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# Urea receptors; mechanism and binding properties DFT Study

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**ABSTRACT**

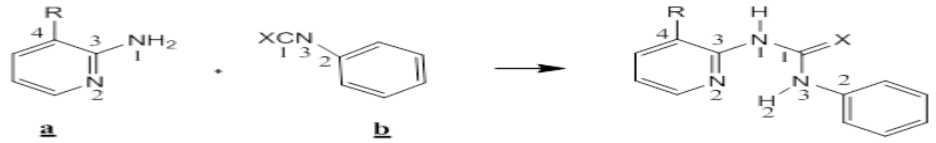
In the present study, first the reactivity of 3-R-2-aminopyridine with two electrophiles (namely phenyl isothiocyanate and phenyl isocyanate) has been investigated using density functional theory (DFT) and interpreted using chemical reactivity descriptors, to get further insights on the mechanism, the transition state corresponding was characterized for each reaction. Second the different interactions between *N*-Phenyl-*N*´-2-pyridyl thiourea receptors and (Br, Cl, $BF_4$, $CF_3CO_2$) anions have been investigated theoretically, the help of Bader's atoms in molecules (AIM) are used to understand the binding properties of N, N-pyridyl phenyl thiourea receptors.

**KEY WORDS**: N,N-pyridyl thiourea, switchable receptors, DFT calculation, AIM methods.

## 1. INTRODUCTION

The design and synthesis of anion selective receptors has received a significant amount of attention in recent years because anions play an important role in a wide range of biological, environmental, and chemical processes. Thiourea molecule has large dipole moment and has the ability to form extensive network of hydrogen bonds. Thioureas and various N-substituted derivatives represent one of the most promising classes of anticancer agents because of their good activities against various leukemia and solid tumors. Recently, Rashdan (2006), have studied the switching ability, the structure and the binding properties for 2-pyridyl-phenylthiourea and urea analogues using X-ray diffraction and $^1$H NMR spectroscopy analysis.

The aims of the research are twofold: First in order to better understand the mechanism of synthesis of N-Phenyl-N´-2-pyridyl thiourea receptors [1C-4C] (Scheme.1), several reactivity descriptors based on Density Functional Theory (DFT), such as chemical potential, hardness, Fuckui function and dual descriptors are calculated. Next, to get insight on the reaction mechanism, the transition state was characterized. Second, to elucidate the electronic effect of various anions $Y^-(Y = \mathrm{Br}, \mathrm{Cl}, \mathrm{BF4}, \mathrm{CF3CO2})$ on the relative binding affinity of the urea functionality, we reported a theoretical study of both the host-guest interaction and the signaling properties of this system.



1a R=H 1b X=O 1C R=H, X=O 2C R=H, X=S
2a R=CH3 2b X=S 3C R=CH3, X=O 4C R=CH3, X=S

**Scheme 1**

## 2. COMPUTATIONAL PROCEDURES

Full geometry optimizations and frequency calculations for minimum energy were performed within the GAUSSIAN 09 software package using density-functional theory (DFT) with the hybrid B3-LYP functional and (6-31G(d)) basis set. All the stationary points have been characterized by a vibration analysis, leading to zero imaginary frequency for minima, and one imaginary frequency for transition states. Vertical ionisation potentials (IP) and electron affinities (EA) were evaluated as the energy difference between the neutral species and charged species according to [11] as: IP = E(N -1) - E(N) and EA = E(N) - E(N + 1). The electronic chemical potential (μ) and the chemical hardness (η) of each system were next derived from the ionization potentials and electron affinities as

$$\mu = -\frac{IP + EA}{2} \quad (1)$$

$$\eta = IP - EA \quad (2)$$

The Fukui functions are often convenient to describe chemical reactivity on an atom by another atom in a molecule. Condensed Fukui functions may be evaluated as

$$f_k^+ = q(N+1) - q(N) \quad (3)$$

$$f_k^- = q(N) - q(N-1) \quad (4)$$

k represents the ability of atoms k to reacts with a nucleophile. A high value of $f_k^+$ indicates that atom k presents an electrophilic character thus indicating a high probability for a nucleophilic attack.

## 3. RESULTS AND DISCUSSION

Intermolecular descriptors: The ionization potential (IP), electron affinity (EA), electronic chemical potential (μ), chemical hardness (η) are collected in Table.1.

