ORIGINAL ARTICLE

Halide Recognitions of *p*-substituted Isophthalmide-Based Anion Receptors: Experimental and Theoretical Studies

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Abstract. Two synthetic anion receptors, *N,N'*-bis-(4-fluorophenyl) isophthalamide, **1**, and *N,N'* -bis-(4-chlorophenyl)isophthalamide, **2**, have been studied their structures and their anions recognitions using the experimental and computational methods. The optimized structures and thermodynamic properties have been investigated with the density functional theory (DFT) at the B3LYP/6-31G(d) level of theory. The nuclear magnetic resonance titration techniques have been also used to obtain their associate constants (K_{asso}) with tetrabutylammonium fluoride (TBAF), tetrabutylammonium chloride (TBACl) and tetrabutylammonium bromide (TBABr). The experimental results show agreement with the theoretical results that these receptors bind Br^- selectively.

Keywords: Anion receptor, Isophthalamide derivatives, NMR titration, DFT.

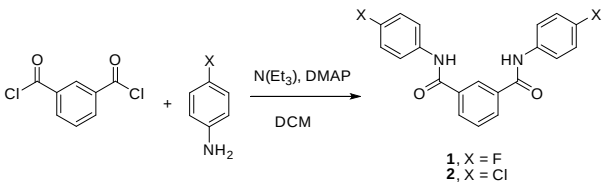
1. Introduction

Anions play an importance role in agricultural, environmental and medicinal applications due to their variety of functions. To study anion coordination chemistry, it is necessary to design the anion receptor host structures suitable for the target ion guest species (Gale et al 2017; Gale et al 2018). It has to consider that what is the nature of these anions and in which environment they are in. Moreover, the functional groups including in the receptor molecule are also important (Camiolo et al 2002; Gale et al 2002). The molecular structure of isophthalamide has been studied most extensively as anion receptor molecules. Addition of substitutes which is the electron withdrawing groups in isophthalamide structure causes the increasing of anion receptor efficiency (Kim et al 1996; Kavallieratos et al 1997; Coles et al 2003; Light et al 2006). Moreover, the use of molecular orbital calculation method could help the researches to understand the physical properties of the anion receptors (Navakhun and Ruangpornvisuti 2006, 2007, 2008, 2009; Navakhun et al 2014). Therefore, the research in this area would be a guidance to obtain the effective new synthetic anion receptors, optimize factors of the binding, and finally to be the nano tools. In this work, we report the synthesis of two *p*-substituted isophthalamide-based anion receptors, the optimized structures, thermodynamic properties and their fluoride, chloride and bromide ions recognition properties.

2. Materials and Methods

2.1 Experimental

The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a AVANCE 400 MHz NMR spectrometer. All studied ligands were dissolved in deuterated dimethylsulfoxide (DMSO-d_6). Elemental analysis experiments were carried out on CHNS/O analyzer (Perkin-Elmer PE2400 series II). The electrospray mass spectra (ESMS) were measured using a Finnigan LC-Q mass spectrometer. Synthesis of **1** and **2** was shown in Scheme 1.



Scheme 1. Synthesis of **1** and **2**

*2.1.1 Prepareation of N,N'-Bis-(4-fluorophenyl)isophthalamide, **1***

N,N'-Bis-(4-fluorophenyl) isophthalamide, **1** was synthesized by the coupling reaction in dichlorometane (DCM) (30 mL) between isophthaloyl chloride (0.25 g, 1.23 mmol, 1 equiv.) and 4-fluoroaniline (0.34 g, 3.06 mmol, 2.5 equiv.). Triethylamine (0.7 mL, 4 equiv.) and 4-*N*,*N*-dimethylamino pyridine (DMAP) (10 mg) were used as base and catalyst. The reaction mixture was stirred at room temperature for 24 hours. After removal of the solvent, the residue was washed with water, DCM and methanol to give product **1** as a white solid (0.28 g, 64% yield). **^{1}H NMR** (DMSO-d_6, **400MHz**) δ(ppm) 7.21 (t, 4H meta to F, J = 8.7), 7.71 (t, 1H, meta to C_6H_4F , J = 7.7), 7.81 (m , 2H ortho to F), 8.13 (dd, 2H ortho to C_6H_4F J = 7.7), 8.50 (s, 1H ortho to C_6H_4F). **^{13}C NMR** (DMSO-d_6, **400MHz**) δ(ppm) 159.6, 157.2, 135.4, 135.1, 130.7, 128.7, 127.0, 122.3, 122.2, 115.4, 115.2. **ESMS (+ve)**: m/z (%): 353.12 (100) [M+ H] $^{+}$. **M. p.** > 250 ˚C. **Elemental analysis,** Calc. for $C_{22}H_{14}F_6N_2O_2$: C 68.18, H 4.01, N 7.95. Found: C 68.03, H 3.94, N 7.74.

