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## A novel intramolecular through-space interaction between F and CN: a strategy for the conformational control of an acyclic system<sup>†</sup>

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Received (in Cambridge, UK) 8th August 2001, Accepted 11th October 2001 First published as an Advance Article on the web 2nd November 2001

X-Ray crystallographic analyses of fluorocyanides *anti*-1 and 2 revealed a novel *intramolecular through-space interaction between F and CN* in an acyclic system, which was applied to a stereoselective protonation of acyclic fluorocyanides 2 having flexible conformation.

The discovery of interactions between functional groups, such as hydrogen-bonding,  $\pi$ - $\pi$  stacking, and CH- $\pi$  interactions, is a pivotal area of investigation in organic and bioorganic chemistry. In organic synthesis, these interactions have controlled the stereochemistry in Diels-Alder and ene reactions.<sup>1</sup> Based on theoretical studies of the 'Bürgi-Dunitz trajectory' in nucleophilic additions to carbonyl groups,2 Dunitz et al., discovered in 1978 the interaction between the ethereal oxygen and the carbonyl group in 8-methoxy-1-naphthyl methyl ketones.3a The newly coined 'nucleophilic-electrophilic interaction' was also found between the nitrogen and the carbonyl carbon and between the oxygen and the cyanide carbon.<sup>3</sup> Recently, intramolecular nonbonded interactions between oxygen and sulfur or selenium in heterocycles have also been observed.<sup>4</sup> Because of their unique characteristics of metabolic inhibition and high lipophilicity, organofluorine compounds are widely used in pharmaco- and agrochemistry. However despite their extensive use, the interaction of fluoride with organofunctional groups has remained virtually unexplored,5 whereas interactions between fluoride and metals<sup>6</sup> and hydrogenbonding interactions with fluoride7 are often observed. We report herein the discovery of a novel through-space interaction between F and CN, which serves as a conformational regulation of a flexible acyclic carbon chain.

A molecule having two functional groups with large dipole moments in an acyclic system usually adopts a stable conformer in which the dipole moments oppose each other. However, we have observed the unusual phenomenon in which two functional groups in an acyclic system align to give the maximum dipole moment. Namely, during studies on ferroelectronic crystals,<sup>8</sup> a large spontaneous polarization was observed in liquid crystals doped with optically active 3-fluorocyanide derivatives. It is possible that in this case the two functional groups with large dipole moments aligned in the same direction to make a large spontaneous polarization; therefore, we postulated the existence of a novel through-space interaction between F and CN, as depicted in Fig. 1. In order to prove this hypothesis, we carried out X-ray crystallographic analyses of the crystalline fluorocyanides **1** and **2**.

The crystallographic analysis<sup>9</sup> (see ESI<sup>†</sup>) of optically active *anti*-**1**, which was prepared from 4-methoxyphenylacetonitrile and (*R*)-epoxyoctane,<sup>10</sup> is shown in Fig. 2. The distance between F and C(1) was found to be 2.890 Å, which is 0.28 Å



Fig. 1 Novel through-space  $n_F \to \pi^*{}_{CN}$  interaction to freeze the conformation in an acyclic system.

shorter than the sum (3.17 Å) of their van der Waals radii. The angle between these atoms when projected in the C2–C4 plane was 8.6°. These two functional groups formed an envelope-shaped *pseudo* five-membered ring which includes the three carbons C2–C4. The F moiety of the *pseudo* five-membered ring was distorted toward the CN group. Among the angles concerned with the *pseudo* ring,  $\theta_1$  and  $\theta_2$  were shorter than a right angle, and  $\theta_4$  was found to be less than 180°, unlike the usual cyanide having the linear sp configuration. These data suggest that the lone pair of the fluorine (n<sub>F</sub>) is being donated to the  $\pi^*$  orbital on the cyanide carbon ( $\pi^*_{CN}$ ).