**Table.1. Intramolecular chemical descriptors (eV)**

| | IP | EA | η | μ | ω |
|---|---|---|---|---|---|
| 1a | 7.948 | -1.9094 | 9.857 | -3.019 | 0.462 |
| 2a | 7.774 | -1.946 | 9.720 | -2.914 | 0.436 |
| 1b | 8.502 | -1.352 | 9.854 | -3.575 | 0.648 |
| 2b | 8.175 | -0.566 | 8.741 | -3.804 | 0.827 |

First of all, qualitatively we can notice that all computed chemical potentials of two pyridyl derivatives (1a, 2a) are higher than that of b (- 3.575 , - 3.804 ) thereby confirming that, if any, a charge transfer will take place from pyridyl derivatives nucleophiles towards b here acting as an electron acceptor. The analysis of the IP computed for pyridyl derrvatives a and b confirmed this fact. The chemical potential of the nucleophile is higher than that of the electrophiles confirming the direction expected for the electronic transfer from the nucleophile with a high chemical potential to an electrophile with a lower chemical potential. Furthermore, the relatively large electrophilicity index computed for 2b (0.827eV) accounts for its facile participation in these reactions.

**Site selectivity:** The Fukui functions were determined using Eq. (3 and 4). Local reactivity indexes have been calculated with Milliken population analysis (MPA) and natural population analysis (NPA) to characterize the sites for nucleophilic or electrophilic attack; they are quoted in Table.2.

**Table.2.The Mullikan Population Analysis (MPA) and Natural Population Analysis (NPA) derived Fukui function of compounds.**

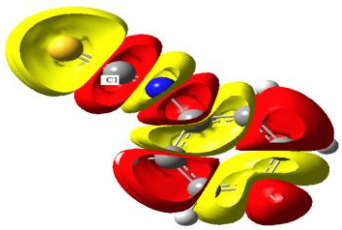
| | MPA | | | | NPA | | | |
|---|---|---|---|---|---|---|---|---|
| | $f_k^-$ | | | | | | | |
| | $N_1$ | $C_3$ | $C_4$ | $N_2$ | $N_1$ | $C_3$ | $C_4$ | $N_2$ |
| **1a** | 0.148 | 0.024 | 0.065 | 0.066 | 0.240 | 0.021 | 0.14 | 0.073 |
| **2a** | 0.134 | 0.039 | 0.041 | 0.059 | 0.216 | 0.029 | 0.147 | 0.061 |
| | $f_k^+$ | | | | | | | |
| | $N_3$ | $C_1$ | $C_2$ | $C_1$ | $N_3$ | $C_1$ | $C_2$ | $C_1$ |
| **1b** | 0.004 | 0.158 | 0.068 | 0.054 | 0.003 | 0.139 | 0.132 | 0.105 |
| **2b** | 0.003 | 0.110 | 0.045 | 0.027 | 0.007 | 0.123 | 0.088 | 0.052 |

This table shows that for two electrophile (1b, 2b), the higher $f_k^+$ values are on atom $C_1$. This means that the nucleophilic attack would be preferential on this site. Inspection of Table.2 shows also, that a large value of $f_k^-$ for two nucleophiles (1a, 2a) are calculated for $N_3$ atoms, indicates an electron donating site (atom N).

On the other hand, the reactivity–selectivity descriptor $\Delta f(r)$, introduced by Morell (2005; 2006) characterizes the variations of the absolute hardness when the external potential changes, upon, for instance, an approach of reactants during a bimolecular reaction. It is defined as:

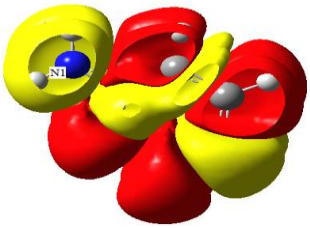
$$\Delta f(r) = f^+(r) - f^-(r) \qquad (5)$$

Accordingly, when $\Delta f(r) > 0$, then the point r favors a nucleophilic attack, whereas if $\Delta f(r) < 0$ then the point r favors an electrophilic attack. Therefore, positive values of $\Delta f(r)$ identify electrophilic regions within the molecular topology; whereas negative values of $\Delta f(r)$define nucleophilic regions. It has been decided to represent in red the regions with positive values of the dual descriptor ($\Delta f(r) > 0$) and those with negative value in yellow ($\Delta f(r) < 0$). This descriptor has been calculated and the results are shown on Fig. 1. It can be seen that the $\Delta f(r)$ descriptor is positive for the C1 atoms (red) for the tow electrophiles'1b and 2b. While the $\Delta f(r)$ descriptor is negative for the $N_1$ atoms (yellow) for the tow nucleophiles' (1a, 2a) The Fig. 1 displays, also, a map of the nucleophilic/electrophilic behavior of the different sites within the molecule according to the $\Delta f(r)$ descriptor.