*2.1.2 Prepareation of N,N'-Bis-(4-chlorophenyl)isophthalamide, **2***

N,N'-Bis-(4-chlorophenyl) isophthalamide, **2** was synthesized by the coupling reaction in dichlorometane (DCM) (30 mL) between isophthaloyl chloride (0.25 g, 1.23 mmol, 1 equiv.) and 4-chloroaniline (0.39 g, 3.06 mmol, 2.5 equiv.). Triethylamine (0.7 mL, 4 equiv.) and 4-*N*,*N*-dimethylamino pyridine (DMAP) (10 mg) were used as base and catalyst. The reaction mixture was stirred at room temperature for 24 hours. After removal of the solvent, the residue was washed with water, DCM and methanol to give product **2** as a white solid (0.33 g, 70% yield). **^{1}H NMR** (DMSO-d_6, **400MHz**) δ(ppm) 7.42 (t, 4H meta to Cl, J = 8.7), 7.69 (t, 1H, meta to C_6H_4Cl, J = 7.7), 7.83 (dd, 4H ortho to Cl J = 8.7), 8.14 (dd, 2H ortho to C_6H_4Cl J = 7.7), 8.51 (s, 1H ortho to C_6H_4Cl). **^{13}C NMR** (DMSO-d_6, **400MHz**) δ(ppm) 138.0, 135.0, 130.8, 128.7, 128.6, 127.5, 127.1, 121.9. **ESMS (+ ve)** : m/ z (%) : 385.06(100) [M+ H] $^{+}$. **M. p.** > 250 ˚C. **Elemental analysis,** Calc. for $C_{22}H_{14}F_6N_2O_2$: C 62.35, H 3.66, N 7.27. Found: C 62.02, H 3.41, N 6.94.

2.2 Computational method

The optimized structures of receptors **1** and **2** and their complexes with tetrabutylammonium fluoride (TBAF) , tetrabutylammonium chloride (TBACl) and tetrabutylammonium bromide (TBABr) have been computed with the density functional theory (DFT) at the B3LYP/6-31G(d) level of theory in gas phase using the GAUSSIAN09 program (Frisch et al 2009).

2.3 Nuclear magnetic resonance titration techniques

The anion binding properties receptors **1** and **2** have been studied in dimethylsulfoxide-d_6 (DMSO-d_6) by the nuclear magnetic resonance spectroscopy (NMR) titration techniques. The anion salts have been used as tetrabutylammonium fluoride (TBAF) , tetrabutylammonium chloride (TBACl) and tetrabutylammonium bromide (TBABr). The EQNMR program has been used to calculate the binding constants (K_{asso}) of receptors **1** and **2** with various anions by monitoring the proton chemical shifts of the receptors (Hynes 1993).

3. Results

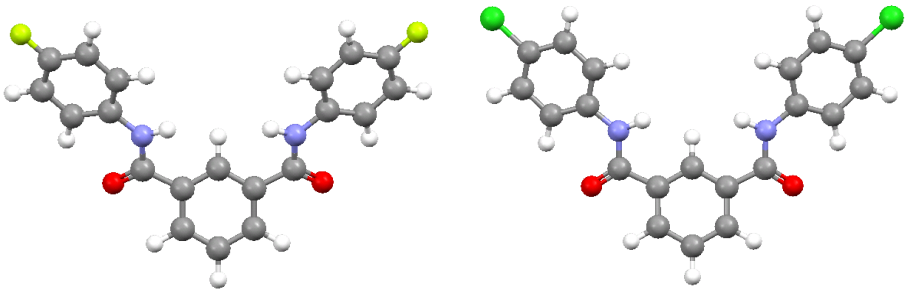
p-Substituted isophthalamide-based anion receptors, *N,N'*-Bis-(4-fluorophenyl) isophthalamide, **1**, and *N,N'*-bis-(4chlorophenyl)isophthalamide, **2**, were synthesized by the coupling reaction of isophthaloyl chloride and 4-fluoroaniline and 4-chloroaniline to obtain compounds **1** and **2** in 64 and 70 %yield respectively. Their structures were elucidated based on ^{1}H-NMR, ^{13}C-NMR, elemental analysis and mass spectrometry.