Unlike the *anti*-1, the crystallographic analysis<sup>11</sup> (see ESI<sup>†</sup>) of the other diastereomer *syn*-1 has revealed that the angle between these atoms when projected in the C1–C3 plane is  $-118.6^{\circ}$ . Instead of a through-space interaction, an intermolecular hydrogen-bonding between phenolic hydrogen and cyano nitrogen was observed in the packing structure. This suggests that the observed through-space interaction between F and CN is weaker than the hydrogen-bonding interaction. Since the phenol moiety of the *syn*- and *anti*-1 had drastically affected their conformation through the hydrogen-bonding interaction, we next decided to investigate the conformation of their methyl ethers *syn*- and *anti*-2.

The crystallographic analysis<sup>12</sup> (see ESI<sup>†</sup>) of *anti*-**2** has shown that the distance between F and C(9) is 2.872 Å, which is 0.30 Å shorter than the sum of their van der Waals radii. The conformation of *anti*-**2** was found to be almost the same as that of *anti*-**1**; therefore, the novel through-space interaction was



Fig. 2 Crystal structure of anti-1.

<sup>†</sup> Electronic supplementary information (ESI) available: experimental procedure for the syntheses of *syn-* and *anti-***1** and **2**, spectroscopic data for all compounds, a procedure for the stereoselective protonation of **2**, full crystallographic data of *syn-* and *anti-***1** and *anti-***2**. See http://www.rsc.org/suppdata/cc/b1/b107213g/

proved to be independent of the intermolecular hydrogenbonding of the phenol moiety. However, conformational data on *syn-2* in solid state could not be obtained because it is an oil.

Since the through-space interaction between F and CN had been established in the crystal, we turned our attention to the existence of this new interaction in solution. The <sup>1</sup>H-NMR signals of the methylene protons (ABXX' type) in syn-1 were observed at 1.98 and 2.34 ppm in CDCl<sub>3</sub>, whereas those of anti-1 were at 1.94–2.13 (2H). These chemical shift values and the coupling patterns in *syn*- and *anti*-1 were very similar to those of the corresponding cis-y-lactone (1.99 and 2.72) and the trans-y-lactone (2.35 and 2.46), respectively.<sup>8a,b</sup> This observation suggests that the through-space interaction also occurs via a *pseudo* five-membered ring in both the *syn* and *anti*-fluorocyanides 1 in solution. To demonstrate the conformational control of an acyclic system utilizing this interaction, we investigated the stereoselective protonation of the  $\alpha$ -anion of the cyanide derived from an equimolar mixture of syn- and anti-2. Our working hypothesis is that the diastereoselective protonation of the naked anion intermediate<sup>13</sup> with a bulky proton source would give syn-2 preferentially by 1,3-asymmetric induction, based on a chiral carbon bearing a fluorine atom, if the through-space interaction between F and CN existed in the naked anionic molecule in solution. Our results are summarized in Table 1. Bulky phenols as proton sources gave products with higher diastereoselectivity than benzoic acid derivatives. 2,5-Dichlorobenzoic acid gave a product with lower selectivity than did benzoic acid, probably due to its higher acidity. The major diastereomer obtained was syn-2, with a very significant diastereoselectivity (5.3:1). We interpret this result as follows: the 1,3-asymmetric induction would arise from the *pseudo* five-membered ring intermediate formed by the through-space interaction between a lone pair of F and an spcarbon of the naked  $\alpha$ -anion of the cyanide, as in the control experiment under the same reaction conditions using an equimolar mixture of the corresponding cis- and trans-y lactones to give predominantly the cis-y-lactone (94% yield, cis: trans = 10.6:1). From the above experiments, this throughspace interaction, even in a solution containing the carbanion, is able to affect the conformational regulation of an acyclic carbon chain, but the ring formed by the interaction is not completely fixed as in the  $\gamma$ -lactone. However, this novel conformational regulation in an acyclic compound is valuable because of (1) the diastereoselective reaction of the  $\alpha$ -anion of the 3-fluorocyanide and (2) the stereochemical prediction of the product, both of which are usually difficult in acyclic systems.

