Computational Studies on the Stability of [Amide]Br^- Complexes†

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Theoretical studies on supramolecules have provided insight into their structure as well as their electronic distribution. While a number of such studies are found in the literature for neutral or cationic receptors, much less is known about anionic systems. Recently, we have published (Stibor, I.; Haffed, D. S. M.; Lhoták, P.; Hodačová, J.; Koča, J.; Čajan, M. *Gazz. Chim. Ital.* **1997**, *127*, 673) a study of amide bond activation for anion complexation where association constants were measured. In this paper, we present the results of calculations on single amides substituted on both sides of the amidic bond by an aromatic group with different substituents, as well as their complexes with anions using different methods of energy calculations. It is revealed that (i) only DFT methods give realistic results, while neither semiempirical quantum chemistry nor molecular mechanics CVFF force field give a realistic insight; (ii) the ligands (amides) themselves exhibit a different scale of nonplanarity which is caused by the repulsion between the ortho substituents of the aromatic moieties and the oxygen atom of the amidic group; (iii) the stability of the complexes is mainly correlated to three factors, the length of the hydrogen bond between the anion and amidic hydrogen, the interaction energy for the calculated complex, and the charge on the bromine atom within the complex.

Introduction

Theoretical studies of supramolecular complexes have provided much-needed insight into the structure and conformation as well as the electronic distribution in these extremely interesting species. In addition to molecular mechanics modeling of host−guest systems, molecular dynamics simulation has become increasingly popular in recent years. However, theoretical studies have mainly focused on macrocyclic receptors for cations, and therefore anion chemistry has developed more slowly. Despite this fact, theoretical studies on anion complexation have recently been reviewed where mainly polyammonium, organotin, organoboron, and calixarene-based ligands were discussed.[1] To the best of our knowledge, there is only one paper published on the Monte Carlo investigation of selective anion complexation by a calixarene-based receptor using (urea)N−H···anion interaction.[2]

Recently, we have published[3] a study of amide bond activation for anion complexation. We have found that even simple amides are capable of forming 1:1 complexes with many different anions and spherical anions in particular. Here, we present the detailed theoretical study of this important phenomena.

Methods

The equilibrium constants data has been obtained[3] by titration ^{1}H NMR spectroscopy of the solution of the corresponding amide in CCl_4 with $(nBu)_4N^+Br^-$ added.

Geometry optimization of single amides was initially done by molecular mechanics using the DISCOVER package[4] with CVFF force field[5] and also semiempirical methods AM1[6] and PM3[7] using the MOPAC[8] program were used. Semiempirical methods were also used for the analysis of conformational behavior of the amidic functional group. The final results were obtained using the DFT method[9] on the B3LYP/dzvd level.[10,11] The base selection was limited by the size of the studied molecules and by the parametrization of the bromide ion. No corrections were applied to SCF results because we were only interested in relative values. All DFT calculations were performed with the TURBOMOLE 95.0/3.0.0 program.[12] The results were visualized by INSIGHT II.[13]

The optimized geometries of single amides were used as starting coordinates to optimize complexes with a bromide anion. Neither the molecular mechanics CVFF force field nor semiempirical quantum chemistry provided satisfactory results in this case. Therefore, DFT was used for all energy minimizations of complexes. The same parameters used for single amides were employed.

The interaction energy corresponding to complex creation (ΔE_{int}) was calculated using eq 1 as the difference of the energy of the complex (E_{comp}) and the energy of the system with two separate particles (amide and anion, E_{sep}). In the latter case, the distance between the amide and the bromide anion was fixed at 25 Å, which has been confirmed as being long enough to ensure that the amide and anion do not interact with each other.

$$\Delta E_{int} = E_{comp} - E_{sep} \quad (1)$$

The energy minimization of each complex was carried out in such a way that first a starting inspection was carried out using a single-point calculation for several geometries, and then the best (lowest energy) geometry was fully minimized. The reason for applying such a relatively complicated procedure is

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† Dedicated to Professor Milan Kratochvíl on the occasion of his 75th birthday.