The optimized structures of receptors **1** and **2** obtained by the computational methods in gas phase are shown in Fig. 1. The optimized complexes structures of these compounds with TBAF, TBACl and TBABr have been shown in Fig. 2 and 3 respectively. These anions in this study represent to halide ions which impact to both living organism and environment. The results show that their NH-

amide and CH-phenyl protons have been used to bind the anions. Changes of energies (ΔE), enthalpy (ΔH^0_{298}) and standard Gibbs free energy (ΔG^0_{298}) of **1** and **2** with TBAF, TBACl and TBABr computed at B3LYP/ 6-31G(d) in gas phase have been shown in Table 1.

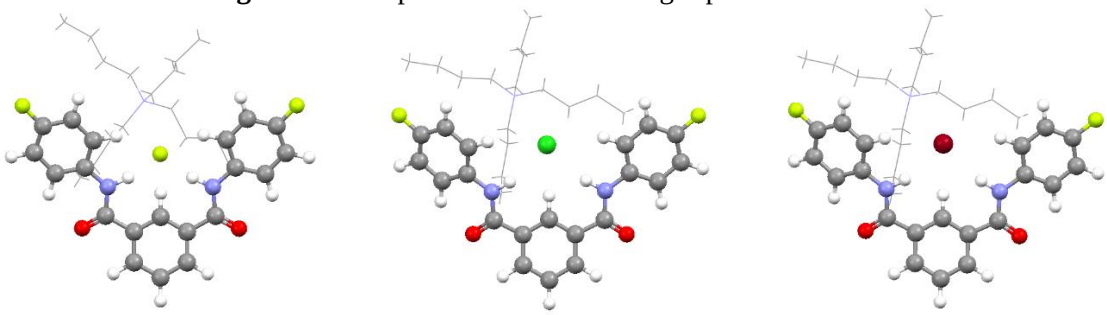
Table 1. Changes of energies (ΔE), enthalpy (ΔH^0_{298}) and standard Gibbs free energy (ΔG^0_{298}) of **1** and **2** with TBAF, TBACl and TBABr computed at B3LYP/6-31G(d) in gas phase

Anions	**ΔE (kcalmol^{-1})**		**ΔH^0_{298} (kcalmol^{-1})**		**ΔG^0_{298} (kcalmol^{-1})**	
	1	**2**	**1**	**2**	**1**	**2**
TBAF	-38.89	-43.78	-27.58	-29.65	-39.88	-43.27
TBACl	-31.36	-30.94	-13.88	-16.31	-23.28	-26.52
TBABr	-31.38	-32.16	-13.15	-16.53	-30.19	-34.24



