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Anion recognition by a novel Fipronil-based receptor: efficient deprotonation or stable intermolecular hydrogen bonding

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Abstract

Strong electron-deficient heterocycles of acetyl Fipronil (**F3**) was designed and synthesized, its ability for anion recognition was investigated by UV and NMR analyses. This novel Fipronil-based receptor **F3** shows strong binding affinity with acetate ($\geqslant 10^7\ M^{-1}$), phosphate or fluoride ion through efficient deprotonation. In addition, its interaction with chloride anion or other weak base anions through stable intermolecular H-bonding was also reported.

Anions play vital roles in biological and chemical processes.[1] The development of novel synthetic receptors[2] bearing biologically importance for anions is recently emerged as a significant important research area. Generally, synthetic receptors for anions employ various combinations of pyrroles, guanidiniums, Lewis acids, amides, and urea/thiourea groups as binding sites to form N–H···X hydrogen bonds. According to a recent view,[3] 'all hydrogen bonds can be considered as incipient proton transfer reactions, and for strong hydrogen bonds, this reaction can be in a very advanced state'. Thus, it may be the potential occurrences of an acid–base process for comprehend the intrinsic interaction between a given –NH-containing receptor, speciously those biomolecules possibly binding with anions.

In general, the following four possible equilibriums (Fig. 1) may take place in solution, involving the neutral receptor LH and anion A^-. Several groups[4] have discussed Eqs. 1 and 2 in detail by interaction of amide, urea or thiourea, pyrrole-based receptors with anions. A genuine H-bond complex was formed (Eq. 1) and further to leave

$$LH + A^- \rightleftharpoons [LH\cdots A]^- \quad (1)$$
$$[LH\cdots A]^- + A^- \rightleftharpoons L^- + [HA_2]^- \quad (2)$$
$$LH + A^- \rightleftharpoons L^- + HA \quad (3)$$
$$LH + A^- \rightleftharpoons L'H + A^- \quad (4)$$

Fig. 1. The possible equilibria of **LH** and $\mathbf{A}^-$.

the deprotonated L^- (Eq. 2), which can be ascribed to a 'frozen' proton release from the donor (the acid) to the acceptor (the base) and the more advanced proton release process. In Eq. 4, the proton releases in the neutral receptor LH itself to further generate the new receptor L′H, which can be ascribed to anion-catalyzed organic reaction.[5] We were interested to verify whether Eq. 3 can be found through simple biologically important receptor interacting with anions in solution. For a definitive proton release from the receptor to anion (Eq. 3), which mainly related to the intrinsic acidity of LH,[4n] its acidity should be stronger than those of the general urea or thiourea derivatives. And also, the stability of HA in solution would be beneficial to the proton release process according to the rule of Eq. 2. Thus, further polarizing the N–H bonds and increasing its hydrogen-bond donor tendencies are indispensable through introducing the stronger electron-withdrawing

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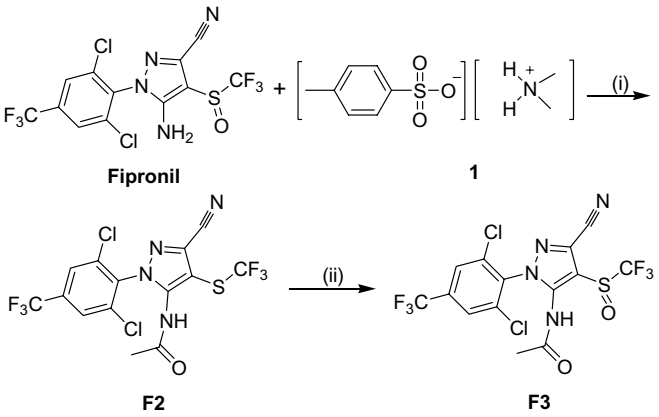
substituents (e.g., $-NO_2$, CF_3), which should be appended to the NH framework.[4a] The potential occurrence of a strong acid–base process should be investigated with efficient proton release from receptor to anion.

With these considerations in mind, we observed that a derivative of Fipronil[6] *N*-(3-cyano-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(trifluoromethylsulfinyl)-1*H*-pyrazol-5-yl)acetamide (**F3**, Fig. 2), which provides with three strongly electron-withdrawing groups (–CN, $-CF_3$, 2,6-Cl_2-4-CF_3-phenyl) appended to the NH framework. Herein, we report an example of novel Fipronil-based receptor **F3**, which can recognize anions through efficient deprotonation or stable intermolecular hydrogen bonding.

