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Anion recognition by *N,N′*-diarylalkanediamides

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ABSTRACT

The preparation of *N,N′*-diarylalkanediamides from the respective aliphatic dicarboxylic acids and 4-nitroaniline via microwave-prompted reactions is presented. The most positive effect of microwave irradiation was observed for *N,N′*-bis(4-nitrophenyl)butanediamide. Anion binding studies on the obtained diamides were carried out in DMSO and acetonitrile using UV–vis and ^{1}H NMR spectroscopy. A mechanism for selective fluoride recognition by *N,N′*-bis(4-nitrophenyl)butanediamide in DMSO is proposed.

Amides occur widely in Nature (peptides, proteins), and many synthetic amides are used in various fields of science. In medicinal chemistry they attract attention due their antitumour activity,[1] and they are also used as antibacterial agents[2] and HIV inhibitors.[3] The presence of the N–H residue makes amides interesting for supramolecular chemists as potential artificial anion receptors.[4] Investigations of synthetic receptors allows natural systems to be copied and information on the mechanisms of biochemical processes to be derived. Synthetic receptors are also useful analytical tools. The incorporation of a chromophore into anion sensitive molecules results in chromo-ionophores. Chromogenic receptors enable the application of simple and inexpensive spectrophotometric methods for anion detection and determination. Such compounds may also work as 'naked-eye' anion sensors.[5]

In many cases, the main factor limiting the possible applications of a receptor is its synthesis which can be complicated, for example, by time and energy consumption, utilizing harmful reagents, etc. Amides are among those compounds which can be obtained relatively easily, in high yields using the corresponding acid chlorides as substrates. Elimination of hazardous organic compounds is one of the essential requirements of green chemistry. High yielding and environmentally friendly synthetic methods can, among the others, be based on microwave-assisted protocols.[6] Microwaves (MWs) were found to be an effective tool in amide preparation. Loupy et al.[7] synthesized amides by the direct irradiation of an amine and monocarboxylic acid mixtures. The yields of the obtained products were 2 to 10-fold higher in comparison to conventional methods. Zare and co-workers[8] proved that the presence of a quaternary ammonium salt increases the microwave effect resulting in improved conversions into the desired amides. Khalafi-Nezhad et al.[9] applied microwaves for the preparation of primary amides using imidazole as a base. It was found that the presence of imidazole leads to the formation of polar salts with carboxylic acids, which results in greater absorption of microwave energy.[10] The low melting point of imidazolium carboxylates (they melt even when low microwave power is applied) provides homogeneity to the reaction mixture.

Herein, we describe simple amides, being derivatives of aliphatic dicarboxylic acids and *p*-nitroaniline, their MW assisted synthesis and ion complexation properties.

N,N′-diarylalkanediamides were previously obtained and studied as cytotoxic agents by Chacón-Gracía and Martínez.[11] In this work, amides of succinic (**1**, $n = 2$), glutaric (**2**, $n = 3$), adipic (**3**, $n = 4$), pimelic (**4**, $n = 5$) and suberic (**5**, $n = 6$) acids (Fig. 1) were obtained using a previously described method[12] (see Supplementary data). This method, although well proven in the case of 2,6-pyridine dicarboxylic acid amides[12] allowed amides of the above mentioned aliphatic acids to be obtained in rather moderate yields (15–45%). A more efficient and less time-consuming method was proposed by Martínez.[11] However, both the above synthetic procedures use acid chlorides as substrates, the preparation of which required toxic and rather unpleasant reagents. Thus, investigations on the preparation of amides of aliphatic dicarboxylic acids **1–5** (Fig. 1) in reactions promoted by microwave irradiation were performed (for experimental details, see Supplementary data). The effect of solvent, type of base, microwave power, temperature, and reaction time were investigated in order to obtain the highest yield of the desired product with the least amount of by-product formation. Traces of amides were observed using DMF, acetonitrile, and

