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1-(Methylamino)anthracene - accessible building block for photoresponsive compounds

Filip Ulatowski*[a] and Karolina Melaniuk [a]

Abstract: In this paper we present a convenient and scalable synthesis of 1-(methylamino)anthracene, which is a potent building block for the construction of photoresponsive materials. With this structural motif we have synthesized an anion receptor bearing two anthracene groups. Interaction of a chloride anion with the anthracene moieties increases the association constant. Photocycloaddition allows to obtain a single macrocylic receptor, which exhibits higher binding constants due to the macrocyclic effect.

Introduction

Many of contemporary fields of organic chemistry, such as responsive materials or drug activation/release, which are currently extensively investigated, make use of the possibility to switch molecular structures (geometry) by means of external stimuli.[1,2] Light is particularly useful in this context because of its unique features such as spatial, temporal, and energetic resolution, as well as cleanness. Advancement in the aforementioned fields has resulted in the development of multiple photoresponsive scaffolds such as azobenzenes, stilbens and dithiophenealkynes. Light stimulus can either induce E-Z isomerization or trigger a sigmatropic reaction, thus leading to a new covalent bond.

Light-induced [4+4] cycloaddition of two anthracene moieties differs from the above examples and typically provides more profound changes in molecular geometry. This reaction results in the formation of two covalent bonds, which changes the hybridization of four carbon atoms (from sp^2 to sp^3). This process can be considered a 'click' reaction. Intermolecular reactions lead to oligomers, while intramolecular cycloaddition results in macrocylic species.

Many reports describe photoresponsive systems based on the anthracene moieties substituted in position 9, which are readily accessible.[3–14] Substitution of anthracene in position 1 or 2 provides a wider diversity of possible products (Figure 1), however, such building blocks are basically less available.[15–19] In all cases, it is not the chemist's imagination that limits the design of novel photoresponsive functional molecules, but the availability of building blocks and the efficiency of synthetic methods of connecting them. Therefore, designing novel synthetic routes to novel, useful building blocks is particularly important for the development of this field. In this paper we present a straightforward and efficient 7-step synthesis of 1-(methylamino)anthracene (**1**) and its application in a construction of a model photoresponsive anion receptor.

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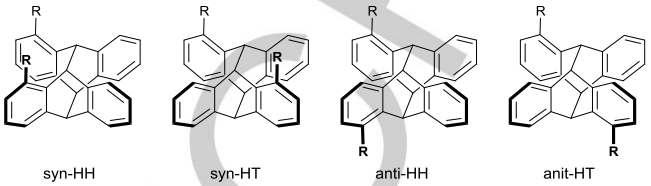

Figure 1. Structures of all possible isomers formed in a [4+4] cycloaddition reaction of anthracene substituted in position 1 or 2. HH: head-to-head, HT: head-to-tail.

Results and Discussion

The choice of **1** as our target molecule is supported by its several anticipated properties. First of all, primary amines are particularly useful building blocks as they can be attached to the molecular scaffold via an amide, urea, or a secondary amine group, which all act as hydrogen bond donors. Moreover, the aliphatic linker between aromatic fused rings of anthracene and the amine group prevents electronic conjugation and ensures that substitution of a nitrogen atom does not affect the electronic properties of the anthracene moiety. Finally, the methylene group in **1** adds conformational freedom, which may be necessary for the [4+4] cycloaddition reaction to occur.

The synthetic pathway presented in Scheme 1 proceeds via anthracene-1-carboxylic acid (**5**), which is commercially available, but its price is unacceptably high. Our modification of synthetic route originally developed by Golden *et al*.[20] provides **5** in multigram quantities from inexpensive 1-chloroanthroquionone **2** with 57% yield over 3 steps. Subsequent reduction of acid with borane provides alcohol **6** in a very good yield, which gives respective bromide **7** upon Appel reaction. This is the only step that requires chromatographic purification of the product; however, the isolation of the product is facile. We have found that the reduction of azide **8** is the most convenient method for obtaining the target amine **1**. Precipitation of a respective hydrochloride provides pure product. The synthetic path consists of seven steps, all of which are scalable to a multigram scale, and the entire procedure requires only one chromatographic separation. Apart from the target amine, bromide **7** is also a potentially very useful reagent for the introduction of the anthracene group via alkylation.

