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Benzopyrrole derivatives as effective anion receptors in highly competitive solvents*

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Abstract: Neutral anion receptors working in highly demanding solvents are new materials being sought. Benzopyrroles are more acidic than amides and pyrrole itself, and are promising building blocks in the design of host compounds. A whole series of receptors based upon benzopyrroles were synthesized and evaluated. They include carbazole, dipyrrolonaphthalene, and 7-aminoindole-based hosts. Most of them demonstrate moderate binding affinities in dimethyl sulfoxide (DMSO) and have good selectivity toward tetrahedral oxyanions. Recently, a group of receptors utilizing 7-aminoindole and urea moieties proved to work in a very competitive solvent—methanol.

Keywords: benzopyrroles; neutral anion receptors; oxyanions; polar solvents; supramolecular chemistry.

INTRODUCTION

Neutral anion receptors are potentially superior to the charged ones in terms of selectivity, however, their affinities are remarkably lower. A great effort is paid to increase the binding strength while retaining the significant selectivity. One of the main approaches to reach this goal is to develop simple, yet strongly binding building blocks that could be used for the construction of more elaborate and more selective receptors.

Binding abilities of neutral hosts toward anions arise from a proper combination of many weak interactions such as hydrogen bonding, π-stacking, and hydrophobic effect. Optimal fit between the host and guest molecules requires both functional and spatial arrangement.

Primary amides are one of the most popular hydrogen bond donors used for the construction of neutral anion receptors [1]. However, other functional groups such as heterocyclic NH moiety can also play an important role in these systems. The comparison of primary amides with pyrrole and its derivatives is presented in Table 1. Hydrogen bond strength can be estimated based on pK_a values of the donors, which are higher for pyrrole and its derivatives than amide [2,3]. A more accurate comparison can be performed through the use of Abraham's parameters α_2^H and β_2^H [4,5]. The α_2^H parameter refers to the ability of the molecule to act as a hydrogen donor (acidity), while β_2^H measures the predisposition to act as a hydrogen bond acceptor (basicity). An association constant of a complex based on hydrogen bond formation can be estimated according to the equation: $\log(K) = 7.354 \cdot \alpha_2^H \cdot \beta_2^H - 1.094$. Both p$K_a$ and α_2^H indicate that heterocyclic NH groups are better hydrogen bond donors than amides. Moreover, in contrast to amides, they cannot serve as hydrogen bond acceptors as outlined by signifi-

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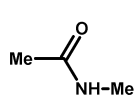
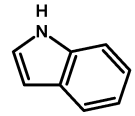
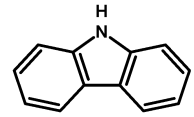
cantly lower β_2^H values. The latter property prevents self-association and intramolecular hydrogen bonds, which often hamper guest binding. Finally, their rigid structure can help to preorganize the geometry of the binding pocket of the host molecule, adjusting all its binding points toward the complementary functions of a guest molecule. Therefore, pyrrole and its derivatives have considerable advantages as building blocks when compared to amides.

Table 1 Comparison of pK_a, Abraham's hydrogen bond acidity, and basicity values of four model compounds.







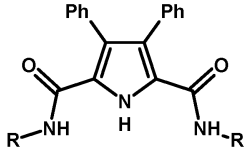
pK_a (in DMSO)	25.9[a]	23.0[b]	20.9[b]	19.9[b]
α_2^H	0.40[c]	0.41[c]	0.44[d]	0.47[d]
β_2^H	0.72[c]	0.29[c]	0.22[d]	0.26[d]

[a]Ref. [2].
[b]Ref. [3].
[c]Ref. [4].
[d]Ref. [5].

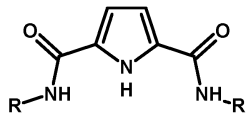
Taking into account the above considerations, Gale and co-workers investigated receptors **1a,b** [6], while our group independently studied receptors **2a,b** [7], both classes of which are based on pyrrole ring functionalized with two amide groups. Their central heterocyclic NH groups are crucial for anion binding, as suggested by NMR and crystallographic evidence as well as by comparison with analogous furan derivatives [8]. Anion binding constants were encouraging (Table 2), but still not satisfactory for receptors intended to work in protic solvents.

These results prompted us to search for even more powerful building blocks in order to enhance receptors' affinity toward anions.