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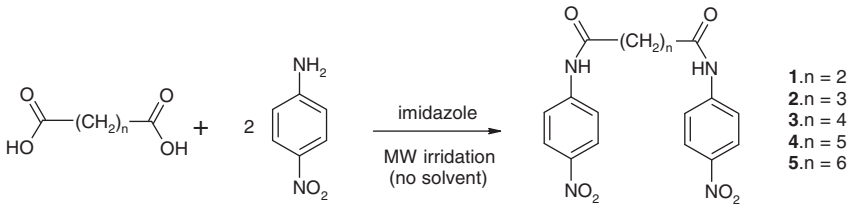


Figure 1. Microwave-assisted preparation of amides **1-5**.

Table 1
The conditions and yields of the direct MW-assisted synthesis of amides **1**–**5**

Product	Acid	Temperature (°C)	Time (min)	Power (W)	MW Yield[a] (%)
1	Succinic (n = 2)	90	10	500	26
2	Glutaric (n = 3)	110	10	500	30
3	Adipic (n = 4)	110	30	500	29
4	Pimelic (n = 5)	110	10	600	**40**
5	Suberic (n = 6)	110	30	500	15

By bold the highest obtained yield is marked.
[a] Estimated from the ^{1}H NMR spectra.

water as the solvent. No beneficial effect of the kind of the used base (anhydrous potassium carbonate, triethylamine, imidazole, potassium *tert*-butanolate) was apparent. The best results were obtained for reactions carried out under solvent-free conditions, as schematically shown in Figure 1. The optimum reaction conditions and the best obtained yields are collected in Table 1. For more details, see Supplementary data (Table S1).

The most beneficial effect of MW irridation was observed for succinic acid diamide. The yield of succinic acid diamide is usually low, due to preferential cyclic imide formation. Under conventional conditions, the yield of *N,N′*-bis(4-nitrophenyl)butanediamide (**1**) usually does not exceed 20%. The microwave-assisted reaction gave the same amide within 10 min in 26% yield. In the cases of amides with longer aliphatic chains, the yields were not spectacular, the highest being for pimelic acid diamide (**4**). However, significantly shorter reaction times and the avoidance of toxic reagents (e.g., thionyl chloride) were the principal advantages of the described method.

The atomic arrangement and the presence of the chromophore in the amides obtained make them possible ion complexing agents. To our knowledge, their ion recognition ability has not been tested using UV–vis spectrophotometry. Both metal cations (used as perchlorates) and anions (as tetra-*n*-butylammonium salts) of different shapes and sizes in various organic solvents were used for ion complexation studies. No color or spectral changes were observed in the presence of alkali and alkaline earth metal cations in DMSO. Among the studied anions were halides, oxygen-containing inorganic anions (hydrogen sulfate, dihydrogen phosphate, nitrate, nitrite, and perchlorate) and carboxylic acid anions (acetate, benzoate). In DMSO, spectral changes were observed only in the presence of fluorides and dihydrogen phosphates. Spectral changes upon spectrophotometric titrations with tetra-*n*-butylammonium dihydrogen phosphates (TBADHP) are exemplified with pimelic acid diamide (**4**) in Figure 2a. Spectral changes in the presence of TBADHP for all the investigated amides have the same trend, that is, no particular selectivity in their colorimetric response to dihydrogen phosphate anion recognition was found. On the basis of titration experiments the stability constant values of the diamide complexes with dihydrogen phosphates were estimated. Calculations using the OPIUM[13] program showed the best fit for 1:1 complexes. The obtained values of the stability constants, shown in Figure 2b, for the dihydrogen phosphate complexes did not differ dramatically. From the obtained results it might be concluded that, to some extent, the dihydrogen binding strength is dependent on the number of carbon atoms in the amides aliphatic chain. In the studied range of amide homologues, the stability constants were higher for shorter analogs (ligands **1–4**). The lowest stability constant was obtained for suberic acid diamide (**5**). Moreover, there was relationship between the stability constant value and the parity of carbon atoms in the aliphatic chain. They were slightly higher for amides with an even number of carbon atoms. This observed trend might be explained by the flexibility of the diamide molecules affecting the shape of the formed molecular "cavity" upon