Generally, most pesticides such as Fipronil, which has a functional group ($-NH_2$), show only slightly reactive or, indeed, non-reactive.[7] Not surprisingly, the NH_2 of Fipronil is considerable unreactive with acetyl chloride through the conventional methods. Thus, it appeared necessary to use a novel strategy for the preparation of receptor **F3**. Interestingly, compound **F2**[8] was obtained by introducing a strongly dimethylammonium 4-methylbenzene-sulfonate (**1**) into the above unreactive system. Further, oxidation of compound **F2** with equimolar of mCPBA gave the final receptor **F3**[9] in good yields (Scheme 1).

The anion sensing ability of **F3** was evaluated by UV and proton NMR analyses. Figure 3 shows the spectroscopic changes observed when **F3** is treated with increasing quantities of tetrabutylammonium acetate (TBAA) in CH_3CN. In this case, the new peaks at 285 nm increased upon the addition of TBAA, with saturation being observed after the addition of ca. 1 equiv. There is a clear isosbestic point at 238 nm, which indicates a clean conversion throughout the titration process. This new band reflects electronic modification of receptor takes place, induced by N–H deprotonation. Standard 1:1 curve-fitting procedures were then used to derive binding constants,[10] which is at least equal to $4 \times 10^7\ M^{-1}$ in CH_3CN and exceeds that reported urea or thiourea[4n] ($10^6\ M^{-1}$). We propose that the high oxoanions affinity of **F3** results from its stronger acidity than that of urea or thiourea derivatives.

The ^1H NMR titration experiments of **F3** with TBAA was investigated in CD_3CN. Upon the addtion of 0.34 or 2.58 equiv of TBAA, the NH proton signal (8.93 ppm) of



Scheme 1. Reagents and conditions: (i) CH_3COCl, CH_2Cl_2, reflux (35%); (ii) mCPBA, rt, CH_2Cl_2 (70%).

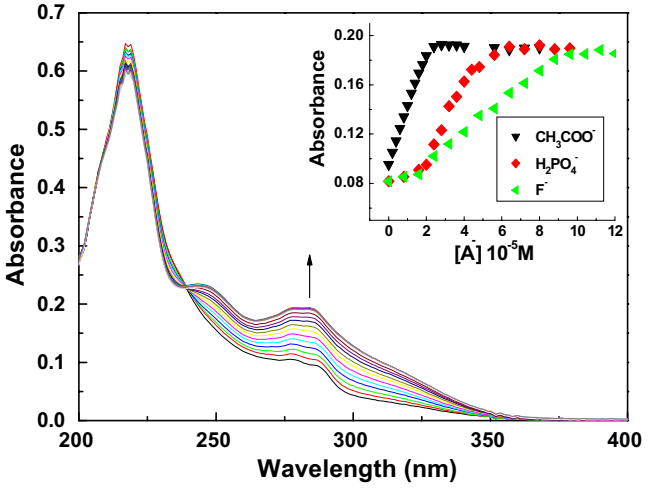


Fig. 3. UV–vis titration of 20 μM **F3** with $Bu_4N^+AcO^-$ in CH_3CN. Arrows show changes due to increasing concentration of A^-. The inset shows the absorbance at 285 nm as a function of [AcO^-], [$H_2PO_4^-$] and [F^-].

F3 disappeared, which indicates that the proton fleetly release from receptor **F3**. In addition of a further excess of TBAA (9.30 equiv and more), we observed the NH proton appeared at much downfield (13.96 ppm, Fig. 4), which coincides with the –OH proton signal of the acetate acid and indicates the proton transfer is almost finished.

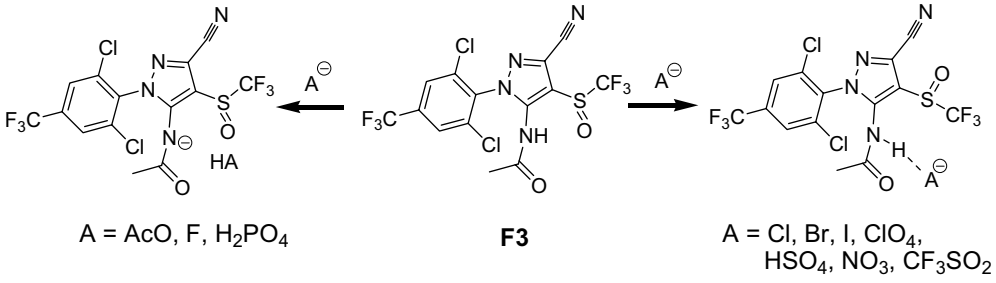


Fig. 2. The binding motif of **F3** with $\mathbf{A}^-$.