Table 2 Association constants of receptors **1a,b**, **2a,b** with various anions determined by ^{1}H NMR titrations using TBA salts as the source of anions in DMSO-d_6 + 0.5 % H_2O.



1a R = n-Bu
1b R=Ph



2a R = n-Bu
2b R=Ph

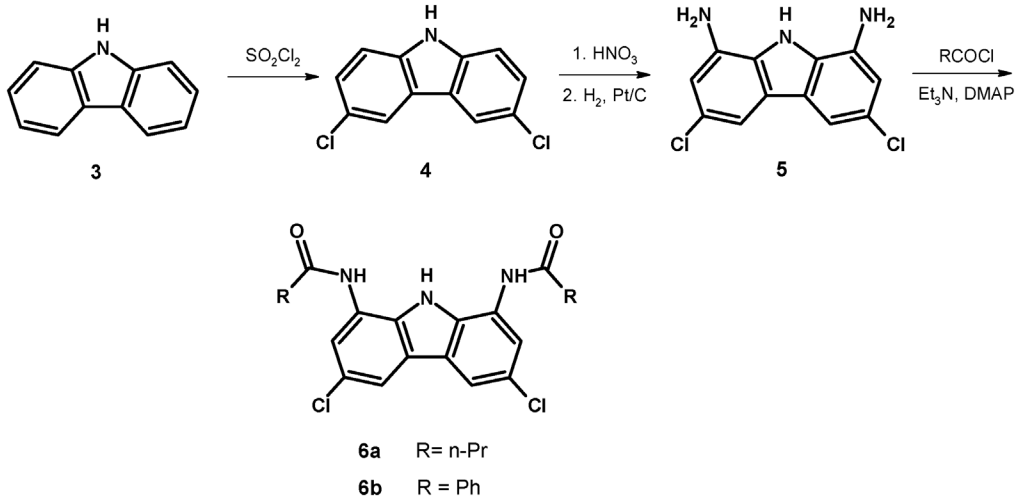
Anion	K [M^{-1}]			
	1a[a,b]	**1b**[b]	**2a**[c]	**2b**[c]
$PhCO_2^-$	2 500	560	49	80
$H_2PO_4^-$	357	1 450	150	203
Cl^-	138	11	1.7	3.8

[a]In acetonitrile-d_3.
[b]Ref. [6].
[c]Ref. [7].

RESULTS AND DISCUSSION

Carbazoles

As depicted in Table 1, fusing of the pyrrole ring with two benzene rings significantly increases the acidity of NH proton. Therefore, carbazole seems to be a very promising building block for anion receptors providing a rigid platform and a strong hydrogen bond donor. Receptors **6a,b** being bisamides of 1,8-diamino-3,6-dichlorocarbazole [9] were synthesized in four steps from carbazole **3** (Scheme 1). The geometry of binding groups is similar to that of receptors **1** and **2**, with two amide groups flanking the central heterocyclic NH bond. ^{1}H NMR titrations revealed that these carbazole-based hosts bind anions with association constants up to 100-fold higher compared to the analogous pyrrole-based receptors (Table 3). The binding constants values of **6b**, measured in DMSO + 0.5 % water, being 8340 and 19 800 M^{-1} for benzoate and dihydrogenphosphate, respectively, are remarkable for the receptor equipped with just three anchoring points.



Scheme 1 Synthesis of carbazole-based receptors **6a,b**.

Table 3 Comparison of association constants of receptors **2a,b** and **6a,b** with various anions determined by ^{1}H NMR titrations using TBA salts as the source of anions in DMSO-d_6 + 0.5 % H_2O.

Anion	K [M^{-1}]			
	2a[a]	**2b**[a]	**6a**[b]	**6b**[b]
$PhCO_2^-$	49	80	8 340	1 230
$H_2PO_4^-$	150	203	19 800	1 910
Cl^-	1.7	3.8	115	13