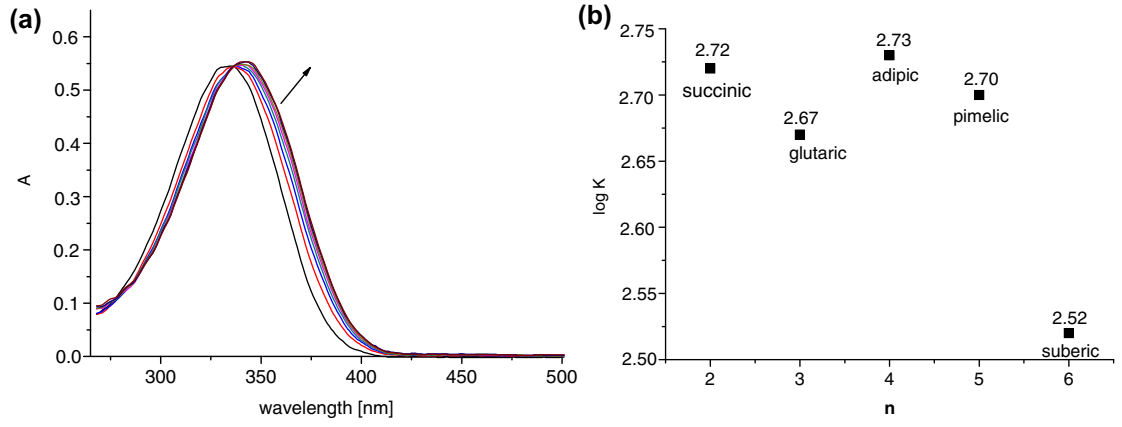
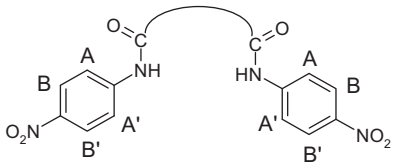


Figure 2. (a) Spectral changes upon titration of **4** (2.08×10^{-5} M) with tetra-*n*-butylammonium dihydrogen phosphate (TBADHP) (c_{TBADHP} = 0–2.52×10^{-3} M) in DMSO; (b) The relationship between the stability constant value (log*K*) of TBADHP complexes (DMSO) and the number of carbon atoms (*n*) in the aliphatic chain of *N,N′*-diarylalkanediamide **1**–**5**.

Table 2
The chemical shift (δ [ppm]) changes in the ^{1}H NMR spectra of *N,N′*-diarylalkanediamides **1**, **3,** and **4** in the presence of an equimolar amount of tetra-*n*-butylammonium dihydrogen phosphate in DMSO-d_6



Ligand	NH	AA′	BB′	Log$K$[a]
1	10.67	7.82	8.21	2.72 ± 0.06
1 + $H_2PO_4^-$	11.72	7.92	8.18	
$\Delta\delta$ [ppm]	**+1.05**	**+0.10**	**−0.03**	
3	10.53	7.83	8.20	2.73 ± 0.19
3 + $H_2PO_4^-$	11.72	7.94	8.16	
$\Delta\delta$ [ppm]	**+1.19**	**+0.11**	**−0.04**	
4	10.50	7.82	8.19	
4 + $H_2PO_4^-$	11.42	7.89	8.16	2.70 ± 0.01
$\Delta\delta$ [ppm]	**+0.92**	**+0.07**	**−0.03**	

By bold $\Delta\delta$ [ppm] are marked.
[a] Determined from UV–vis measurements (DMSO).