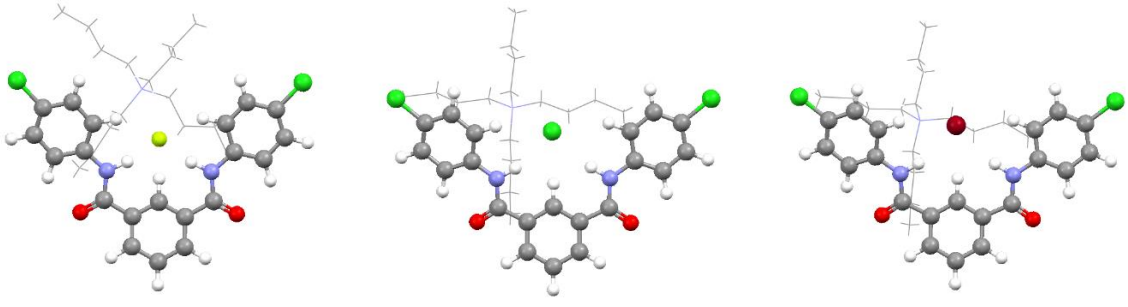
1 **2**

Figure 1. The optimized structures in gas phase of **1** and **2**



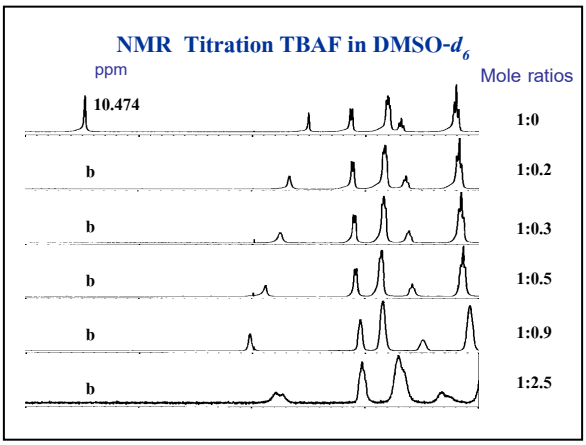
1+TBAF **1**+TBACl **1**+TBABr

Figure 2. The optimized structures in gas phase of complexes between **1** and TBAF, TBACl and TBABr

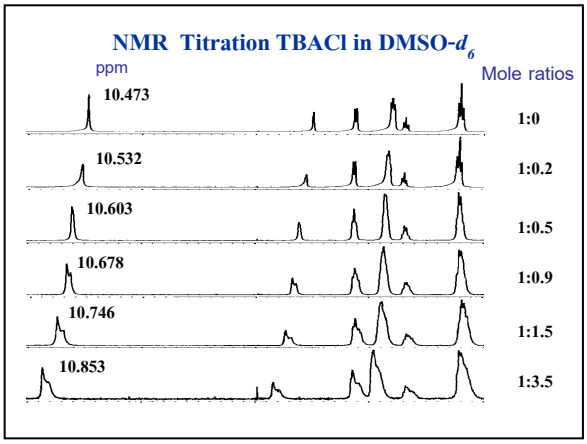


2+TBAF **2**+TBACl **2**+TBABr

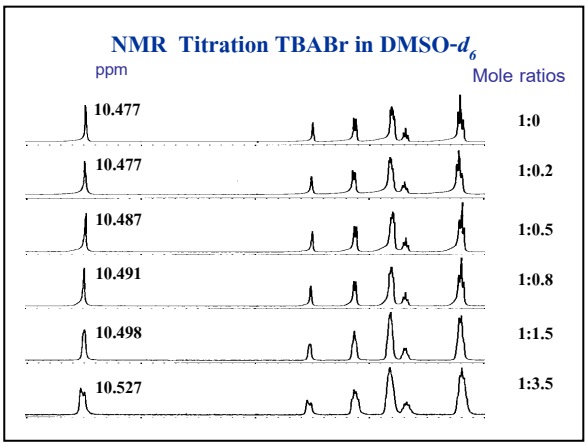
Figure 3. The optimized structures in gas phase of complexes between **2** and TBAF, TBACl and TBABr