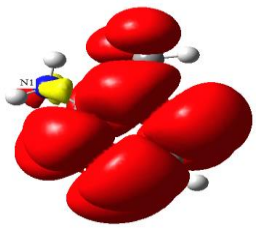



1b


2b




1a




2a

**Fig.1. Δf (r) calculated at the B3LYP/6-31G(d) level.**

**Thermodynamics:** An exhaustive exploration of the potential energy surface (PES) for the reactions between 3-R-2-aminopyridine (R=H, $CH_3$) and two electrophiles phenyl isothiocyanate and phenyl isocyanate was performed. In all cases we were able to locate only one transition state, schematically depicted in Fig.2. The structural parameters calculated for four receptors 1C-4C are presented in Table.3. The calculated bond lengths and bond angles of the four receptors are remarkably close to the experimental values obtained by X-ray crystal diffraction.

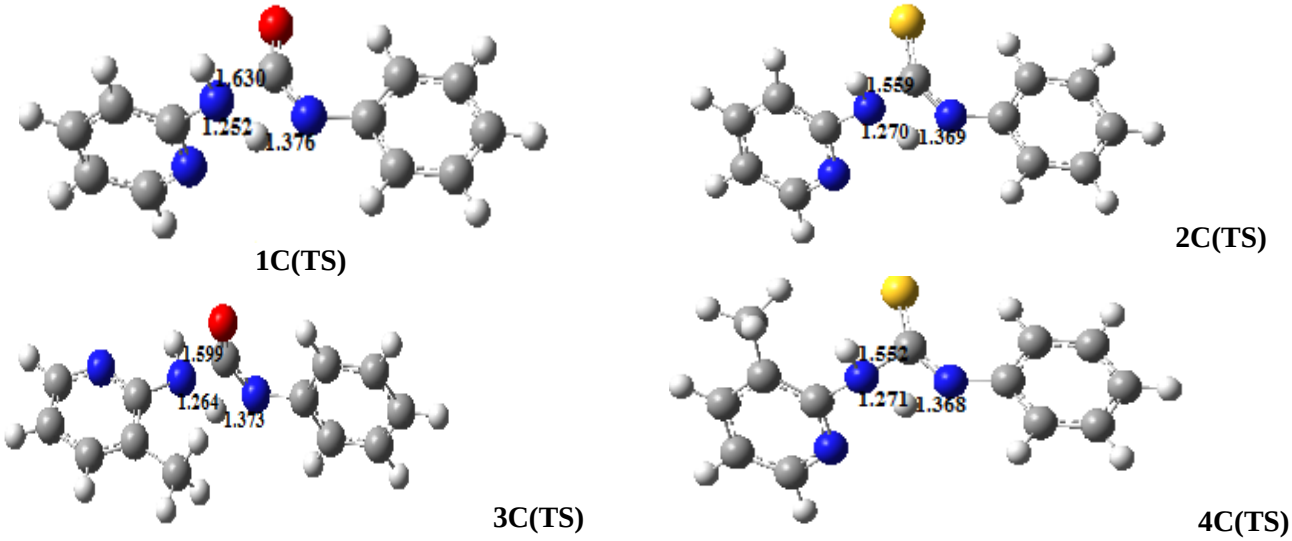



**Fig.2. B3-LYP/6-31G(d) optimized geometries for the transition structures. The important distances between atoms are shown.**

