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1,8-Diamino-3,6-dichlorocarbazole: A Promising Building Block for Anion Receptors

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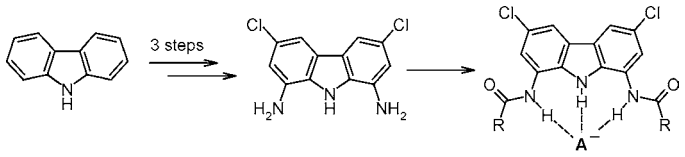
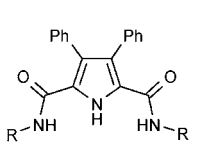
ABSTRACT

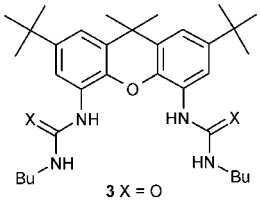


Advantages of the carbazole moiety as a new skeleton for the construction of anion receptors are illustrated by two model amide receptors derived from 1,8-diamino-3,6-dichlorocarbazole.

Designing of receptors capable of anion binding by hydrogen bonds continues to be an area of active research.[1] Among many possible hydrogen bond donors, the pyrrole ring was extensively used to construct several types of anion receptors such as calixpyrroles,[2] expanded porphyrins,[3] dipyrroquinoxalines,[3] and others.[3] Gale and co-workers[4] equipped the pyrrole ring with two amide sidearms obtaining the simple cleft receptors **1** and **2** with interesting anion binding properties. The same research team[5] showed also that the substitution of the pyrrole ring of the receptor with the electron-withdrawing groups could significantly enhance its anion binding ability. It is believed that the more acidic a pyrrole N−H is, the stronger the hydrogen bond-donating ability it has. However, the acidity of the pyrrole ring can be enhanced not only through an attachment of the electron-withdrawing groups but also by conjugation with benzene ring, as evidenced by pK_a values of pyrrole (23.0), indole (20.9), and carbazole (19.9) measured in DMSO.[6] Apart from its enhanced acidity, the carbazole moiety is attractive also because of its rigidity. Rigid receptors often perform better in anion recognition; for example, exceptionally strong anion binding by Umezawa's[7] receptors **3** and **4** was ascribed to, inter alia, the rigidity of their xanthene scaffold.



1 R = Ph
2 R = Bu



3 X = O
4 X = S

The carbazole unit is even more rigid than xanthene, and, furthermore, it provides one more anchoring point N−H

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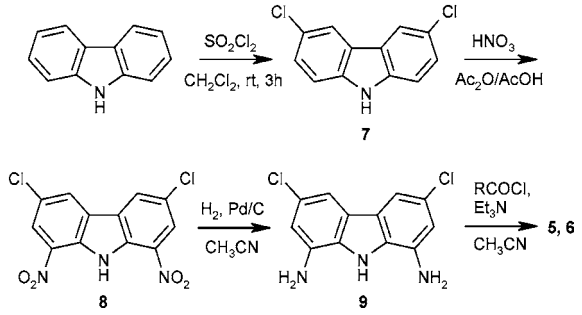
instead of repulsive xanthene oxygen. Amides and ureas derived from 1,8-diaminocarbazole, having geometry similar to that of compounds **1**−**4**, should thus be even better anion receptors. Trying to prove this hypothesis, we encountered synthetic problems: although 1,8-diaminocarbazole, the precursor of this new family of receptors, has already appeared in the literature, its synthesis was very lengthy and impractical.[8] On the contrary, 1,8-diamino-3,6-dichlorocarbazole **9** was synthesized by Mužík et al.[9] via a more promising, three-step procedure involving chlorination of carbazole, nitration, and hydrogenation (Scheme 1). Therefore, we decided to prepare and study model receptors **5** and **6** having positions 3 and 6 substituted with chlorine atoms. We envisaged that such a substitution with electron-withdrawing atoms could be beneficial for anion binding and also open some possibilities for further modification of the structure through palladium-catalyzed reactions.[10]

Scheme 1



Selective chlorination of carbazole is a difficult problem[11] that, despite several attempts, still has not been solved satisfactorily. The original procedure for the chlorination of carbazole by Mužík et al.[9] was difficult to follow in our laboratories because it involved the usage of controlled amounts of gaseous chlorine. Therefore, we turned our attention to an old method of Mazzarra and Lamberti−Zanardi[12] employing sulfuryl chloride as a chlorinating agent. After some improvements we were able to obtain the desired 3,6-dichlorocarbazole **7** in 60% yield simply by mixing the suspension of carbazole in CH_2Cl_2 with sulfuryl chloride at room temperature followed by filtration and leaching of the product with hot hexane. Nitration of **7** with absolute nitric acid in an AcOH/$(AcO)_2$ mixture[9] gave 3,6-dichloro-1,8-dinitrocarbazole **8** in 73% yield. This material may be hydrogenated in a Paar apparatus on Raney nickel under 4 atm of hydrogen.[9] Searching for a more convenient method, we have found that the reduction of **8** by atmospheric pressure of hydrogen in methanol catalyzed by 10% Pd/C is accompanied by partial dehalogenation leading to an inseparable mixture. We solved this problem using acetonitrile as a solvent and obtained 1,8-diamino-3,6-dichlorocarbazole **9** in 89% yield. The key diamine **9** was subsequently acylated with two different acid chlorides, giving the desired amides **5** (69%) and **6** (60%).