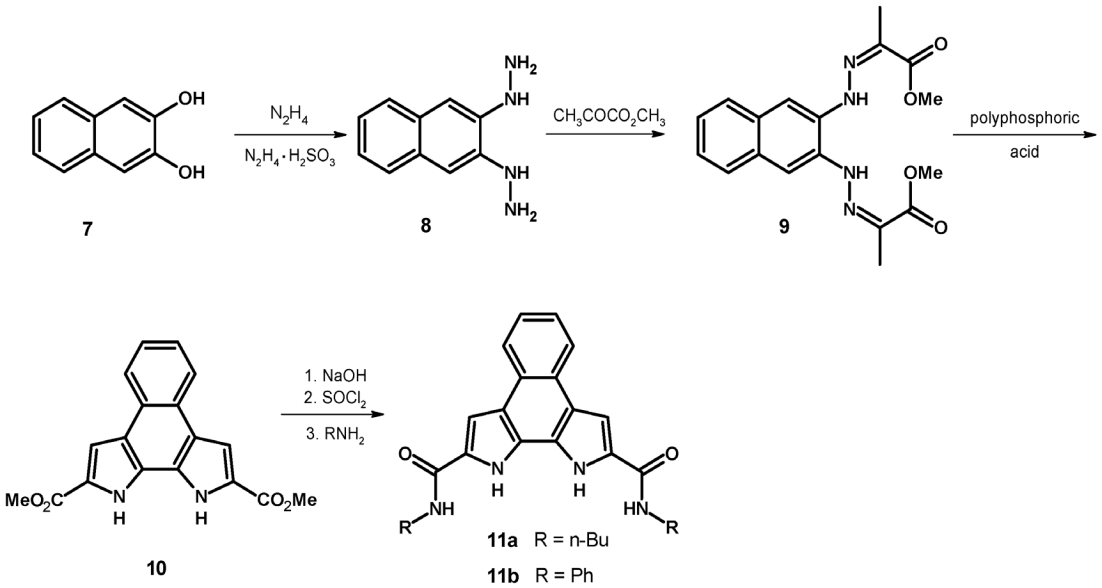
[a]Ref. [7].
[b]Ref. [9].

Later, 1,8-diamino-3,6-dichlorocarbazole **5** was used as a platform for the construction of chromofluorogenic receptors by Kim et al. [10]. Analogous receptor, possessing *n*-butyl groups in place of chlorine atoms, was also evaluated in the group of Sessler [11], however, its binding constants are

considerably lower. Recently, a multigram synthesis of the parent compound, the unsubstituted 1,8-diaminocarbazole, was developed [12], and this building block is now under investigation.

Dipyrrolonaphthalenes

An increase in binding affinity can be achieved either by increasing the strength of each particular interaction or by increasing the number of binding points. The latter approach led us to design a group of receptors with dipyrrolonaphthalene as a backbone unit. This unit donates two hydrogen bonds with a fixed *syn* orientation suitable for anion binding. Furthermore, its large conjugated π-system shows promise as a chromo/fluorophore for anion sensors. Receptors **11a,b** were synthesized from 2,3-dihydroxynaphthalene as depicted in Scheme 2 [13,14].



Scheme 2 Synthetic pathway for the preparation of dipyrrolonaphthalene receptors **11a,b**.

A significant increase in binding properties in comparison with the pyrrolic analogues of the type **2** was found (Table 4). However, association constants of **11a,b** are still lower than those of **1a,b**. The binding pocket of these receptors seems to be too spacious to accommodate the relatively small chloride anion, however, it fits well the bigger oxyanions such as carboxylate and dihydrogen phosphate.

Table 4 Association constants of receptors **11a,b** with various anions determined by ^{1}H NMR titrations using TBA salts as the source of anions in DMSO-d_6 + 0.5 % H_2O [13].

Anion	K [M^{-1}]	
	11a	**11b**
$PhCO_2^-$	102	113
$H_2PO_4^-$	450	–
Cl^-	–	2

An excellent match between the carboxylate anionic group and the binding pocket of the host was found in the X-ray crystal structure of **11b** complex with benzoate (Fig. 1). Due to some steric hindrance, the benzoate is slightly inclined to the plane of the receptor, but all four hydrogen bond donors are involved in the guest binding, showing a great spatial and directional fit.