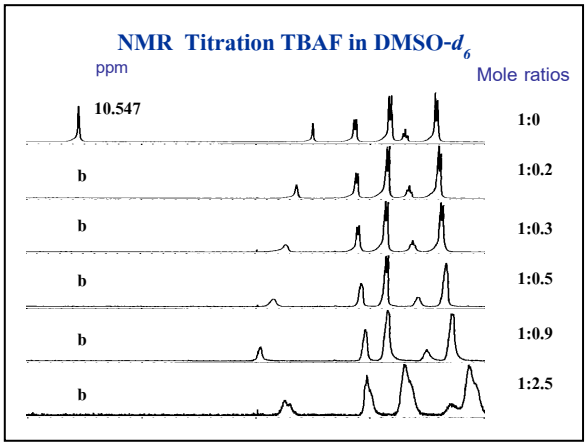
1+TBAF



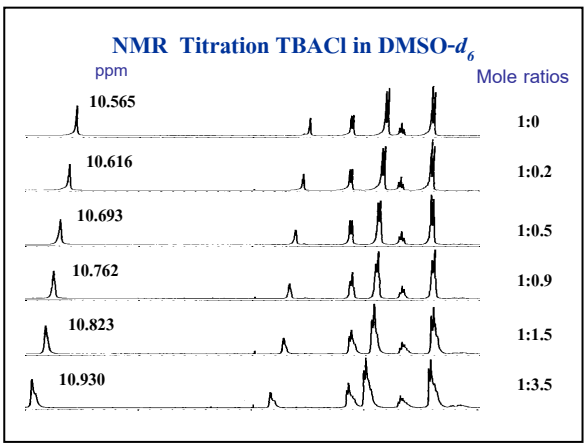
1+TBACl



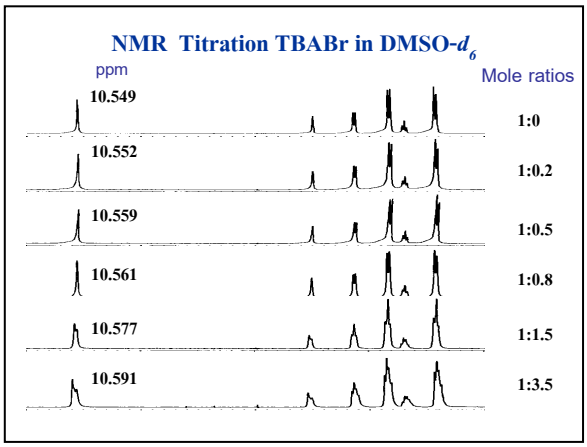
1+TBABr



2+TBAF

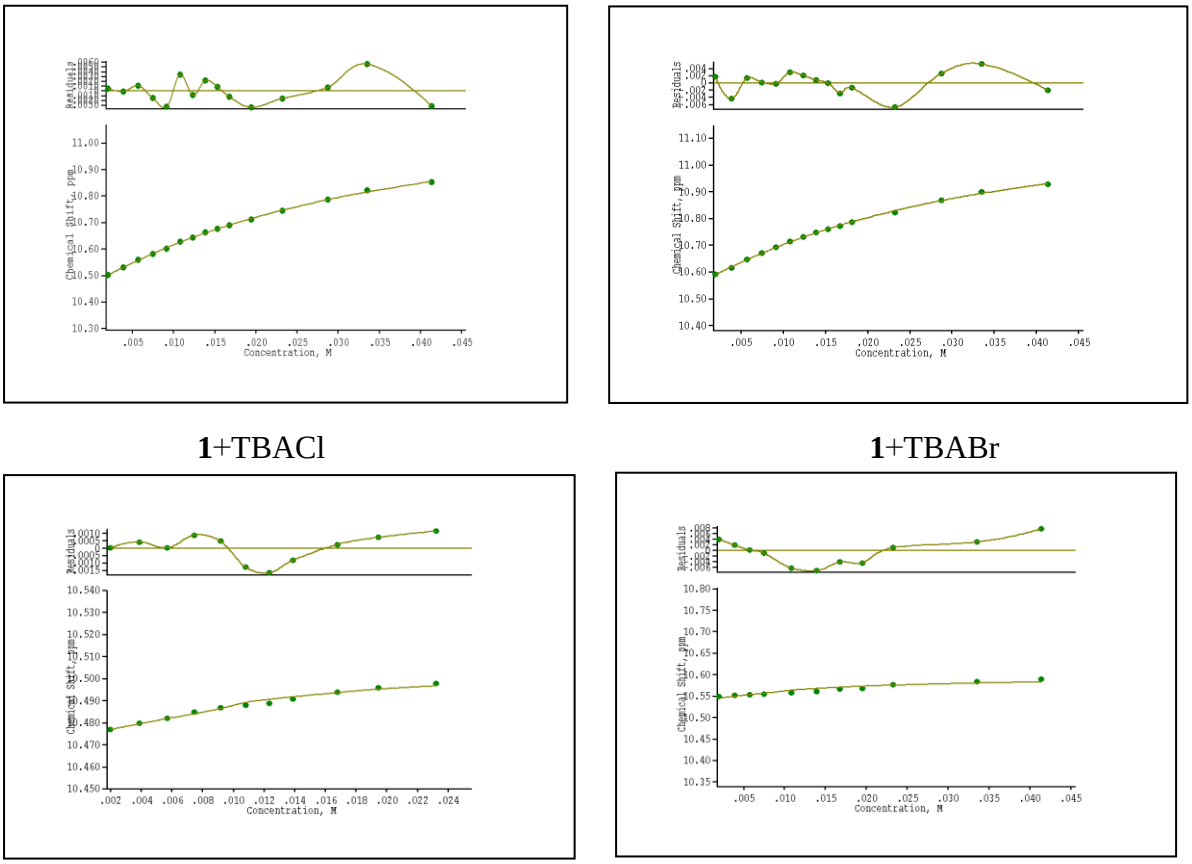


2+TBACl



2+TBABr

Figure 4. The ^{1}H NMR Spectrum of **1** and **2** showing the chemical shift of NH-amide protons with increasing amounts of TBAF, TBACl and TBABr in DMSO-d_6



1+TBACl **1**+TBABr

2+TBACl **2**+TBABr

Figure 5. Calculated of change in chemical shift of NH-amide resonance of **1** and **2** showing the chemical shift of NH-amide protons with increasing amounts of TBACl and TBABr in DMSO-d_6.

The ^{1}H NMR Spectrum of **1** and **2** showing the chemical shift of NH-amide protons with increasing amounts of TBAF, TBACl and TBABr in DMSO-d_6 have been shown in Figure **4**. However, the change could not be monitored in the TBAF titration systems as the proton signals of the NH-amide of the receptors were disappeared at high concentration of fluoride due to the hydrogen atom at NH-amide could be deprotonated by fluoride at high concentrations (Elmes et al 2013). Whereas hydrogen bonding to fluoride occurred at low concentration of fluoride. This protonation was not observed with less basic anions as chloride and bromide. Calculated of change in chemical shift of NH-amide resonance of **1** and **2** with increasing amounts of TBACl and TBABr in DMSO-d_6 have been shown in Figure **5**. It was found that the NH-amide proton chemical shifts of receptors **1** and **2** in the systems with TBACl and TBABr in DMSO-d_6 moved to downfield shift when the mole proportion of anions increase during the titrations. These shifts occurred because of the compounds interacted with the anions. The associate constants (K_{asso}) of **1** and **2** with chloride and bromide ions in DMSO-d_6 have been investigated via the EQNMR program using the NH-amide proton chemical shifts data, shown in Table 2. The binding data of chloride and bromide fitted a 1: 1 receptor: anion binding model well according to the calculated results. These results show that both receptors bind Br^- more than Cl^- in similar values. These results indicate that these receptors can provide suitable binding sites for the bromide ion.