**Table.3. Structural parameters of receptors (Bond distance (Å), angle (°)) compared to X-ray**

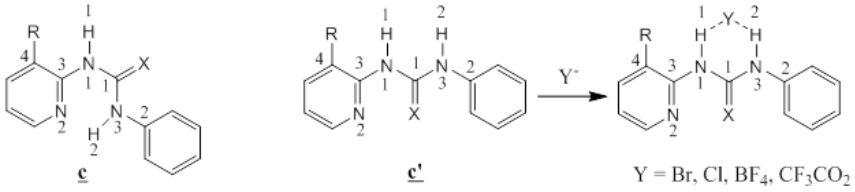
| | 1C | | 2C | | 3C | | 4C | |
|---|---|---|---|---|---|---|---|---|
| | Calc | Exp | Calc | Exp | Calc | Exp | Calc | Exp |
| $N_3$-$H_2$ | 1.022 | - | 1.027 | 0.891 | 1.022 | - | 1.027 | - |
| $N_1$-$H_1$ | 1.011 | - | 1.012 | 0.891 | 1.009 | - | 1.010 | - |
| $N_3$-$N_2$ | 2.758 | - | 2.732 | 2.646 | 2.749 | - | 2.722 | - |
| $C_1$-X | 1.224 | - | 1.683 | 1.682 | 1.225 | - | 1.684 | - |
| $C_1$-$N_3$ | 1.363 | - | 1.350 | 1.336 | 1.363 | - | 1.350 | - |
| $C_1$-$N_1$ | 1.415 | - | 1.399 | 1.371 | 1.416 | - | 1.400 | - |
| $N_3$-$C_1$-$N_1$ | 115 | - | 114.62 | 116.83 | 115.31 | - | 114.76 | - |
| $N_1$-$C_1$- X | 118 | - | 116.16 | 118.62 | 117.66 | - | 116.06 | - |
| $N_3$-$C_1$- X | 127 | - | 129.22 | 124.62 | 127.02 | - | 129.158 | - |

**Table.4. Thermodynamics parameters (barriers (ΔE≠, kJ mol$^{-1}$), activation enthalpies (ΔH≠, kJ mol$^{-1}$) and Gibb's activation free energies (ΔG≠, kJ mol$^{-1}$) at 298.15 K of the reactions (1), all calculations performed with 6-31G (d) basis set.**

| | 1C | 2C | 3C | 4C |
|---|---|---|---|---|
| ΔE | -78.76 | -21.00 | -84.01 | -15.76 |
| $\Delta E^{\neq}$ | 136.53 | 154.90 | 126.02 | 152.27 |
| $\Delta H^{\neq}$ | 131.28 | 149.65 | 123.39 | 149.65 |
| $\Delta G^{\neq}$ | 297.21 | 202.68 | 178.53 | 204.78 |

Table.4 shows the thermodynamics parameters for the four reactions calculated at the B3LYP level of theory. First of all one can note that all the reactions are found to be exothermic (ΔE < 0), the reaction becomes more exothermic when oxygen atom is included as compared to sulfur atoms (from 57 to 68 kJ/mol). When the activation energies computed for four reactions are compared, the value of barrier's calculated for receptors with sulfur atoms are higher.

**Host-guest interactions:** First, calculated energies at the B3LYP/6-31G (d) level of theory for the two conformational C and C' indicates that the conformational C' is more stable than the conformational C (between 16-34 KJ). Then, the conformational C' it's more switch and potentially strong anion binding. (Scheme.2)




**Scheme.2**

To elucidate the electronic effect of various anions $Y^{-}(Y = \mathrm{Br, Cl, BF4, CF3CO2})$ on the relative binding affinity of the urea functionality, we have carried out calculations on respective 1:1 adducts of $Y^{-}$ and urea derivatives, C'. The complexes consisting of C' and $Y^{-}(Y = \mathrm{Br, Cl, BF4, CF3CO2})$, were optimized at the B3LYP/6–31G* level of theory. The main geometrical parameters, of complexes C'Y$^{-}$ $(Y = \mathrm{BR, Cl, BF4, CF3CO2})$ are given in Table.5. According to the suggested geometry cutoffs for the definition of a D–H…..A hydrogen bond, i.e. H….A distance < 3.0 Å and D–H…A angle > 110°, the interactions between Y and H of N–H fragments in C'. Y$(Y = \mathrm{Br, Cl, BF4, CF3CO2})$ can be identified as hydrogen bonds. Comparing the optimized geometries in complex C'. Y$(Y = \mathrm{BR, Cl, BF4, CF3CO2})$ , the hydrogen bond lengths $H_1$…Y and $H_2$…Y in complex C' (Br and Cl) are larger than the corresponding distances in C' ($BF_4$ and $CF_3CO_2$).