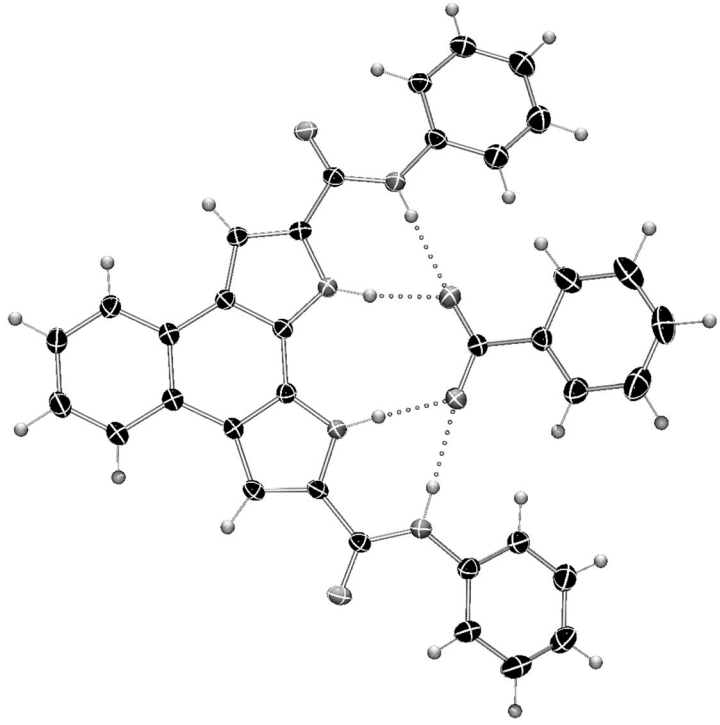
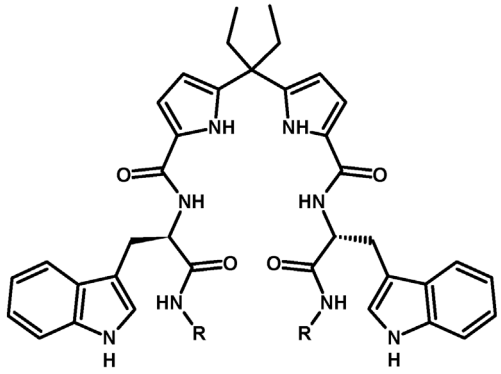


Fig. 1 X-ray crystal structure of the complex of **11b** with benzoate. TBA cation was omitted for clarity.

Similar receptors based on dipyrrolobenzene instead of dipyrrolonaphthalene have been recently synthesized and investigated by Curiel and co-workers. One of them, appended with amido-pyrrolic side arms, showed potent anion binding properties, especially toward pyrrophosphate anions [15].

Indoles

The indole moiety is a part of natural amino acid—tryptophan. This amino acid is found in the binding pocket of sulfate binding protein and in the active site of enzyme haloalkane dehalogenase where it serves as a hydrogen bond donor taking part in anion binding [16]. Tryptophan is therefore a readily available homochiral building block for enantio-differentiating anion receptors [17,18]. Receptor **12**, which we currently investigate, demonstrates very promising results in the chiral recognition of various carboxylates.



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As far as the non-natural indole-based building blocks are concerned, 7-aminoindole is a very promising candidate. It offers a similar arrangement of hydrogen bond donors as the 2-carboxyamidopyrrolic group, widely used for the construction of many efficient hosts [16]. However, owing to the fusion with the benzene ring, its pyrrole NH bond should be even better hydrogen bond donor. Also, it is a very rigid building block, what is beneficial for anion binding. Thanks to the presence of the amino group, the 7-aminoindole building block can be incorporated in nearly all kinds of amide and urea receptors with various backbones. This last feature makes the 7-aminoindole an interesting alternative to the commonly used aniline, since it provides one additional binding site and improves anion binding properties.

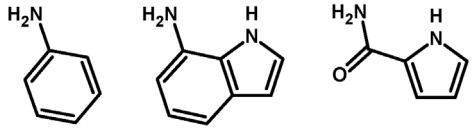
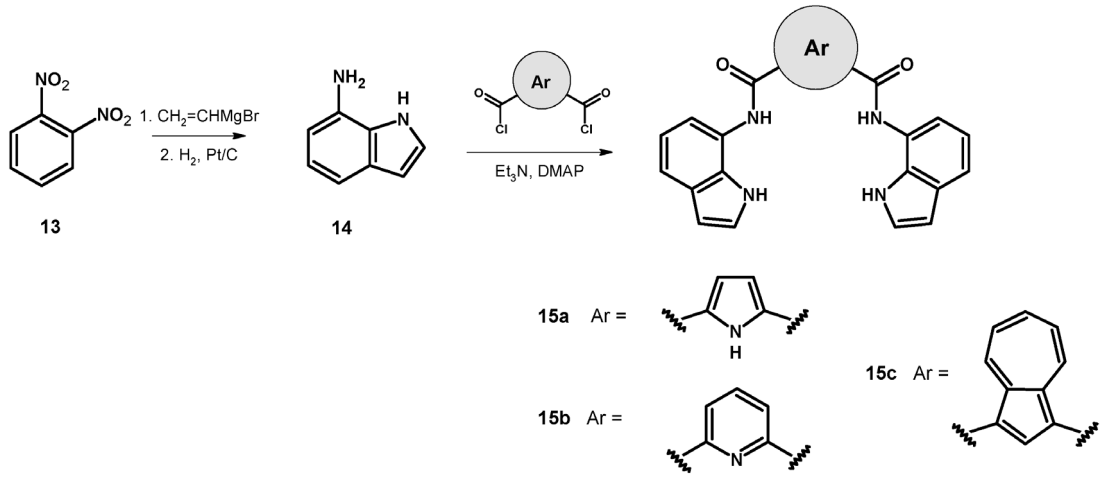


