-L. Hou, X.-B. Shao, G.-J. Chen, Y.-X. Zhou, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2004**, *126*, 12386; c) D. Kanamori, T. Okamura, H. Yamamoto, N. Ueyama, *Angew. Chem.* **2005**, *117*, 995; *Angew. Chem. Int. Ed.* **2005**, *44*, 969.
[5] a) Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1996**, *118*, 7529; b) E. Kolomiets, V. Berl, I. Odriozola, A.-M. Stadler, N. Kyritsakas, J.-M. Lehn, *Chem. Commun.* **2003**, 2868; c) B. Huang, M. A. Prantil, T. L. Gustafson, J. R. Parquette, *J. Am. Chem. Soc.* **2003**, *125*, 14518; d) H. Jiang, J.-M. Léger, I. Huc, *J. Am. Chem. Soc.* **2003**, *125*, 3448; e) J. Garric, J.-M. Léger, I. Huc, *Angew. Chem.* **2005**, *117*, 1990; *Angew. Chem. Int. Ed.* **2005**, *44*, 1954.
[6] a) S. A. Harrell, D. H. McDaniel, *J. Am. Chem. Soc.* **1964**, *86*, 4497; b) S. J. Coles, J. G. Frey, P. A. Gale, M. B. Hursthouse, M. E. Light, K. Navakhun, G. L. Thomas, *Chem. Commun.* **2003**, 568.
[7] a) L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**, p. 464; b) B. Dietrich, J.-M. Lehn, J. Guilhem, C, Pascard, *Tetrahedron Lett.* **1989**, *30*, 4125.
[8] H. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12613.
[9] a) J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89; b) J. D. Dunitz, *ChemBioChem* **2004**, *5*, 614.
[10] X. Zhao, X.-Z. Wang, X.-K. Jiang, Y.-Q. Chen, Z.-T. Li, G.-J. Chen, *J. Am. Chem. Soc.* **2003**, *125*, 15128.
[11] B. Gong, *Chem. Eur. J.* **2001**, *7*, 4337.
[12] a) Z.-Q. Wu, X.-K. Jiang, S.-Z. Zhu, Z.-T. Li, *Org. Lett.* **2004**, *6*, 229; b) J. Zhu, X.-Z. Wang, Y.-Q. Chen, X.-K. Jiang, X.-Z. Chen, Z.-T. Li, *J. Org. Chem.* **2004**, *69*, 6221.
[13] The proximity of the F and HN groups in **2** and other compounds may be partially caused by the repulsion of the F and C=O groups. Nevertheless, the coplanarity of the benzene units in **7–9** in the solid state supports the formation of intramolecular hydrogen bonds. We thank the referees for the stimulating comments on this issue.
[14] P. S. Corbin, L. J. Lawless, Z.-T. Li, Y. Ma, M. J. Witmer, S. C. Zimmerman, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5099.
[15] Z. Yin, L. Jiang, J. He, J.-P. Cheng, *Chem. Commun.* **2003**, 2326.
[16] P. R. Ashton, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 729.
[17] Complexes between fluorine-containing cyclophanes and ammonium, based on intermolecular F···HN^+ hydrogen bonding has been reported, see: H. Takemura, N. Kon, M. Yasutake, S. Makashima, T. Shinmyozu, T. Inazu, *Chem. Eur. J.* **2000**, *6*, 2334.
[18] This is the largest value for the dialkylammonium ions investigated, see: P. R. Ashton, P. J. Campbell, E. J. T. Chrystal, P. T. Glink, P. S. Menzer, D. Philip, N. Spencer, J. F. Stoddart, P. A. Tasker, D. J. Williams, *Angew. Chem.* **1995**, *107*, 1902; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1865.
[19] a) A. Tanatani, T. S. Hughes, J. S. Moore, *Angew. Chem.* **2002**, *114*, 335; *Angew. Chem. Int. Ed.* **2002**, *41*, 325; b) A. Petitjean, H. Nierengarten, A. van Dorsselaer, J.-M. Lehn, *Angew. Chem.* **2004**, *116*, 3781; *Angew. Chem. Int. Ed.* **2004**, *43*, 3695.