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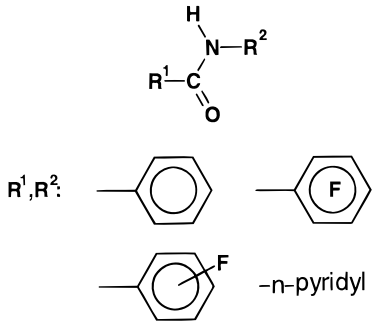
TABLE 1: Experimental and Calculated Characteristics for the Complexes between Amides and the Bromide Anion[a]

no.	compound	K_{assoc}	ΔE_{int} [kcal mol^{-1}]	d(NH−Br) [Å]	q(Br)
1	$C_6F_5-CONH-o-F-C_6H_4$	62 ± 16	9.28	3.35	−0.8890
2	o-F−C_6H_4−CONH−C_6H_5	64 ± 18	9.53	3.32	−0.9229
3	$C_6H_5-CONH-C_6H_5$	145 ± 12	22.49	2.58	−0.8383
4	m-F−C_6H_4−CONH−C_6H_5	210 ± 25	21.49	2.52	−0.8180
5	3-pyridyl−CONH−C_6H_5	258 ± 22	21.56	2.52	−0.8165
6	$C_6H_5-CONH-p$-F-C_6H_4	297 ± 10	25.16	2.54	−0.8306
7	$C_6H_5-CONH-m$-F-C_6H_4	340 ± 15	24.18	2.54	−0.8247
8	$C_6H_5-CONH-C_6F_5$	368 ± 9	23.13	2.50	−0.8263
9	p-F-C_6H_4−CONH−C_6H_5	434 ± 30	24.25	2.53	−0.8364
10	C_6H_5−CONH−2-pyridyl	530 ± 36	11.12	2.50	−0.8409
11	m-F−C_6H_4−CONH−m-F−C_6H_4	700 ± 29	26.88	2.47	−0.8115
12	p-F−C_6H_4−CONH−p-F−C_6H_4	880 ± 28	27.44	2.47	−0.8133
13	p-F−C_6H_4−CONH−m-F−C_6H_4	930 ± 38	26.24	2.44	−0.8073
14	$C_6F_5-CONH-C_6H_5$	1320 ± 12	23.85	2.36	−0.8207
15	4-pyridyl−CONH−C_6H_5	1650 ± 14	24.85	2.36	−0.8085
16	C_6H_5−CONH−3−pyridyl	1680 ± 17	25.52	2.34	−0.8153
17	$C_6H_5-CONH-p$-F-C_6H_4	1687 ± 18	27.25	2.31	−0.8147
18	$C_6H_5-CONH-m$-F-C_6H_4	2305 ± 13	25.90	2.25	−0.8009
19	C_6H_5−CONH−4-pyridyl	2684 ± 15	29.99	2.24	−0.8090
20	C_6H_5−CONH−2-pyridyl	3200 ± 18	28.52	2.23	−0.8042
21	C_6H_5−CONH−3,5-F_2-phenyl	4750 ± 15	30.75	2.22	−0.7915
22	4-pyridyl−CONH−3,5-F_2-phenyl	5400 ± 29	27.16	2.21	−0.7647

[a] K_{assoc} is the experimental association constant[3], ΔE_{int} is the binding energy calculated by eq 1, d(NH−Br) is the length of the key hydrogen bond, and q(Br) is the partial charge calculated on the bromine atom.

SCHEME 1. General formula for the Set of Studied Amides[a]



[a] The substituents R^1 and R^2 mean one of the following functional groups: phenyl, fluorophenyl, perfluorophenyl, pyridil.

that the energy surface around the true minimum contains several shallow minima and the minimizer can end in any of them.

Mulliken,[14] Löwdin,[15,16] Roby-Davidson,[17] and ESP[18] methods have been tested to calculate partial charges. The ESP method applied on complexes gave unrealistic results, while all the remaining methods produced results of similar quality. Finally, we used Mulliken population analysis.