anion complexation. A lower value of stability constant for simple *N*-methylacetamide[4e] (log$K$ = 1.41, chloroform-d_3), proves a chelate effect in phosphate binding by synthesized diamides **1–5**. Comparing to previously described[12] *N,N′*-bis(4-nitrophenyl)pyridine-2,6-dicarboxamide, where no spectrophotometric response toward dihydrogen phosphate was found, the change of aromatic acid residue to aliphatic chain seems to have beneficial effect for anion recognition. In the series of chromogenic pyridine-2,6-dicarboxylic acid amides mentioned above selective phosphate binding in DMSO was found for *N,N′*-bis(2-hydroxy-4-nitrophenyl)pyridine-2,6-dicarboxamide. However the stability constant value, log$K$ = 2.51, is in this last case lower than that for investigated aliphatic acid diamides. Flexible aliphatic chains of various length, besides aromatic acid residues, were building blocks in a series of macrocyclic tetraamides obtained by Chmielewski and Jurczak.[4a–d] The highest affinity toward anions was found for 20-membered compounds[4b] with binding constant for dihydrogen phosphates log$K$ ~ 3.9 (DMSO-d_6). The anion affinity of their open chain analogs was significantly lower.

To support our dihydrogen phosphate complexation theory, the ^{1}H NMR spectra of the diamides **1**, **3,** and **4** in the presence of equimolar amounts of dihydrogen phosphate were recorded in DMSO-d_6. The chemical shifts [ppm] for the free ligands and their changes in the presence of TBADHP are summarized in Table 2. The respective spectra are shown in Supplementary data (Fig. S1).

The chemical shift values of the NH signals for the free ligands suggest the presence of intramolecular hydrogen bonds (NH···O=C) of increasing strength, inversely proportional to the alkyl chain length. In the presence of dihydrogen phosphates, in all cases, the NH signal was shifted downfield indicating stronger intermolecular hydrogen bond formation, that is, between the ligand and anion. The most significant change in the chemical shift of the NH signal ($\Delta\delta$ = +1.19) was observed for adipic acid diamide (**3**). Analysis of the chemical shift changes for the NH and aromatic proton signals again showed the correlation between the length of the alkyl chain and the strength of dihydrogen phosphate binding.