Fig. 2 Comparison of aniline, 7-aminoindole, and 2-carboxyamidopyrrole.

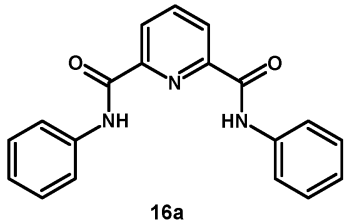
To assess the influence of the additional hydrogen bond donating group on anion binding, we investigated a series of receptors **15a–c** utilizing the 7-aminoindole moiety in place of aniline. The synthetic pathways and structures of receptors studied are shown in Scheme 3 [19].



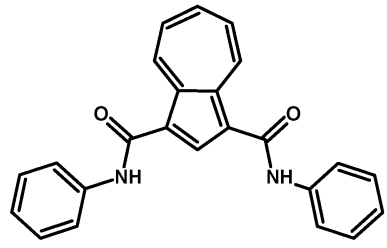
Scheme 3 Synthesis of 7-aminoindole-based receptors **15a–c**.

As confirmed by titration experiments (Table 5), binding abilities of these host molecules (**15a–c**) are greatly enhanced in comparison to analogous receptors containing aniline as a side arm (**2b**, **16a,b**), with the exception of receptor **15a**. In this case, an intramolecular hydrogen bond between the indole NH and the carbonyl group suppresses the influence of the additional hydrogen-bonding group on the anion binding abilities.

Table 5 Association constants of receptors **2b**, **15a–c**, and **16a,b** with various anions determined by ^{1}H NMR titration using TBA salts as the source of anions in DMSO-d_6 + 0.5 % H_2O.