In order to examine the usefulness of **1**, we employed it as a building block for the construction of a model photoresponsive receptor **10**. The structural motif of dipicolinic acid diamide was successfully applied in linear and macrocyclic anion receptors, including dynamic systems. A facile reaction of amine **1** with dipicolinic acid dichloride **9** provides bisamide **10** in 73% yield (Scheme 2).

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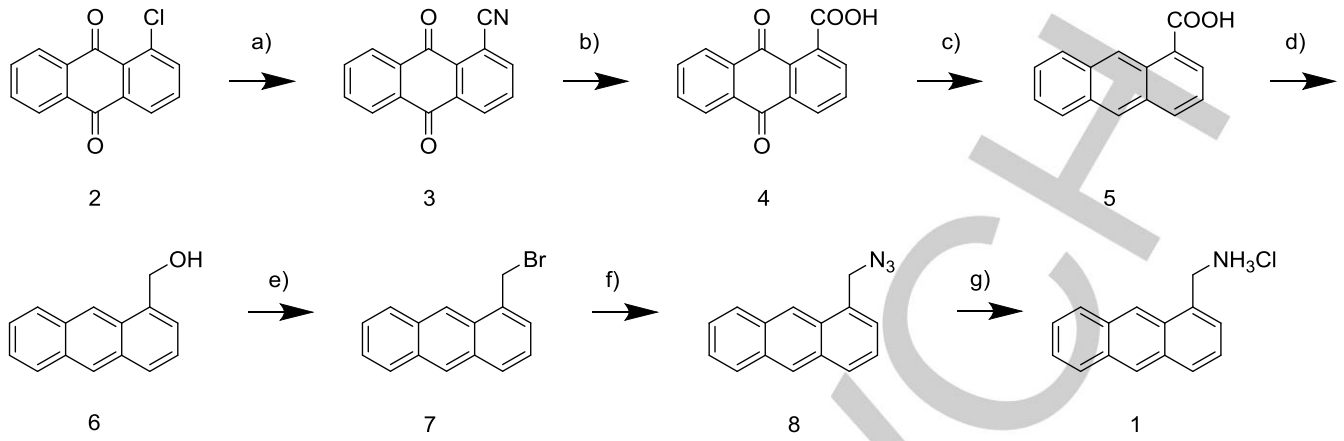
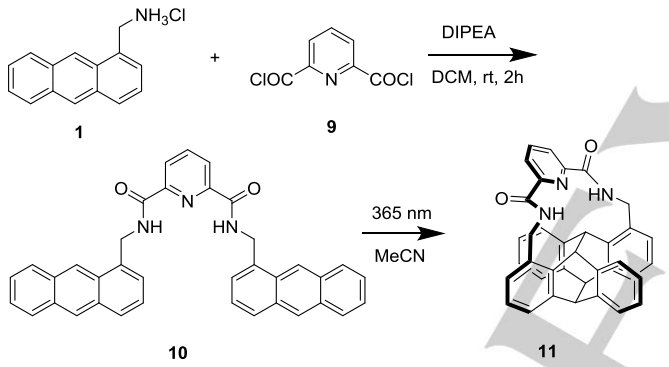


Scheme 1. Synthesis of 1-(methylamino)antracene **1**. Reagents and conditions: a) CuCN, DMF, 80°C, 4 h, 92%; b) 10% $NaOH_{aq}$, 80°C, 2h, 83%; c) Zn, $NH_{3(aq)}$ reflux, 4 h, 75%; d) BH_3*Me_2S, THF, reflux, 3 h, 80-95%; e) CBr_4, PPh_3, DCM, 0°C to rt, 2h, 73%; f) NaN_3, DMF, 80°C, 4 h, 95%; g) i) H_2, Pd/C rt, 4 h; ii) HCl, Et_2O, 70%.



Scheme 2. Synthesis of receptor **10** and its transformation into **11**.