**Table.5. Distances of RN–H and RH…Y (in angstroms) for complexes C'Y$^{-}$$(Y = \mathrm{Br, Cl, BF4, CF3CO2})$at the B3LYP/6-31(d) level**

| | $R_{N1-H1}$ | $R_{N3-H2}$ | $R_{H1-Y}$ | $R_{H2-Y}$ |
|---|---|---|---|---|
| **1 C'** | 1.011 | 1.011 | - | - |
| **1C'. Br** | 1.029 | 1.044 | 2.369 | 2.184 |
| **1 C'. Cl** | 1.038 | 1.067 | 2.159 | 1.940 |
| **1 C'. $BF_4$** | 1.030 | 1.044 | 1.732 | 1.608 |
| **1 C'.$CF_3CO_2$** | 1.051 | 1.072 | 1.694 | 1.604 |
| **2 C'** | 1.012 | 1.013 | - | - |
| **2 C'.Br** | 1.063 | 1.054 | 2.109 | 2.197 |
| **2 C'.Cl** | 1.068 | 1.053 | 1.952 | 2.079 |
| **2 C'.$BF_4$** | 1.043 | 1.039 | 1.605 | 1.658 |
| **2 C'.$CF_3CO_2$** | 1.078 | 1.062 | 1.562 | 1.646 |
| **3 C'** | 1.010 | 1.011 | - | - |
| **3 C'.Br** | 1.026 | 1.044 | 2.444 | 2.175 |
| **3 C'.Cl** | 1.033 | 1.067 | 2.242 | 1.925 |
| **3 C'.$BF_4$** | 1.031 | 1.035 | 1.717 | 1.721 |
| **3 C'.$CF_3CO_2$** | 1.049 | 1.076 | 1.713 | 1.586 |
| **4 C'** | 1.012 | 1.013 | - | - |
| **4 C'.Br** | 1.054 | 1.056 | 2.180 | 2.160 |
| **4 C'.Cl** | 1.058 | 1.056 | 2.019 | 2.035 |
| **4 C'.$BF_4$** | 1.040 | 1.035 | 1.632 | 1.704 |
| **4 C'.$CF_3CO_2$** | 1.062 | 1.063 | 1.632 | 1.621 |

**AIM analysis:** The atoms in molecules (AIM) theory are often employed to study hydrogen bonds. The characteristics of bond critical points (BCPs) are a very useful way of estimating the strength of hydrogen bonds. To gain additional insight into the bonding characteristics of the complexes consisting of C' and Y$^{-}$ $(Y = \mathrm{Br, Cl, BF4, CF3CO2})$, we used the AIM theory at the B3LYP/6-31G (d) level. Table VI presents the topological parameters of complexes C'Y$^{-}$. As a general rule, hydrogen bonds are characterized by positive values of $\nabla^2\rho(r)$ and low $\rho(r)$ values (< 0.1). Covalent bonds have negative $\nabla^2\rho(r)$values and high values of $\rho(r)$, whereas the values of $\nabla^2\rho(r)$become positive when the bonds contain ionic character.

**Table.6. The electronic density at BCP $\rho(r)_{bcp}$ , the Laplacian $\nabla^2\rho(r)_{bcp}$ of complexes C'Y $(Y = \mathrm{Br, Cl, BF4, CF3CO2})$ at the B3LYP/6-31G(d) level. (all in a.u.)**