16a



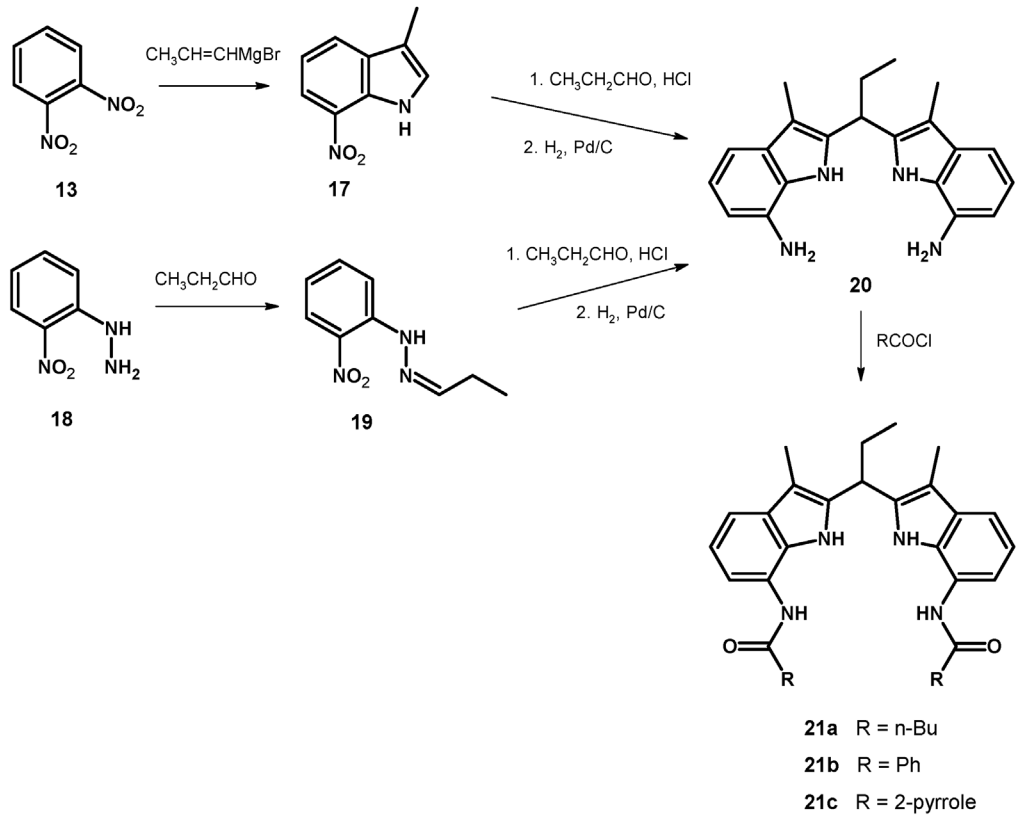
16b

Anion	K [M^{-1}]					
	2b[a]	**15a**[b]	**16a**[b]	**15b**[b]	**16b**[c]	**15c**[b]
$PhCO_2^-$	80	83	3.4	24	105	544
$H_2PO_4^-$	203	84	9.5	100	496	2300
Cl^-	3.8	5	–[d]	1.7	9.3	50

[a]Ref. [7].
[b]Ref. [19].
[c]Ref. [20].
[d]Binding too weak.

2,3-Dimethyl-7-aminoindole was used previously in systems based on the urea [21] and benzene cores [22]. Recently, the 7-aminoindole has also been used in the construction of a neutral receptor based on bipyridine core which undergoes metal-induced preorganization for anion binding [23].

In the above examples, the 7-aminoindole was used as a pendant group to increase the anion binding strength of receptors. By further functionalization at the position 2, it can be also incorporated into the backbone of an anion receptor. This approach was pioneered by Gale and co-workers through the use of 7-amino-2-carboxyamidoindole [24]. In our laboratory, an indole-based analogue of dipyrromethane, a common building block in the field of anion receptors chemistry [16], was designed and synthesized following the procedure outlined in Scheme 4 [25]. Key bisamine **20** can be easily obtained via two different three-step synthethic pathways. One of them starting with *o*-nitrophenylhydrazine is based on Fisher's indole synthesis [26], another method employs Bartoli reaction [27] of nitroaryl with appropriate vinyl magnesium bromide. The diindolomethane **20** is then readily transformed into a series of indole-amide receptors **21a–c** in a single step. These amides exhibit outstanding affinities toward various anions, with significant preference toward oxyanions, whose geometries fit well the wide cavity of the ligands (Table 5). Importantly, the receptors are particularly selective for dihydrogen phosphate, and this anion is bound even in highly demanding media—25 % (v/v) of water in DMSO as well as pure methanol (Table 6).



Scheme 4 Synthesis of diindolomethane-based receptors **21a–c**.

Table 6 Association constants of receptors **21a–c** with various anions determined by ^{1}H NMR titration using TBA salts as the source of anions in various solvents [25].

Anion	Solvent	K [M^{-1}]		
		21a	**21b**	**21c**
$PhCO_2^-$	0.5 % H_2O in DMSO-d_6	>10 000	2 140	1 660
$H_2PO_4^-$		>10 000	>10 000	–[a]
Cl^-		470	30	80
$PhCO_2^-$	5 % H_2O in DMSO-d_6	2060	340	300
$H_2PO_4^-$		>10 000	980	400
Cl^-		150	7	20
$PhCO_2^-$	10 % H_2O in DMSO-d_6	590	–[b]	–[b]
$H_2PO_4^-$		5 640	–[b]	–[b]
$H_2PO_4^-$	25 % H_2O in DMSO-d_6	210	<2	–[b]
$H_2PO_4^-$	CD_3OH	8	–[b]	–[b]

[a]Fitting failed.
[b]Not determined.

An X-ray crystal structure of the chloride complex of diindolomethane **21c** reveals that its binding pocket is too large to accommodate this relatively small anion. Only two out of six hydrogen bond donating groups of the receptor can strongly bind to the chloride, the next two form only long hydrogen bonds of moderate strength, while the remaining two do not take part in anion binding at all, forming instead intermolecular H-bonds with neighboring molecules (Fig. 3a). On the contrary, the crystal structure of **21a** complexing benzoate anion shows perfect geometric fit with all four NH bonds engaged in anion binding (Fig. 3b).