UV-Vis spectrum of solution of **10** in MeCN exhibits absorption bands in the range of 330-380 nm, which is characteristic for the anthracene moiety. To perform a photochemical reaction we used a 3 W 365 nm UV lamp whose emission spectrum overlapped with the absorption band of **10**. After 90 s of irradiation, a stationary state is obtained, the aforementioned bands disappear and the band at 250 nm is reduced by about 12 times (Figure 2).

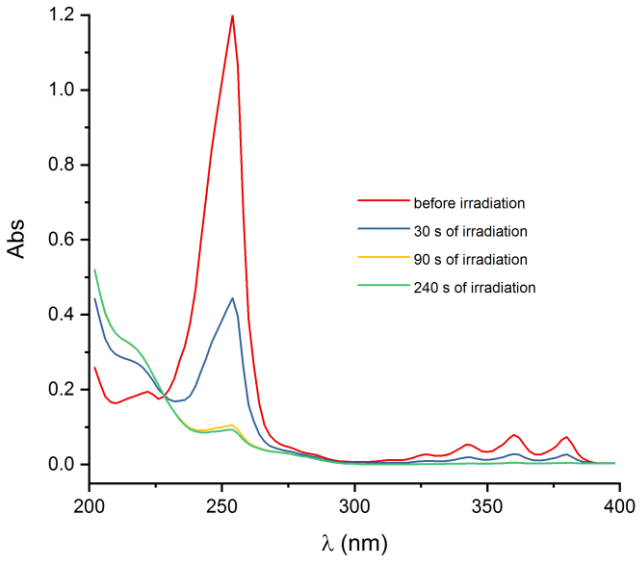


Figure 2. Progress of a photochemical [4+4] cycloaddition in **10** monitored by UV-Vis spectroscopy.

The same transformation carried on a larger scale in MeCN-d_3 was monitored by ^{1}H NMR spectra. With 100% conversion of substrate **10**, product **11** forms nearly quantitatively with traces of side products. The comparison of NMR spectra clearly indicates a [4+4] cycloaddition (Figure 3), while mass spectrometry analysis proves that **11** is a product of an intramolecular reaction. Out of four possible isomers depicted in Figure 1, simple molecular modeling excludes anti-HH and anti-HT isomers, which would require a much longer linker between the anthracene subunits. The distinction between syn-HH (achiral) and syn-HT (chiral) isomers cannot be made by NMR analyses (including NOESY experiment) and the structure of **11** was elucidated by HPLC

analyses on chiral columns, which indicate that **11** is a racemic mixture of chiral syn-HT isomers.

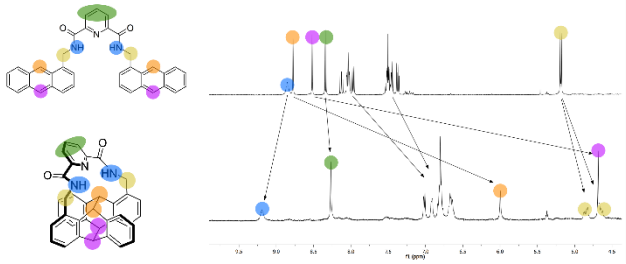


Figure 3. ^{1}H NMR spectra of **10** before and after irradiation with a 365 nm lamp (CD_3CN).

Multiple reports indicate that [4+4] cycloaddition can be reversed either thermally or photochemically. In case of **11**, no change in UV-Vis spectra is observed after heating at 80°C for 3 days, indicating that this compound is thermally stable. In turn, irradiating the solution of **11** in MeCN with a 254 nm lamp results in 100% conversion of the substrate but only partial reversion of cycloaddition. Product **10** is accompanied by an even larger amount of various side products. These results indicate restricted reversibility of cycloaddition in case of **11**.

For receptors **10** and **11** we have evaluated their anion binding properties with chloride and benzoate (BzO^-) as model anions. Since the receptors are equipped with just two hydrogen bond donors, the measurements were carried in acetonitrile, which is a noncompetitive solvent (Figure 4). A simple 1:1 host:guest model proves to be correct in all cases based on the analysis of residuals in data fitting.[21] Association constants (K_a) of receptor **10** were determined by direct ^{1}H NMR titrations. In case of receptor **11** we employed competitive NMR titration in which aliquots of guest and added to a mixture of **10** and **11**. This kind of experiment provides higher accuracy with a simpler experimental setup.[22–25] Results are presented in Table 1.