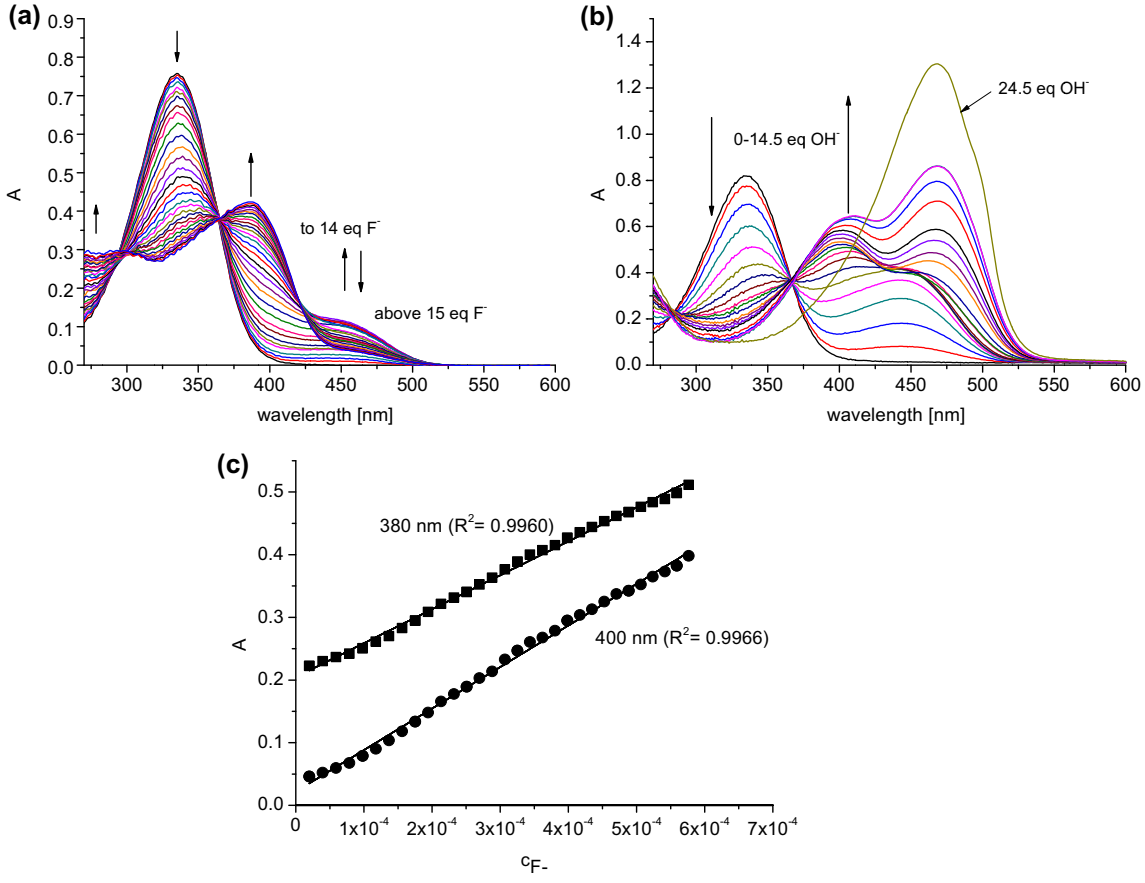


Figure 3. Comparison of the spectral changes upon titration of **1** (3.05×10^{-5} M) with: (a) TBAF (b) TBAOH, and (c) the absorbance changes as a function of fluoride concentration, in DMSO.