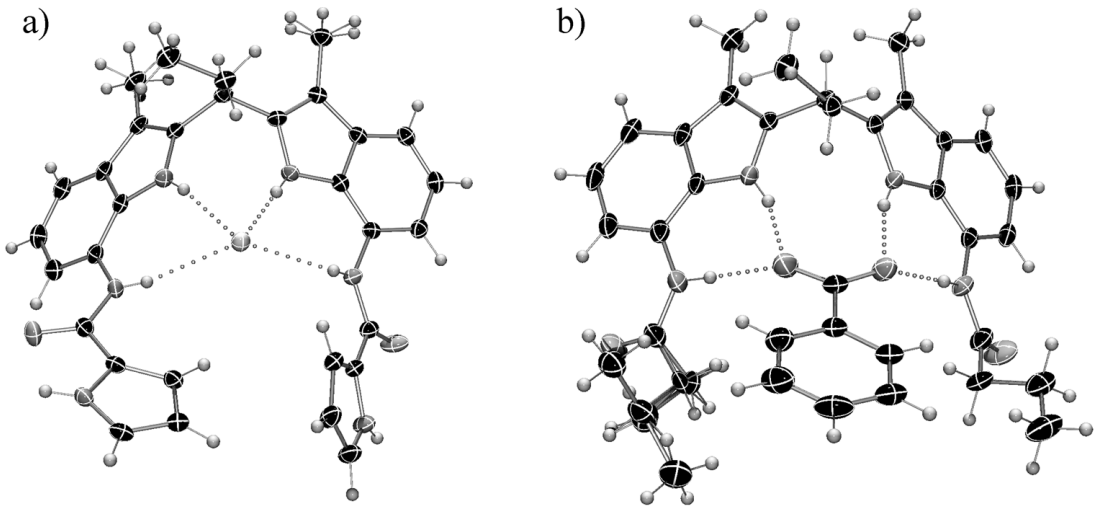
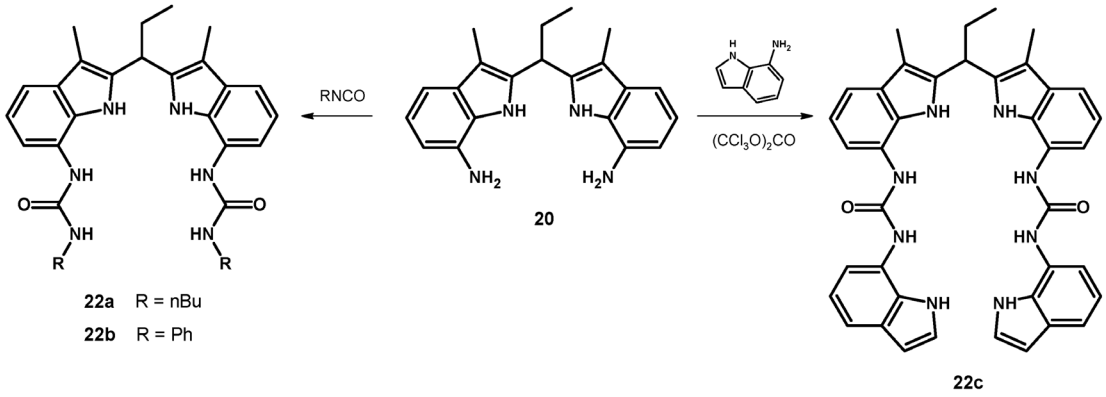


Fig. 3 Crystal structures of (a) complex of **21c** with chloride, and (b) complex of **21a** with benzoate. TBA cations are omitted for clarity.

Interestingly, the binding pocket of receptors **21** has been recently used to remote control of selectivity of a transition-metal catalyst [28]. In this case, interactions between anionic groups of substrates and the anion binding pocket built into the catalyst's molecule gives rise to the remarkably high regioselectivity in the hydroformylation of a variety of anionic olefins.

Finally, simple modification of receptors **21a–c** by the replacement of amide moieties with urea ones, leads to receptors **22a–c** with exceptionally high anion affinity (Scheme 5). The synthesis of receptors **22a–c** is straightforward and consists of one additional step from the above-mentioned bisamine **20** with appropriate isocyanate or with another amine and triphosgene [29].