Table 1. Association constants K_a (M^{-1}) of the complexes of receptors **10** and **11** with chloride and benzoate.[a]

	Guest	
Host	Cl-	BzO-
10	95	80
11	147	198

[a] ^{1}H NMR titration in CD_3CN, 303 K; anions used as tetrabutylammonium salts; estimated error ±10%

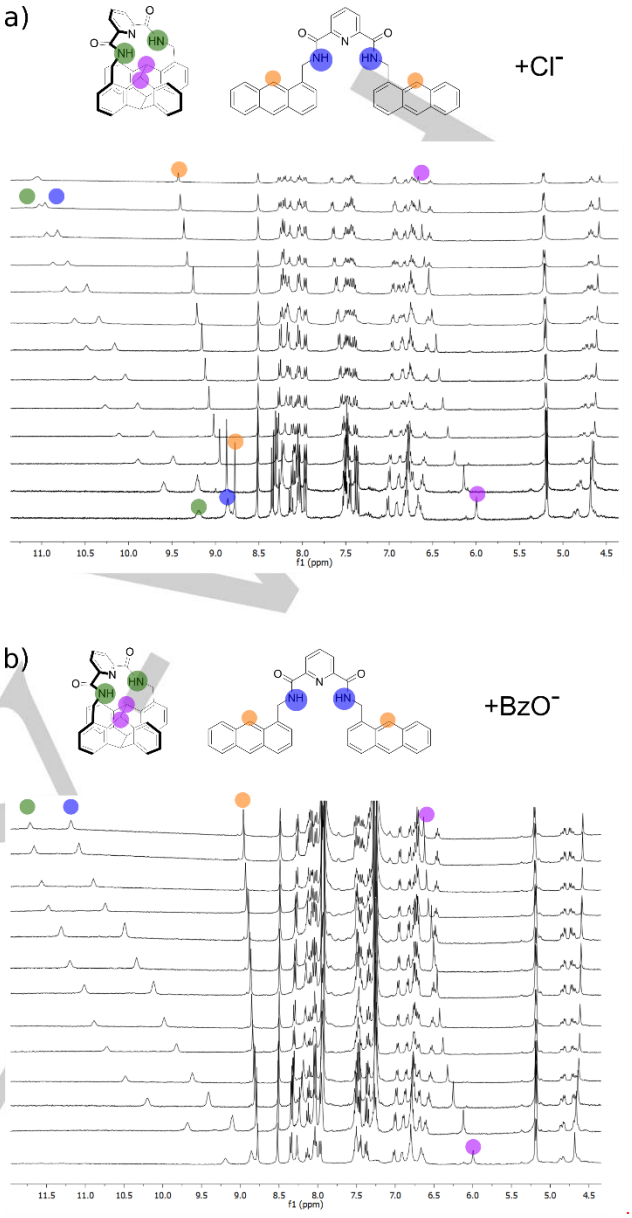


Figure 4. Competitive ^{1}H NMR titrations of a mixture of **10** and **11** with Cl^- (a) and BzO^- (b). The relative shift of protons of the two hosts is used to calculate the ratio of association constants.

As we expected, the K_a values are moderate. Quite interestingly, host **10** exhibits similar affinity for chloride and benzoate. Typically, stability constants of benzoate complexes are significantly higher compared to chloride (3 to 20 times), and the same is true for most of other linear and macrocylic receptors with dipicolinic acid bisamide unit.[26] In our case the presence of anthracene groups results in equalization of association constants.