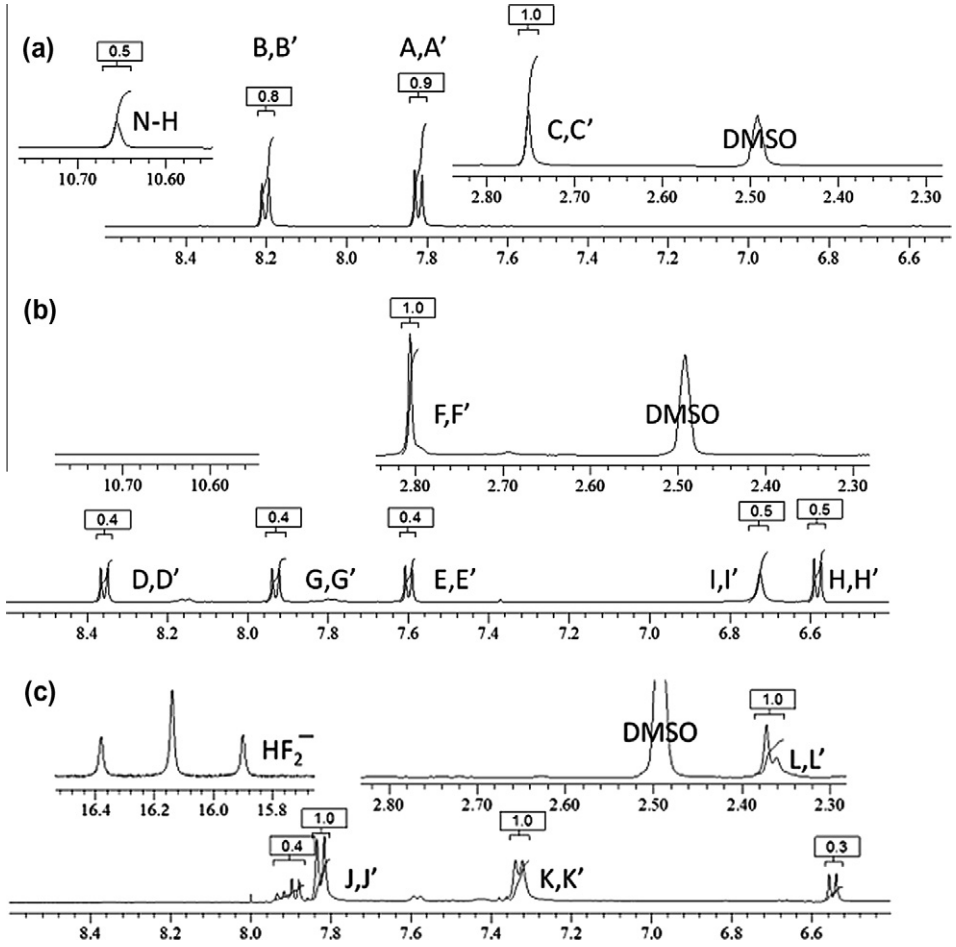


Figure 4. ^{1}H NMR spectra of: (a) succinic acid diamide **1** (1.27×10^{-2} M); (b) upon addition of 0.1 equiv, and (c) 1 equiv of TBAF in DMSO-d_6 (for proton annotations see Fig. 5).

Changes in the chemical shifts of the aromatic protons showed also their different participation in anion binding. Dihydrogen phosphate is bound the strongest by adipic acid diamide. In anion complexation, the NH and aromatic CH protons are involved. In the case of succinic acid diamide, a slightly smaller contribution of these protons, especially NH, was observed. Pimelic acid diamide binds the investigated anion via both the NH and aromatic CH protons, however, to a lesser extent than that for succinic and adipic acid diamides. The results obtained from ^{1}H NMR experiments correlate with the stability constant values obtained from UV–vis titrations in DMSO.

Besides dihydrogen phosphates, changes in the absorption spectra (DMSO) of the investigated diamides **1–5** were also observed in the presence of tetra-*n*-butylammonium fluoride (TBAF). In the presence of a large excess of salt, the color of the ligand solution **2–5** changed to bright yellow, a feature connected with the appearance of a new band (~450 nm) in the UV–vis spectrum. This can be exemplified from the trace derived from the titration of ligand **3** (see Fig. S2 in Supplementary data). Changes in the absorption spectra (no clear isosbestic point, large bathochromic shift), upon titration with TBAF and the molar ratio plots suggest ligand deprotonation rather than fluoride complex formation. This was supported by the ^{1}H NMR spectra recorded in DMSO-d_6. The N-H signal was not observed in the presence of 1 equiv of TBAF (see Supplementary data, Fig. S3) and the aromatic protons were shifted upfield. Opposite to the above, completely different spectral changes were observed in the case of the spectrophotometric titration of succinic acid diamide (**1**) with TBAF in DMSO. The plot for the titration of **1** with TBAF is shown in Figure 3a. An analogous experiment in which TBAOH was used instead of TBAF (Fig. 3b) possibly indicates that the presence of fluoride does not cause only deprotonation of the ligand. Figure 3c shows the dependence, being almost linear, of absorbance changes as a function of fluoride concentration.

Thus the ^{1}H NMR spectra of succinic acid diamide **1** in the presence of tetra-*n*-butylammonium fluoride were recorded (Fig. 4) in DMSO-d_6 (for proton assignments, see Fig. 5). Upon addition of a small amount (0.1 equiv) of the fluoride salt, unexpected changes in the ^{1}H NMR spectrum were observed (Fig. 4b). There was no evidence for both ligand deprotonation and fluoride complexation via hydrogen bond formation under the measurement conditions. The N–H protons were not observed and four doublets and one broad singlet were apparent in the aromatic region. The aliphatic CH_2 protons were shifted downfield slightly. These spectral changes suggest that fluoride promotes amide bond cleavage, as a result the ^{1}H NMR spectra exhibit signals which can be attributed to 1-(4-nitrophenyl)-pyrrolidine-2,5-dione (**1a**) and 4-nitroaniline (**1b**) (Fig. 5).