Results and Discussion

All the studied amides are collected in Table 1 together with experimentally obtained equilibrium constants. The general formula of the studied molecules is shown in Scheme 1. We have selected molecules for the computational study which would be small enough to ensure that accurate computational methods could be used. The second criterion for the selection has been that the equilibrium constants are spread out enough so that we can draw conclusions over a wider range of equilibria. Amides with alifatic substituents were not studied as they usually create nonstable complexes. Finally, the selection resulted in a set of 22 ligands giving equilibrium constants in the range 50−5500 M^{-1}. The ligands interact with the anion via the hydrogen bond created between the anion and the amidic hydrogen. All the selected ligands create complexes with 1:1 stoichiometry.[3]

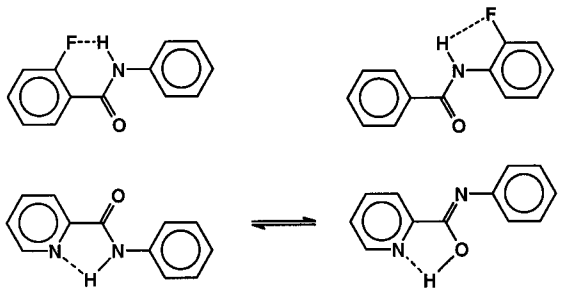


Figure 1. Possible hydrogen bonds in aromatic amides.

The conformational flexibility of the ligands is substantially reduced for aromatic substituents, which makes the computations less time consuming. In this case, the conformational space is reduced only to rotatable bonds between the substituents and the amidic functional group.

Aromatic amides are composed of three conjugated parts, both the aromatic substituents and the amidic functional group itself. When the molecule is planar, it is probably fully conjugated, which increases the possibility of influencing the behavior of the hydrogen on the amidic group. This is confirmed, for example, by complexes with **14** and **17**−**19**, where the stability of the complex is strongly affected by the category of substituent and the position of the substitution on the aromatic ring. Intermolecular hydrogen bonding is another feature which can strongly influence the ability of amides to create complexes with anions (see Figure 1). Below, we first discuss the results obtained on single amides where especially slight differences in conformational behavior will be the center of attention. These results will then be correlated with the results obtained for complexes.

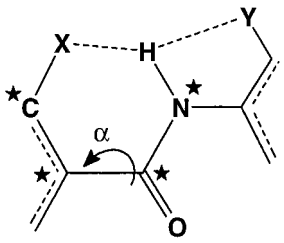
Structure of Single Amides. The key question here is to describe the conformational behavior around the basic planar conformation. We have used molecular mechanics, semiempirical quantum chemistry, and DFT methods. Molecular mechanics suggests that the planar conformation is the only possible solution. The application of semiempirical methods also resulted in planar conformers, but in some cases also in conformers where the aromatic moieties were slightly rotated with respect to the amidic group plane. In the majority of cases,

TABLE 2: Selected Geometrical Parameters for Some Studied Amides Together with Experimental Association Constants (K_{assoc}, in mol^{-1}) and the So-Called "Stabilization Energy ΔE", Which Is Calculated as the Difference between the Energy of the Planar Conformation and the Energy of the Lowest Energy Conformation of the Amide[a]

compd no.	K_{assoc} [M^{-1}]	ΔE [kcal mol^{-1}]	α [deg]	*d*(XH) [Å]	*d*(YH) [Å]
1	62	1.58	41.0	2.27	2.22
2	64	0.18	11.6	1.95	2.27
3	145	0.23	16.2	1.99	2.26
8	368	4.12	23.3	2.54	2.16
9	434	0.39	25.0	2.11	2.27
12	880	0.21	15.8	2.00	2.27
15	1650	0.28	31.2	2.19	2.27
18	2306	1.63	54.7	2.54	2.27
20	3200	1.44	63.6	2.76	*b*
22	5400	0.30	30.4	2.18	2.27

[a] The nonplanarity of the amide is expressed by the dihedral angle, α, and the distance of the amidic hydrogen from the ortho substituents of both aromatic moieties is denoted by *d*(XH) and *d*(YH). For further details see Scheme 2. [b] −NH···N(2-pyridyl).