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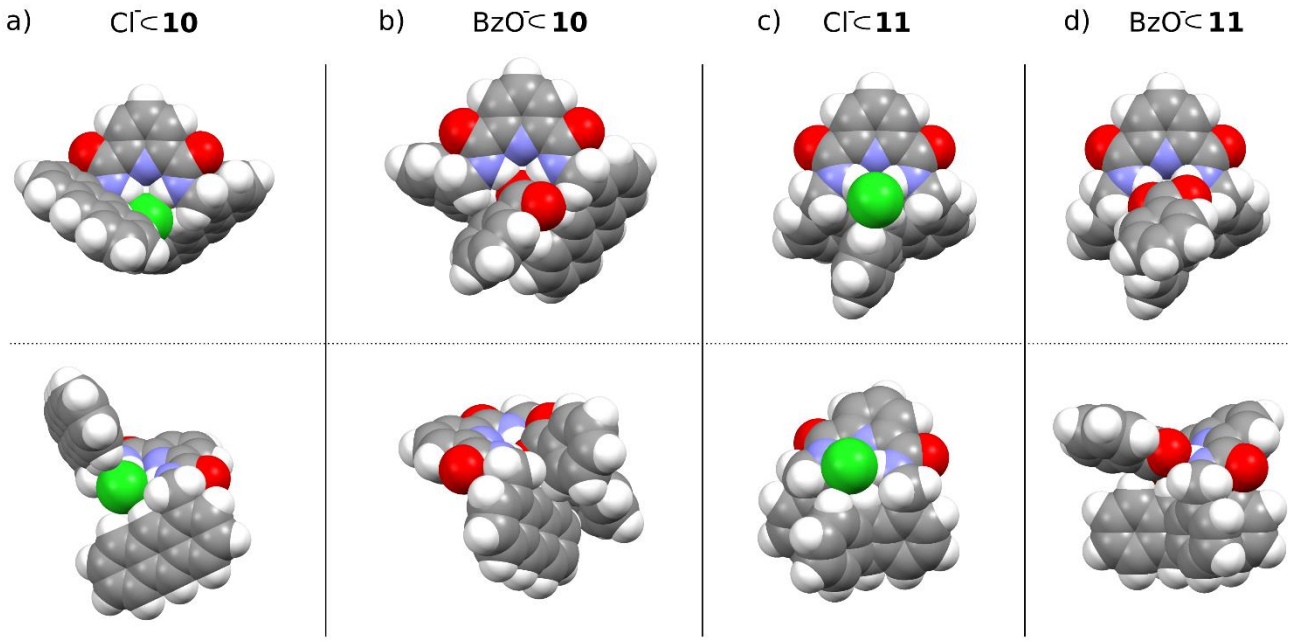

Figure 5. DFT optimised structures of complexes of hosts **10** and **11** with Cl^- and BzO^-.

Quantum mechanical modelling of complexes (see ESI for details) reveals that chloride anion can form hydrogen bonds with both amide groups while the anthracene moieties wrap the guest and form additional C-H···Cl^- interactions (Figure 5a). These interactions are confirmed experimentally by ^{1}H NMR spectra, which clearly show binding-induced deshielding of protons in position 9 in the anthracene groups. As we have recently proved,[26] such interactions with hydrophobic groups are attractive in case of chloride complexes and typically result in their selective binding. On the other hand, benzoate binding requires the flip of the anthracene groups to open the access to hydrogen bond donors. As evidenced by NMR spectra, there is no interaction between the guest and the anthracene groups (Figure 4). In the DFT-optimised structure of **10**-BzO complex the anthracene groups adopt an unfavourable conformation (Figure 5b), which is further associated with the loss of entropy and thus lower association constant. Combination of these two effects results in the inversion of selectivity.

We expected that the photoaddition of the two anthracene moieties in the side arms of the receptor, and the resulting formation of a macrocycle would form a very bulky group that would prevent access of any guest to the binding site of a dipicolinic bisamide. To our surprise, the association constants of host **11** were about twice higher than the respective K_a values for **10**. Apparently, not only does cycloaddition not block the binding site, but also it induces better preorganization of a receptor structure to expose the NH groups. Similar effect was observed by Blažek Bregović *et al.* in their bisurea receptor with 2-aminoanthracene moieties.[19] In the case of host **11** the ratio of association constants for benzoate and chloride complexes is about two, which indicates that the structural features which favor chloride binding have lower impact. Binding of each anion by NH hydrogen bond donors puts the guest in close proximity of CH protons at bridge positions (Figure 5c,d), which induces the interaction of these protons with an anion, and this manifests in the NMR spectra (Figure 4).