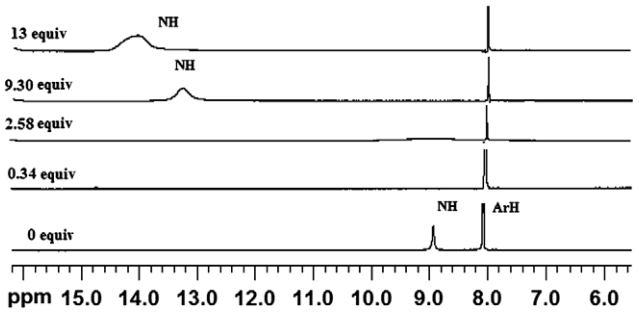


Fig. 4. ^{1}H NMR spectra of **F3** with tetrabutylammonium acetate in CD_3CN at 298 K (only NH and aromatic protons are shown) [**F3**] = 8.0×10^{-3} M, [AcO^-] = 0–2.0×10^{-2} M.

Table 1
Affinity constants for the binding of anions[a] by receptor **F3**

Anion	K_a (M^{-1})	Anion	K_a (M^{-1})
AcO^{-}[b]	4.16×10^7	Br^-	1.32×10^3
$H_2PO_4^{-}$[b]	2.27×10^5	HSO_4^-	4.50×10^2
F^{-}[b]	1.76×10^5	I^-	2.70×10^2
Cl^-	1.50×10^3	$CF_3SO_2^-$	2.06×10^2
NO_3^-	1.40×10^3	ClO_4^-	1.34×10^2

[a] The anions studied were in the form of their tetrabutylammonium salts.
[b] Determined in acetonitrile solvent by UV–vis; error ⩽15%. The other anions were determined by ^{1}H NMR analysis in $CDCl_3$ at 298 K; error ⩽10%.

Similarly, the same detectable spectral changes were observed in the interaction of **F3** with tetrabutylammonium fluoride (TBAF) and tetrabutylammonium phosphate (TBAP). Those absorbances at 285 nm as a function of anions (TBAA, TBAP and TBAF) are shown in Figure 3. The NH proton chemical shifts of **F3** in the presence of TBAF or TBAP were also recorded (Supplementary data). These binding constants are collected in Table 1, along with those for other anions. On the basis of the established binding trend shown in Table 1 ($CH_3COO^- > H_2PO_4^- > F^-$, the binding of the oxoanions is enhanced significantly than F^-, which is presumed to be dependent on the less stability of HF in solution.[4n]

To evaluate chloride ions and other weak base anions, we further study the interaction of **F3** with anions by UV–vis or NMR analyses. No spectral modifications were observed for Cl^-, HSO_4^-, NO_3^-, Br^-, I^-, ClO_4^-, $CF_3SO_2^-$ even if added in large excess (Supplementary data). Thus, the selectivity of **F3** is mainly related to the basicity of the anions. Furthermore, the ^{1}H NMR experiment in $CDCl_3$ reveals that receptor **F3** forms a strong 1:1 complex, which implied the formation of an intermolecular hydrogen bond between receptor **F3** and chloride ions. It is evident from that concerted downfield shifts were observed for amide proton as receptor **F3** was exposed to increasing concentrations of chloride. The downfield shift of amide protons occurred in the 1:1 complex from 8.50 to 12.60 ppm ($\Delta\delta = 4.10$ ppm). The resonances for the acetyl protons of **F3** were also slight shifted (Fig. 5).

The ^{1}H NMR titration of **F3** for HSO_4^-, NO_3^-, Br^-, I^-, ClO_4^-, $CF_3SO_2^-$ was also carried out, respectively (Fig. 6). The association constants of that complexation were calculated by a 1:1 nonlinear curve fitting (Table 1). An inspection of this table, which reveals that the greatest affinity is displayed for AcO^-, followed by $H_2PO_4^- > F^- > Cl^- > NO_3^- > Br^- > HSO_4^- > I^- > CF_3SO_2^- > ClO_4^-$.

One of the most interesting phenomenon is that the acetyl Fipronil **F3** shows most high binding affinity with acetate anion, which might be helpful to comprehend the outstanding performance[11] of Fipronil in biological systems. Although several results were reported on the field of the photoproducts[12] and metabolites[13] of Fipronil pesticides, this report might provide a new viewpoint, from molecular recognition of anions, probably to explain the performance of Fipronil insecticide. In summary, we have demonstrated here that the acetyl Fipronil **F3** is able to associate with anions through efficient deprotonation or stable intermolecular hydrogen bonding.