SCHEME 2. Geometrical Parameters of Amides Important for the Stability of the Amide−Anion Complex[a]



[a] The distances of amidic hydrogen from ortho substituents on both aromatic moieties and the dihedral angle α describing nonplanarity on the C-carbonyl part of the amide are also shown.

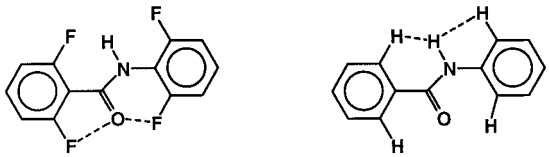


Figure 2. Repulsions in aromatic amides are mainly caused by ortho substituents on either aromatic moiety.

these conformers were energetically unfavorable in comparison with the planar ones. Amides with perfluorinated substituents were the only exceptions. The results obtained by DFT are principally different. They are collected in Table 2 and the denotation is shown in Scheme 2. It is shown that in all cases the rotated conformation is always preferred to the planar one. The aromatic part bonded to the carbonyl carbon of the amide is the moiety which is usually rotated. The aromatic substituent bonded to the amide nitrogen is rotated in only one case (molecule **8**).

There are two reasons why the aromatic moiety bonded to the carbonyl carbon is rotated. The first reason is the repulsive interaction between the amidic hydrogen and the ortho hydrogen atom on the aromatic substituent bonded to the carbonyl carbon (see Figure 2). The distance between the two atoms in the planar conformation is about 1.9 Å, while for the rotated conformation it is 2.0 Å or more. The same type of interaction does not occur between the amidic hydrogen and the ortho hydrogen atom of the aromatic ring bonded to the amidic nitrogen. In this case, the distance of the two atoms in the planar conformation is about 2.3 Å. More details about the differences between the planar and nonplanar amide conformations are given in Figure 3 where

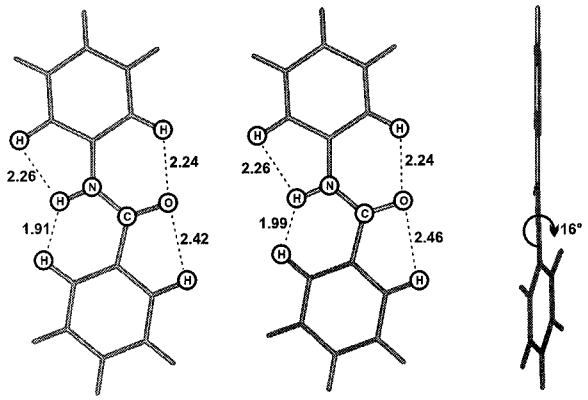


Figure 3. Comparison of substantial geometrical parameters for the planar (A) and the most stable (B) conformers of molecule **3**, distances between atoms in Å, angle between the planes created by the two aromatic moieties in degrees.

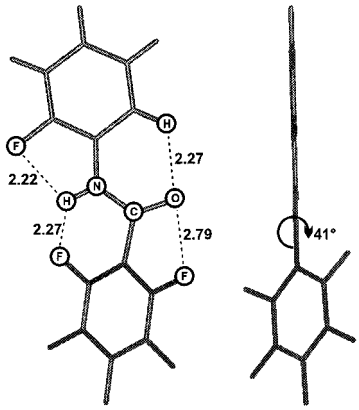


Figure 4. Most important geometrical parameters of the lowest energy conformer of molecule **1**. The nonplanarity (41°) is mainly caused by the repulsion between the ortho substituent on the C-bonded cyclic moiety (fluorine) and the oxygen atom of the amide. Distances between atoms in Å.

the data for the amide **3** is displayed. Both substituents on **3** are phenyls. Here, the distance is changed from 1.91 Å for the planar conformation to 1.99 Å for the nonplanar one, while the aromatic moiety is rotated by 16.2°.