Conclusions

In conclusion, we have developed a scalable and undemanding seven-step synthesis of 1-(methylamino)anthracene **1**, which includes only one chromatographic separation and begins with an inexpensive substrate.. The described amine has been successfully incorporated into a model anion receptor. We have found that the anthracene groups not only make the receptor photoresponsive, but they can also interact with the guest and significantly modify the binding properties. The intramolecular light-induced [4+4] cycloaddition is clean and efficient. These features prove that 1-aminomethylanthracene **1** is an interesting structural motif that can be used in the construction of various photoresponsive materials.

Experimental Section

Receptor 10 To a solution of 1-(aminomethyl)-anthracene hydrochloride (**1**) (1.0 g, 4.10 mmol) and DIPEA (3.4 mL, 20 mmol) in dry DCM (50 mL) under argon was added dipicolinic acid dichloride (350 mg, 1.71 mmol). The mixture was stirred at rt. for 3 h and concentrated in vacuo. The oily residue was purified by chromatography on silicagel with 2-5% MeOH in CH_2Cl_2. Finally the product was crystallised from MeCN. Orange needles, yield 680 mg (73%), mp. 164-167°C.^{1}H NMR (400 MHz, Acetonitrile-d_3)

8.82 (2 H, s), 8.78 (2 H, s), 8.52 (2 H, s), 8.34 (2 H, d, *J* 7.8), 8.13 (1 H, t, *J* 7.8), 8.09 – 8.00 (4 H, m), 7.97 (2 H, d, *J* 8.5), 7.56 – 7.42 (6 H, m), 7.37 (2 H, dd, *J* 8.5, 6.8), 5.19 (4 H, d, *J* 6.2); ^{13}C NMR (101 MHz, DMSO) 163.9, 149.2, 140.1, 134.6, 131.8, 131.7, 131.3, 129.4, 128.8, 128.2, 128.1, 127.2, 126.1, 125.3, 125.1, 123.7, 122.3, 40.9. HRMS (ESI): calc. for $C_{37}H_{27}N_3O_2Na$ $[M+Na]^+$: 568.2001, found: 568.1978

Receptor 11. A solution of **10** in MeCN (c=0.005 m) was placed in a 10 mL clear glass vial and irradiated with a 3W 365 nm UV-lamp with stirring for 10 min. The solution was concentrated in vacuo to provide colourless amorphous solid. ^{1}H NMR (600 MHz, acetone-d6) 9.64 (2 H, s, *J* 6.1), 8.35 (1 H, t, *J* 7.7), 8.29 (2 H, d, *J* 7.7), 7.00 (2 H, d, *J* 7.2), 6.90 (2 H, d, *J* 7.2), 6.81 – 6.70 (8 H, m), 6.58 (2 H, t, *J* 7.4), 6.25 (2 H, s), 4.87 (2 H, dd, *J* 15.8, 6.0), 4.75 – 4.67 (4 H, m). ^{13}C NMR (151 MHz, acetone-d6) 162.4, 149.9, 145.7, 144.0, 143.6, 141.6, 140.4, 133.4, 127.2, 126.6, 126.1, 126.1, 125.6, 125.3, 125.1, 124.1, 53.9, 47.3, 43.0. HRMS (ESI): calc. for $C_{37}H_{27}N_3O_2Na$ $[M+Na]^+$: 568.2001, found: 568.1988

Acknowledgements

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Keywords: photochemistry • cycloaddition • supramolecular chemistry • anthracene dimerization • anion receptor

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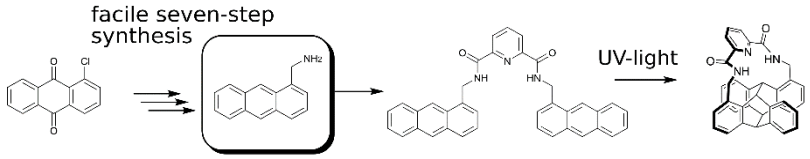

Photoswitchable receptors

Filip Ulatowski and Karolina Melaniuk*

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1-(Methylamino)anthracene - accessible building block for photoresponsive compounds

Facile synthesis provides novel anthracene-based amine which acts as a versatile building block for construction of photoswitchable receptors. Incorporation of this structural motif into dipicolinic amide provides a photoresponsive anion receptor. Upon irradiation with 360 nm lamp cycloaddition occures yielding macrocyclic receptor with higher affinities for anions.