| | $N_1$-$H_1$ | | $N_3$-$H_2$ | | $H_2$…Y | | $H_1$…Y | |
|---|---|---|---|---|---|---|---|---|
| | $\rho(r)$ | $\nabla^2\rho(r)$ | $\rho(r)$ | $\nabla^2\rho(r)$ | $\rho(r)$ | $\nabla^2\rho(r)$ | $\rho(r)$ | $\nabla^2\rho(r)$ |
| **1C'.Br** | 0.3202 | -1.4554 | 0.3074 | -1.3684 | 0.0347 | 0.0617 | 0.0239 | 0.0505 |
| **1 C'.Cl** | 0.3124 | -1.4136 | 0.2879 | -1.2259 | 0.0492 | 0.0821 | 0.0307 | 0.0692 |
| **1 C'.$BF_4$** | 0.3214 | -1.5110 | 0.3107 | -1.4405 | 0.0527 | 0.1656 | 0.0378 | 0.1349 |
| **1C'.$CF_3CO_2$** | 0.3019 | -1.3711 | 0.2856 | -1.2405 | 0.0621 | 0.1297 | 0.0499 | 0.1218 |
| **2 C'.Br** | 0.2876 | -1.2254 | 0.2979 | -1.2842 | 0.0342 | 0.0583 | 0.0411 | 0.0608 |
| **2 C'.Cl** | 0.2825 | -1.2033 | 0.2971 | -1.2997 | 0.0367 | 0.0726 | 0.0484 | 0.0773 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2 C'.$BF_4$** | 0.3079 | -1.4293 | 0.3129 | -1.4429 | 0.0457 | 0.1513 | 0.0528 | 0.1648 |
| **2C'.$CF_3CO_2$** | 0.2765 | -1.1739 | 0.2922 | -1.2847 | 0.0556 | 0.1265 | 0.0688 | 0.1285 |
| **3 C'.Br** | 0.3202 | -1.5347 | 0.3064 | -1.3544 | 0.0353 | 0.0611 | 0.0218 | 0.0409 |
| **3 C'.Cl** | 0.2892 | -1.1454 | 0.2642 | -0.9256 | 0.0479 | 0.0967 | 0.0249 | 0.0651 |
| **3 C'.$BF_4$** | 0.3202 | -1.5023 | 0.3178 | -1.4946 | 0.0393 | 0.1387 | 0.0398 | 0.1403 |
| **3C'.$CF_3CO_2$** | 0.3010 | -1.3641 | 0.2817 | -1.2091 | 0.0650 | 0.1305 | 0.0471 | 0.1177 |
| **4 C'.Br** | 0.2950 | -1.2907 | 0.2962 | -1.2727 | 0.0369 | 0.0599 | 0.0356 | 0.0586 |
| **4 C'.Cl** | 0.2908 | -1.2746 | 0.2945 | -1.2808 | 0.0403 | 0.0754 | 0.0419 | 0.0754 |
| **4 C'.$BF_4$** | 0.3102 | -1.4498 | 0.3156 | -1.4626 | 0.0408 | 0.1432 | 0.0490 | 0.1587 |
| **4C'.$CF_3CO_2$** | 0.2765 | -1.1739 | 0.2922 | -1.2847 | 0.0556 | 0.1265 | 0.0688 | 0.1285 |

As shown in Table.6, the $\nabla^2\rho(r)$ values of H1…Y and H2…Y in complexes 1C'-4C' with $Y^-$ ($Y = \mathrm{Br, Cl, BF4, CF3CO2}$) are positive and $\rho(r)$ values are low to 0.1. This suggests that the interaction between H1 and Y, H2 and Y is hydrogen bonding in nature. The BCPs at $N_1$–$H_1$ and $N_3$–$H_2$ provide negative $\nabla^2\rho(r)$ values and high positive values for $\rho(r)$ which are characteristics of covalent type interactions. The $\rho(r)$ values of $N_1$–$H_1$ are larger than of $N_3$-$H_2$ in 1C'Y and 3C'Y (X is oxygen atoms), while, the $\rho(r)$ values of $N_3$–$H_2$ are larger than of $N_1$-$H_1$ in 2C'Y and 4C'Y. (X is sulfur atoms).

## 4. CONCLUSION

The reaction between 3-R-2-aminopyridine and two electrophiles (namely phenyl isothiocyanate and phenyl isocyanate) was studied using intermolecular quantum chemical descriptors at DFT level. The results of fuckui function and dual descriptors are in good agreement to predict the site of attacks. The uses of transition state theory, allowed us to identify such reaction are exothermic and the reaction becomes more exothermic when oxygen atom is included as compared to sulfur atoms. The results for both the host–guest interaction show that the interactions between Y and H of N–H fragments in C'$Y^-$ ($Y = \mathrm{Br, Cl, BF4, CF3CO2}$) are identified as hydrogen bonds. This result is confirmed by the AIM analysis of the complexes consisting of C' and $Y^-$ ($Y = \mathrm{Br, Cl, BF4, CF3CO2}$).

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