The second reason for the nonplanar conformation being favored is the repulsive interaction between the fluorine atoms in ortho positions on either of the two aromatic moieties and the amidic oxygen (see Figure 2). This interaction only occurs for perfluorinated molecules, because molecules with the fluorine atoms in only one ortho position will prefer such a conformation where the fluorine atoms interact with the amidic hydrogen to create a hydrogen bond. In the case of perfluorinated molecules, the rotation angle is substantially larger (over 40°) than for the hydrogen−hydrogen interaction. For the perfluorinated residue bonded to the amidic carbonyl carbon, a maximum value has been calculated for molecule **20** (about 64°). In the case of the aromatic substituent bonded to the nitrogen atom of the amide part, the largest value calculated for rotation is 23°. The distances of the carbonyl oxygen from the fluorine atom of the aromatic moiety bonded to the amidic carbon and nitrogen are larger than 2.7 and 2.5 Å, respectively. The results obtained for molecules **1** and **8** are pictured in Figures 4 and 5, respectively. In both the cases the interaction between the amidic hydrogen and the fluorine atom of the N-bonded aromatic moiety is also possible.

To summarize briefly, the planar conformation is not a global minimum on the conformational energy surface and the total

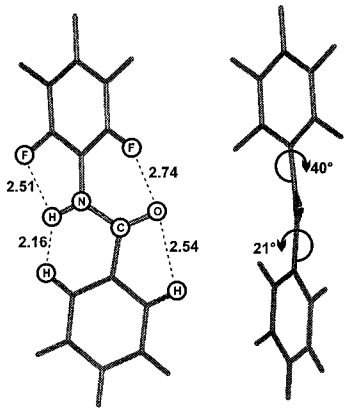


Figure 5. Most important geometry parameters of the lowest energy conformer of molecule **8**. The nonplanarity on C-terminal (21°) is caused by the repulsion between the ortho substituent (hydrogen) and the amidic hydrogen. The nonplanarity (40.1°) on the N-terminal is induced by the repulsion between the ortho substituent on the aromatic moiety (fluorine) and the oxygen atom of the amide. Distances between atoms in Å.

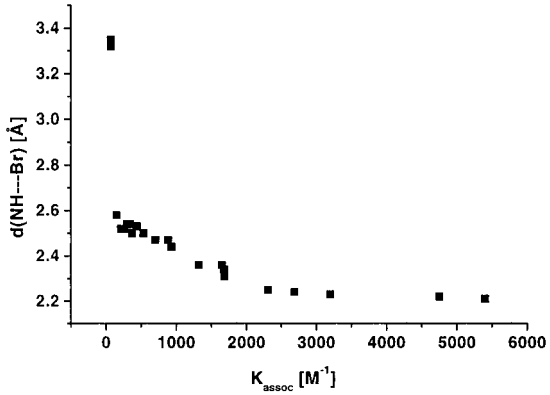


Figure 6. Relationship between the experimental association constant (K_{assoc}) and the length of the hydrogen bond between the amidic hydrogen and the bromine atom (d(NH−Br)).

π-electron system conjugation is slightly damaged by the repulsion of substituents in ortho positions of the aromatic rings on one side and atoms of the amidic group on the other side. This effect is stronger for the C substituent than the N substituent of the amidic group. The energy of the most stable conformer is an equilibrium of three competing parts: a maximum conjugation, a minimum repulsion, and a maximum attraction (H-bonding).

Complexes of Amides with a Bromide Anion. The most stable conformers of amides described in the previous chapter have been used to study complexes with a bromide anion. We have calculated some characteristics of selected 1:1 complexes and then compared them with the experimental values of the equilibrium constant. The interaction energy, the distance between the anion and the amidic hydrogen, and the charge on the bromide atom in the complex were found to be the most important characteristics. The results are summarized in Table 1 and pictured in Figures 6−10. The relationship between the distance of the amidic hydrogen from the bromine anion and the equilibrium constant is shown in Figure 6.