Table 2 The associate constants (K_{asso}) of **1** and **2** with TBAF, TBACl and TBABr

obtained from the NMR titration techniques in DMSO-d_6.

Anions	K_{asso} (M^{-1})	
	1	**2**
TBAF	[a]	[a]
TBACl	34	37
TBABr	124	105

[a] = Can not be obtained

4. Discussion

From these results, it can be concluded that *N,N'*-bis-(4-fluoro-phenyl)is ophthalamide, **1**, and *N,N'* -bis-(4-chloro-phenyl) isophthalamide, **2**, which are the electron withdrawing groups mono halide *p*-substituted isophthalamide derivatives have been synthesized. The optimized structures of the compounds and their complexes have been studied using the DFT methods. Their fluoride, chloride and bromide ions which are represented to halide anions recognitions properties have also been investigated using the nuclear magnetic resonance spectroscopy techniques. The results show that these receptors can bind selectively with bromide anion. However, in the previous work, disubstituted isophthalamide receptors showed the most favorable complex of those compounds with bromide ion found by the NMR techniques (Navakhun et al 2014). Their association constants were more than ten times comparing with our mono halide substituted isophthalamide receptors in this work. It was probably due to their two electron withdrawing moieties were more effective than only one group.

Conclusion

Electron-withdrawing *p*-substituted isophthalamide derivatives, *N,N'*-bis-(4-fluorophenyl)isophthalamide, **1** and *N,N'*-bis-(4-chlorophenyl)isophthalamide, **2** have been synthesized. Their fluoride, chloride and bromide ions recognition properties have also been investigated using the nuclear magnetic resonance spectroscopy techniques. The results show that these receptors can be used as bromide receptors.

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