In conclusion, we have observed for the first time *a novel intramolecular through-space interaction between F and CN* by X-ray crystallographic analyses of the 1,3-fluorocyanides *anti*-1 and 2. Although this through-space interaction is weaker than the hydrogen-bonding interaction, acyclic compounds having flexible conformations were conformationally controlled by this interaction to form the distorted *pseudo* five-membered ring. However, it is particularly noteworthy that the existence of this novel interaction can not be predicted by the semiemperical

Table 1 Stereoselective protonation of the naked  $\alpha$ -anion of cyanide<sup>a</sup>

| MeO | 1) <i>n</i> -BuLi (1.2 ed<br>HMPA (5 eq.)<br>2) H* (12 eq.)<br>2) H* (12 eq.)<br>THF, -78 °C, | a.) MeO<br>H<br>2 h   | F                      |
|-----|---|-----------------------|------------------------|
| Run | 2 <sup>a)</sup><br>H+   | syn:anti <sup>b</sup> | Yield (%) <sup>c</sup> |
| 1   | Benzoic acid  | 3.5:1                 | 100                    |
| 2   | 2,5-Dichlorobenzoic acid  | 1.9:1                 | 90                     |
| 3   | 2,6-Diphenylphenol  | 4.4:1                 | 87                     |
| 4   | 2,6-Di- <i>tert</i> -butyl- <i>p</i> -cresol  | 5.3:1                 | 91                     |

<sup>*a*</sup> syn:anti = 1.2:1. <sup>*b*</sup> Determined by <sup>1</sup>H-NMR of the crude products. <sup>*c*</sup> Isolated yield. PM3 calculation of *anti*-1, and by *ab initio* MP2 6-31G\* and density functional df 6-31G\* calculations of the simplified model compound of *anti*-1.<sup>14</sup> We also demonstrated the utility of the through-space interaction by a stereoselective protonation of an anion in solution. Further studies on through-space interactions between the functional groups are underway in our laboratory.

We are grateful for a Grant-in-Aid (No. 11672126 to K. N.) from the Ministry of Education, Science, Sports and Culture of Japan, in partial financial support of this research. We are also grateful to Professor Tamejiro Hiyama, Kyoto University, for helpful discussions at Sagami Chemical Research Center. We also thank the Japan Energy Corporation, Toda, Saitama, Japan, for its kind gift of (R)-epoxyoctane.

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- 9 Crystal data of anti-1: C<sub>16</sub>H<sub>22</sub>FNO, M = 263.35, monoclinic,  $a = 7.855(2), b = 5.462(2), c = 17.607(1) Å, \beta = 100.90(1)^\circ, V = 741.7(3) Å<sup>3</sup>, <math>T = 23$  °C, space group  $P2_1$  (#4), Z = 2, R = 0.055, Rw = 0.084. CCDC 169361.
- 10 The syntheses of *syn* and *anti*-1 and 2 from *p*-methoxyphenylacetonitrile and (*R*)-epoxyoctane (91% ee) are described in ESI.<sup>†</sup>
- 11 Crystal data of syn-1:  $C_{16}H_{22}$ FNO, M = 263.35, orthorhombic, a = 7.509(1), b = 35.774(4), c = 5.596(1) Å, V = 1503.3(4) Å<sup>3</sup>, T = -130 °C, space group  $P2_{1}2_{1}2_{1}$  (#19), Z = 4, R = 0.043, Rw = 0.057. CCDC 169362.
- 12 *Crystal data of anti-***2**:  $C_{17}H_{24}FNO$ , M = 277.38, monoclinic, a = 7.696(4), b = 5.627(3), c = 18.628(2) Å,  $\beta = 95.02(2)^\circ$ , V = 803.6(6) Å<sup>3</sup>, T = 23 °C, space group  $P2_1$  (#4), Z = 2, R = 0.081, Rw = 0.192. CCDC 169360. See http://www.rsc.org/suppdata/cc/b1/b107213g/ for crystallographic data in .cif or other electronic format.
- 13 The usual lithium anion is considered to have the known intra- and/or intermolecular Li–F coordination.<sup>6</sup>
- 14 All three theoretical calculations showed that the most stable conformer had the angle (*ca.* 120°) between CN and F when projected in the C1–C3 plane. The relative energy differences between the conformers having the through-space interaction and the most stable conformers were 2.72 kcal mol<sup>-1</sup> (PM3), 1.34 kcal mol<sup>-1</sup> (MP2 6-31G\*), and 2.12 kcal mol<sup>-1</sup> (df 6-31G\*).