The graph clearly shows that the distances vary between 2.2 Å for the most stable complexes (K_{assoc} > 3000 M^{-1}) and 3.3 Å for weak complexes with K_{assoc} < 100 M^{-1}. The sharp increase of bonding distance for the two least stable complexes is caused by the fluorine substituents in ortho positions of both aromatic rings. In the two cases, a strong interaction of a fluorine

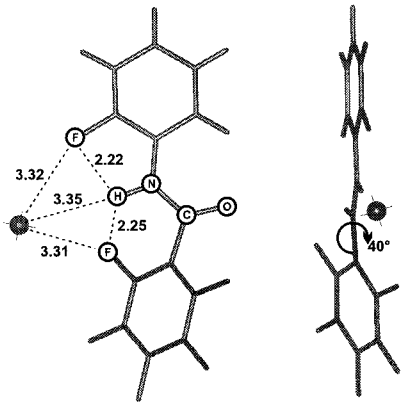


Figure 7. Most important geometry parameters calculated for the complex bromide anion−molecule **1** (distances between atoms in Å, nonplanarity angle in degrees).

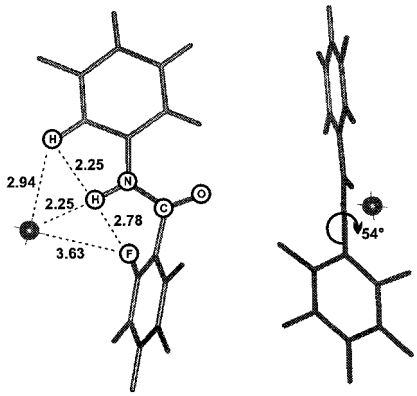


Figure 8. The most important geometry parameters calculated for the complex bromide anion−molecule **18** (distances between atoms in Å, nonplanarity angle in degrees).

atom with an amidic hydrogen occurs which makes the interaction of the amidic hydrogen with the bromide anion more problematic because of the strong repulsion of the fluorine substituent and the bromide anion. The situation for molecule **1** is clearly seen in Figure 7. The structure of the complex with molecule **2** is very similar. The majority of complexes with K_{ass} > 2000 M^{-1} are created by amides containing a perfluorinated aromatic part on the carbon atom of the amidic group and substituted in the meta or para position of the second aromatic ring. The results for molecule **18** which gives one of the most stable complexes are shown in Figure 8.

The distance of the activated amidic hydrogen from the bromide anion is close to 2.2 Å in this case. The repulsion between one fluorine substituent in the ortho position and the amidic oxygen implies that the ring is rotated which creates space for the bromide anion to interact with the amidic hydrogen, which is not inactivated by hydrogen bonding to a fluorine atom in this particular case. The stability of the complex is also influenced by the substitution of the second ring. This is seen when comparing the stability constants for complexes with molecules **17** and **18**. The remaining amides exhibit interaction distances between 2.3 and 2.5 Å and equilibrium constants in between the largest and the smallest values in the set. All the amides belonging to this category are found in almost planar conformations, so the activated hydrogen is more or less sterically hindered. The stability of the complex is then dependent mainly on a combination of the substituent effect on the aromatic moieties and the steric effect.

The second parameter we have considered for complex stability description was the interaction energy (see Table 1 and

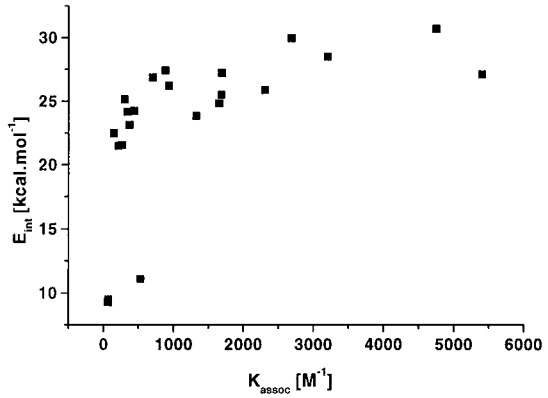


Figure 9. The relationship between the experimental association constant (K_{assoc}) and the calculated binding energy E_{int}.