Scheme 5 Synthesis of diindolemethane-urea-based receptors **22a–c**.

Importantly, the affinity of receptors **22a–c** toward anions was greatly increased by this modification. Remarkably, studied guests form complexes with various anions, even in a very competitive protic solvent such as methanol (Table 7). Further, they pronounce high selectivity toward tetrahedral oxyanions, e.g., dihydrogenphosphate and hydrogensulfate. However, the highest association constant values were observed for the triply charged pyrophosphate anion, in this case, complexes of higher stoichiometry were also observed.

Table 7 Association constants of receptors **22a–c** with various anions determined by ^{1}H NMR titration using TBA salts as the source of anions in CD_3OH [29].

Anion	K [M^{-1}]		
	22a	**22b**	**22c**
$PhCO_2^-$	13	28	39
$H_2PO_4^-$	125	360	235
Cl^-	13	37	26
Br^-	11	29	22
HSO_4^-	97	235	78
$HP_2O_7^{3-}$	–[a]	815 (1:1)[b] 10 000 (2:1)	–[a]

[a]Fitting failed.
[b]Values for formation of 1:1 and 2:1 receptor to anion complexes, respectively.

The exceptionally high anion affinity of receptors **22a–c** in protic solvents is surprising for acyclic hosts donating only six hydrogen bonds. Apparently, geometric fit, rigidity, and strength of each particular hydrogen bond were properly adjusted in these receptors, allowing them to compete successfully for anion binding with huge excess of the solvent molecules.

Unexpectedly, in this case host **22c**, containing the 7-aminoindole as a side arm, is not the most efficient, despite having the highest number of potential anchoring points (Fig. 4). However, a crystal structure of its complex with hydrogenphosphate (HPO_4^{2-}) shows that it binds the anion with all of its eight hydrogen bonding groups and encapsulates it in a pseudo-macrocyclic fashion. The reasons behind this apparent contradiction are still unknown, but the most plausible in our opinion are entropic effects or intramolecular hydrogen bonding.

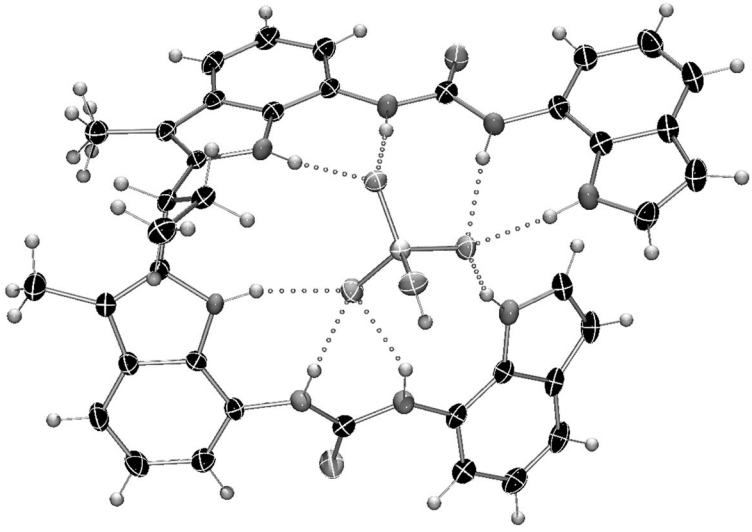


Fig. 4 Crystal structure of **22c** complex with hydrogenphosphate. TBA cations omitted for clarity.

CONCLUSIONS

The above overview illustrates our rational and iterative approach to finding building blocks for efficient and selective neutral anion receptors working in highly competitive solvents. The goal was not achieved by simply increasing the acidity of the donors and increasing their number in the molecule. In order to design a proper host, one needs to meet very demanding requirements of geometrical fit together with providing high energy of each bond. With the above examples we proved that benzopyrroles are very useful building blocks affording the achievement of proper spacial arrangement of the host as well as potent donors of binding sites. They can be widely used as backbone moieties or as side arms in the receptors. Although amide and urea groups are still of main interest in the field of anion receptors, we believe benzopyrroles are an important alternative, as well as, they can serve as an efficient supplement. As we discussed above, a well-suited combination of such heterocyclic fragments with classical binding sites allows one to obtain very strong affinity and good selectivity of new, synthetic anion receptors.

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