These observations were supported by UV–vis absorption spectra. Upon titration with TBAF the increase in the absorption band at about 400 nm might be connected with increasing *p*-nitroaniline concentration (see Fig. 3a), whereas the band in the region below 300 nm can be attributed to 1-(4-nitrophenyl)-pyrrolidine-2,5-dione (**1a**). For comparison, UV–vis and ^{1}H NMR spectra (DMSO) of (**1a**) and *p*-nitroaniline (**1b**) are shown in Figures S4 and S5, respectively (see Supplementary data). Upon addition, for example

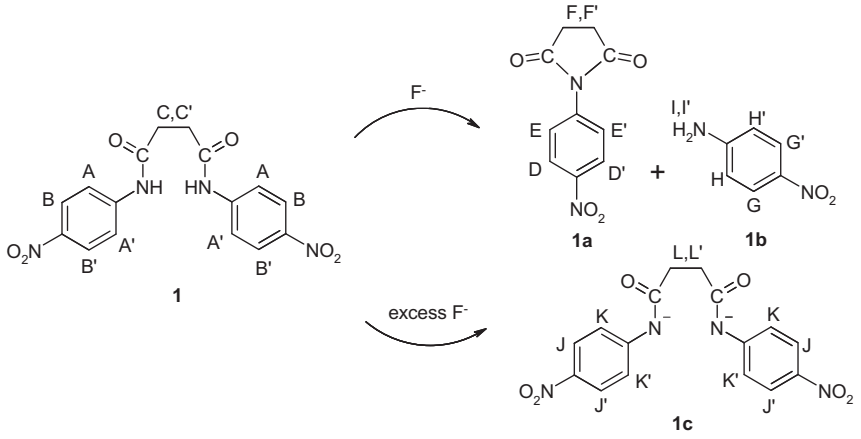


Figure 5. Proposed mechanism for the succinic acid diamide-fluoride interaction in DMSO.

1 equiv of TBAF (Fig. 4c) a signal at 16.2 ppm (t, J = 119 Hz) appeared, which pointed to HF_2^- anion formation. Moreover, the aromatic and aliphatic CH_2 signals were shifted upfield compared to the free ligand. Such spectral changes imply the presence of succinic acid diamide in its deprotonated form (**1c**, Fig. 5) under the ^{1}H NMR measurement conditions. In the presence of excess TBAOH the ^{1}H NMR spectrum signals only indicate the presence of the deprotonated form. Smaller amounts of base promoted proposed reaction in yields not exceeding 10%. On the basis of UV–vis and ^{1}H NMR measurements the most probable mechanism for the **1**-fluoride interaction is proposed as shown in Figure 5. For comparison, TBAF-mediated imide formation (e.g., aspartimide) as a side product was found to occur during solid-phase peptide synthesis.[14]

To establish the influence of the solvent on the anion binding strength, studies were conducted in acetonitrile. Due to the low solubilities of **1**–**3** in this solvent, measurements were carried out on pimelic acid diamide **4**. Changes in the absorption spectra were observed both for fluorides and for dihydrogen phosphates. These changes upon titration of **4** with TBAF and the molar ratio plot