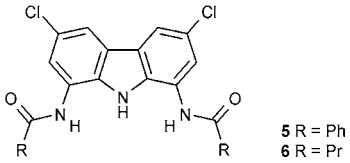


Figure 1.

Both **5** and **6** were poorly soluble in common organic solvents such as dichloromethane, acetonitrile, ethyl acetate, acetone, and methanol. Receptor **5**, practically insoluble in CH_2Cl_2 or 1,2-dichloroethane, solubilized readily after addition of tetrabutylammonium chloride or acetate, providing the first indication of its anion binding ability. Diffusion of ether into such a solution gave a single crystal of the chloride complex of **5**, which was subjected to X-ray analysis. There are two distinct complexes (fragments A and B) in the same crystal structure, differing slightly in conformation, both having chloride anion inside the carbazole cleft (Figures 2 and 3).

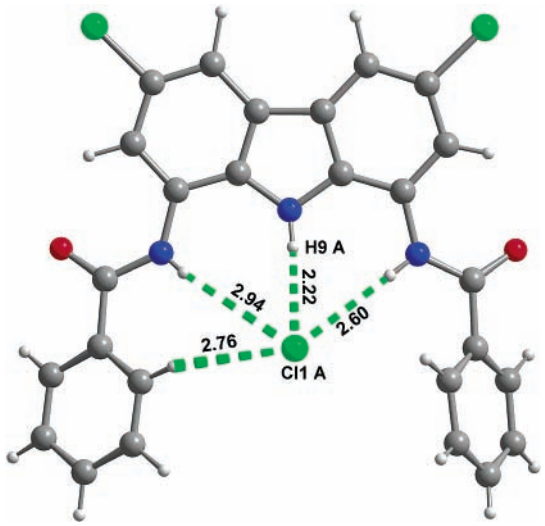


Figure 2. Fragment A of the crystal structure of the complex $(\mathbf{5})_2\times(TBACl)_2\times(C_2H_5)_2O$. Distances are given in Å.

In the first complex (fragment A, Figure 2), the anion lies almost in the plane of carbazole moiety but is asymmetrically disposed with respect to amide arms: a hydrogen bond with one amide group is much shorter than that with the other

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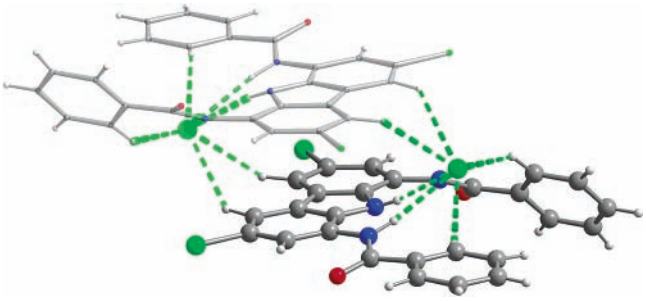

Figure 3. Fragment B of the crystal structure of the complex $(\mathbf{5})_2\times(TBACl)_2\times(C_2H_5)_2O$. The symmetrically dependent fragment is shown in light gray.

($N-Cl^-$ 3.38 vs 3.60 Å). This suggests that the cleft is too wide for chloride anion. In the second complex (fragment B, Figure 3), the anion lies above the mean plane of the carbazole moiety, almost symmetrically located between amide arms ($N-Cl^-$ 3.57 and 3.58 Å). Long $NH-Cl^-$ contacts (2.65 and 2.76 Å) confirm the previous observation about the poor geometric fit between the chloride anion and receptor **5**. The π-stacking interactions of two neighboring carbazole planes result in the formation of centrosymmetric dimer additionally joined by weak $CH-Cl^-$ interactions (Figure 3).

In both complexes, the strongest hydrogen bonds to Cl^- stem from NHs of the carbazole (H(9A)−Cl(1A) 2.22 Å and H(9B)−Cl(1B) 2.33 Å), validating our design. It is also noteworthy that phenyl rings contribute to anion binding in the solid state through $CH-Cl^-$ interactions (Figure 2, 2.76 Å; Figure 3, 2.78 and 2.72 Å).