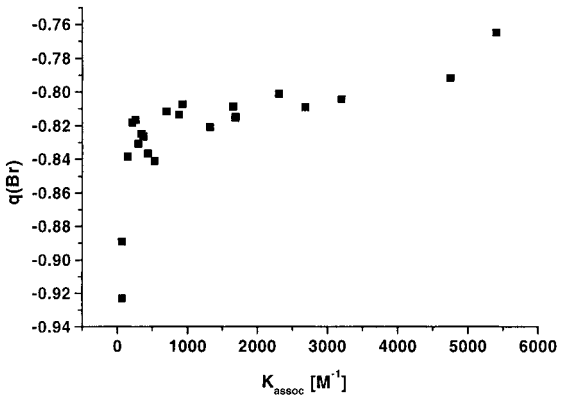


Figure 10. The relationship between the experimental association constant (K_{assoc}) and the calculated relative charge on the bromine atom q(Br).

Figure 9). As expected, the interaction energy calculated by using eq 1 correlates well qualitatively with the equilibrium constant in such a way that a higher interaction energy implies a higher equilibrium constant. The lowest values (about 10 kcal mol^{-1}) of the interaction energy have been calculated for the most unstable complexes. The values for the most stable complexes are close to 30 kcal mol^{-1}. The two systems with the lowest interaction constant exhibit a substantial difference in the calculated interaction energy compared to all the remaining complexes. This is due to intramolecular hydrogen bonding. It is important to note that the calculations presented here show quite a good qualitative picture and give a realistic explanation about "what is going on", but should not be understood as a full description of all the effects playing a role in the system. Substantially, two essential extensions would be necessary to correlate fully the computational data with the equilibrium constants. One would have to consider an explicit (or at least an implicit) solvent and calculate free energy instead of potential.

The effective charge on the bromine atom was the last quantity we were interested in. The value of this parameter should give a good indication about how strong the electrostatic interaction between the bromide anion and the amidic hydrogen atom will be. The graph showing the relationship between the charge and the equilibrium constant is shown in Figure 10. The dependence is similar to that shown in Figure 9. Again, the lowest values are exhibited by systems with intramolecular hydrogen bonds on the ligand itself. In these complexes, the bromide anion almost keeps its original unitary negative charge and does not contribute too much to the complex formation. On the other hand, for stable complexes, the charge on the bromine atom is decreased substantially as the original unitary negative charge is more involved in hydrogen bonding.

Conclusions

This work has been focused on the theoretical study of complexes of simple aromatic amides with a bromide anion. It has been shown that the process of creating a hydrogen bond between the amidic hydrogen and the bromide anion is the driving force to form these complexes. The stability of such complexes is dependent on several factors. The most substantial is the length of the hydrogen bond. Another important factor is the nonplanarity of the entire amide molecule which, in general, decreases steric interactions and makes the formation of the complex easier. The amidic hydrogen is activated by substituents on the aromatic rings. We have shown that ortho fluorine substitution implies a lower stability of complexes because of the repulsion between the fluorine and bromine atoms, while meta and especially para substitution increases the stability of complexes substantially. The reason is the activation of the amidic hydrogen.

We have also shown that only such theoretical methods can be used to study systems like ours, which include electron correlations. The results obtained using DFT on B3LYP/dzvd level are in good qualitative agreement with experimental association constants. DISCOVER CVFF force field doesn't give realistic results which is in agreement with literature.[19] Semiempirical AM1 and PM3 also haven't been successful. The question, which is not discussed here and which still remains unanswered, is whether free energy calculations using thermodynamic cycles and including solvent would bring more precise quantitative results or not.

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