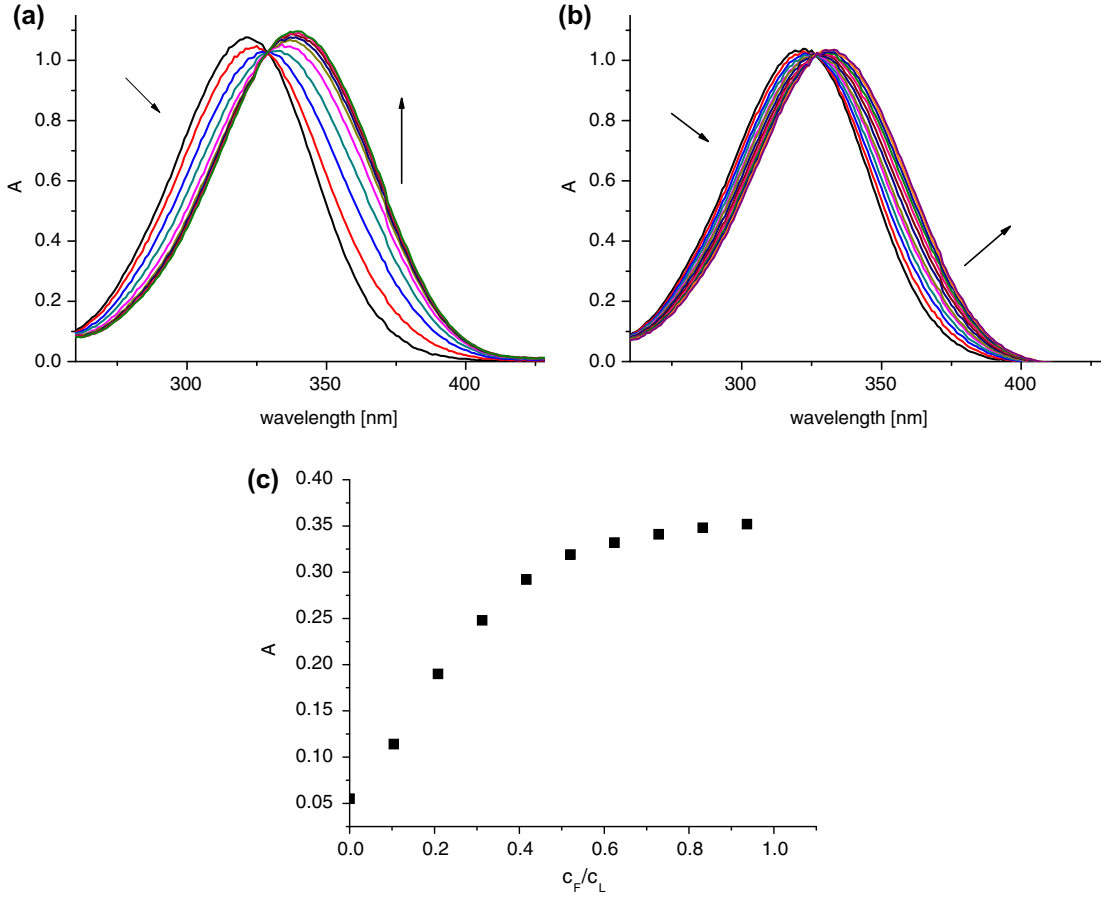


Figure 6. Changes in absorption spectra upon titration of **4** (4.43×10^{-5} M) with: (a) TBAF (0–3.91×10^{-5} M); (b) TBADHP (0–1.01×10^{-4} M); (c) molar ratio plot for the **4**-F^- system in acetonitrile.

are shown in Figures 6a and 6c. Figure 6b shows titration traces for dihydrogen phosphates in acetonitrile.

From the titration experiments the stoichiometries of the formed complexes and values of the respective stability constants were estimated using the OPIUM[13] program. For small spherical fluorides the best fit, in agreement with the molar ratio plot, was obtained for a 2:1 (L:F) complex. For larger, tetrahedral dihydrogen phosphates, 1:1 complex stoichiometry was found. The obtained values of the stability constants ($\log K$) for pimelic acid diamide complexes are: 9.96 ± 0.67 and 2.85 ± 0.10 for fluorides and dihydrogen phosphates, respectively. The change of dipolar aprotic non-HBD (non-Hydrogen Bond Donor) DMSO for less polar acetonitrile, had a beneficial influence on anion complexation. Fluorides in acetonitrile are not as basic as in DMSO, thus ligand deprotonation does not occur under the titration conditions. Additionally, the stability constant with dihydrogen phosphates in acetonitrile was 0.15 ($\log K$) larger than in DMSO.

In conclusion, microwave stimulated reactions, though not spectacularly yielding, may be used as an alternative, simple, and more environmentally friendly method for aliphatic acid aromatic diamide preparation. The short reaction times and less toxic substrates are advantages of the proposed method. The unique behavior of succinic acid diamide in the presence fluorides, after more exhaustive studies (also in a water-containing system), might be the basis of a simple, non-expensive fluoride detection and quantitation method.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.103.

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