The stability constants of receptors **5** and **6** with various anions were determined by ^{1}H NMR titration[13] (Table 1) in DMSO-d_6/0.5% H_2O solution. It turned out that these simple acyclic receptors, equipped with just three anchoring points, could strongly bind anions in this quite competitive medium. Selectivity for hydrogen phosphate and benzoate over chloride follows the common basicity trend, but this is probably enhanced by the aforementioned geometric mismatch between receptors and the chloride anion. This mismatch prevents strong interaction of the anion with amide hydrogens, which is reflected by relatively small shifts of respective signals in ^{1}H NMR spectra following addition of tetrabutylammonium chloride ($\Delta\delta_{max} = 0.20$ ppm for **5** and $\Delta\delta_{max} = -0.18$ ppm for **6**, respectively). On the contrary, the amide sidearms are strongly engaged in binding of larger anions such as benzoate and hydrogen phosphate, as evidenced by large complexation-induced shifts in ^{1}H NMR spectra (up to 2.1 ppm in the case of **6** and $H_2PO_4^-$). Even larger downfield shifts of the carbazole NH signal (2.5−4.2 ppm) support our conclusion from the X-ray analysis that this is the strongest binding site in these receptors. A comparison of the data for receptors **5** and **6** reveals also that in contrast to what might have been expected on the

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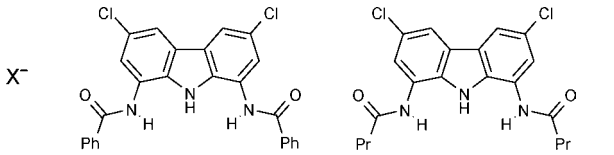
Table 1. Binding Constants for the Formation of 1:1 Complexes of **5** and **6** with Various Anions in DMSO-d_6/0.5% H_2O and Asymptotic Complexation-Induced Chemical Shift Changes in ^{1}H NMR Spectra[a]



	K (M^{-1})[b]	$\Delta\delta_{max}$ (ppm)	K (M^{-1})[b]	$\Delta\delta_{max}$ (ppm)
Cl^-	13	2.60 (NH_{carb})	115	2.92 (NH_{carb})
		0.20 (NH_{amide})		−0.18 (NH_{amide})
$PhCOO^-$	1230	3.75 (NH_{carb})	8340	3.46 (NH_{carb})
		1.28 (NH_{amide})		1.30 (NH_{amide})
$H_2PO_4^-$	1910	≈3.7 (NH_{carb})[c]	19 800[d]	≈3(NH_{carb})[c]
		1.88 (NH_{amide})		2.09 (NH_{amide})

[a] Tetrabutylammonium salts were used as anion sources. $T = 298$ K. [b] Errors estimated to be <15% except where noted. [c] Signal disappears during titration. [d] Error = 31%.

basis of earlier studies,[14] the aliphatic amide **6** binds anions much stronger than its aromatic analogue **5**. This interesting phenomenon deserves further study.

Anion binding of the new carbazole receptors **5** and **6** compares favorably with that of their pyrrole analogues **1** and **2**.[4] Stability constants of anion complexes of **5** in wet DMSO are larger than measured earlier[4] for **1** in the same medium: $K(PhCOO^-) = 1230$ versus 560, $K(H_2PO_4^-) = 1910$ versus 1450. The effect is probably even more pronounced in the case of **6** and **2**; unfortunately, no direct comparison can be made because **2** was studied in acetonitrile solution.[4] However, binding constants for **2** in less polar acetonitrile are already lower than reported here for **6** in a more competitive DMSO/water mix.

In conclusion, diamine **9**, easily available from inexpensive carbazole, is the key substrate for the synthesis of amides, thioamides, ureas, thioureas, guanidines, and other potential anion receptors, exemplified here by simple amides **5** and **6**. 1,8-Diamino-3,6-dichlorocarbazole **9** is therefore more versatile as a building block than 2,5-pyrroledicarboxylic acid. Thanks to the rigidity of the carbazole skeleton, receptors derived from amine **9** may form structurally well-defined complexes with anions, additionally stabilized by strong hydrogen bonding stemming from the central NH of the carbazole. This latter feature makes this building block an attractive alternative to the so far used 4,5-diaminoxantene[7,15] and 1,8-diaminoanthracene[16] in the construction of various anion binding devices.

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Supporting Information Available: Experimental procedures, characterization data for compounds **5**−**9**, details concerning determination of binding constants, and X-ray crystal data for $(\mathbf{5})_2\times(\mathrm{TBACl})_2\times(\mathrm{C_2H_5})_2\mathrm{O}$. This material is available free of charge via the Internet at http://pubs.acs.org.

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