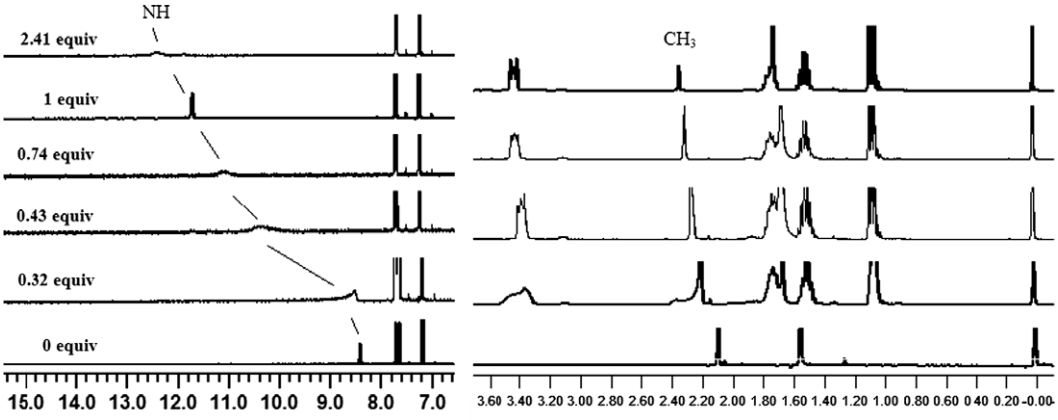


Fig. 5. ^{1}H NMR titration of **F3** with tetrabutylammonium chloride in $CDCl_3$ at 298 K [**F3**] = 8.0×10^{-3} M, [Cl^-] = 0–2.0×10^{-2} M.

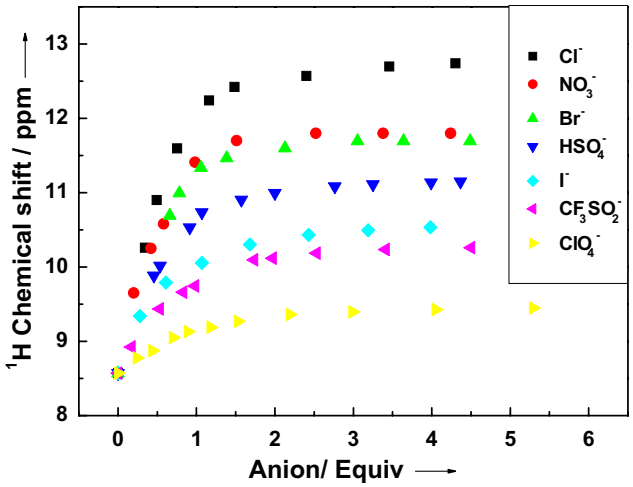


Fig. 6. Plot of the chemical shift of the NH protons of **F3** (3.46×10^{-2} M) upon increasing the concentration of nBu$_4$N$^+$X$^-$ in $CDCl_3$.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.155.

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8. *Preparation of compound* **F2**: A flame-dried flask was charged with Fipronil (436 mg, 1 mmol), dimethylammonium 4-methylbenzenesulfonate (434 mg, 2 mmol) and CH_2Cl_2 (5 mL). Then a solution of acetyl chloride (93.6 mg, 1.2 mmol) in CH_2Cl_2 was added. The reaction mixture was refluxed under nitrogen atmosphere for 4 h. Water (10 mL) was added and extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was purified by flash chromatography on silica gel to give **F2** (161 mg, 35%). Mp 212.7–213.7 °C. IR (KBr): ν 3220, 2250, 1690, 1580, 1500, 1400, 1310, 1080, 720, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.12 (s, 3H, CH_3), 7.20 (s, 1H, NH), 7.77 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 143.5, 136.6, 135.0, 134.5, 134.2, 133.0, 129.8, 126.8, 126.2, 123.3, 120.5, 110.6, 22.9. EIMS, 1.58 eV, m/z: 462 [M]$^+$ (84.86), 420 (28.02), 351 (20.70), 213 (5.56), 43 (100). HRMS calcd for $C_{14}H_6N_4O_1F_6SCl_2$: 461.9521. Found: 461.9544.
9. *The preparation of compound* **F3**: A flame-dried flask was charged with **F2** (462 mg, 1 mmol), mCPBA (190 mg, 1.10 mmol) and CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 24 h. Water (10 mL) was added and extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was purified by flash chromatography on silica gel to give **F3** (334 mg, 70%): Mp 208.9–210.0 °C. IR (KBr): ν 3220, 2250, 1690, 1580, 1310, 1080, 720, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.09 (s, 3H, CH_3), 7.72 (s, 1H), 7.80 (s, 1H), 8.52 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 142.9, 137.0, 135.6, 134.5, 134.0, 126.7, 126.5, 126.0, 125.7, 123.4, 120.5, 109.6, 23.1. EIMS, 1.21 eV, m/z: 478 [M]$^+$, 408 (11.74), 367 (48.67), 213 (7.26), 43 (100). HRMS calcd for $C_{14}H_6N_4O_2F_6SCl_2$: 477.9488. Found: 477.9493.
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