



Chiral anion recognition using calix[4]arene-based ureido receptors in a *1,3-alternate* conformation

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Abstract

The introduction of chiral alkyl substituents into the lower rim of calix[4]arene immobilised in the *1,3-alternate* conformation led to a system possessing a preorganised ureido cavity hemmed with chiral alkyl units in the near proximity. As shown by the ¹H NMR titration experiments, these compounds can be used as receptors for chiral anions in DMSO-*d*₆. The chiral recognition ability can be further strengthened by the introduction of another chiral moiety directly onto the urea N atoms. The systems with double chiral units being located around the binding ureido cavity showed better stereodiscrimination, with the highest selectivity factor being 3.33 (*K*_I/*K*_D) achieved for *N*-acetyl-L-phenylalaninate. The structures of some receptors were confirmed by single crystal X-ray analysis.

Introduction

The recognition and complexation of anions has become undoubtedly one of the most important branches of modern supramolecular chemistry, as can easily be demonstrated by an immense number of recent reviews [1-6] and books [7-11] devoted to this topic. Due to the omnipresence of anions in bio-

logical systems, their irreplaceable roles in cell functioning have gradually been revealed and are well recognised to date. Consequently, given the importance of anions in many areas of everyday life, including, e.g., biology, medicine, environmental pollution issues, or industrial processes, the design and develop-

ment of novel artificial receptors/sensors for anions is becoming more and more significant [12–14].

There are many strategies aiming at anion recognition in the literature. Most of the receptors, however, rely on electrostatic interactions. These systems are represented by positively charged molecules, such as quaternary N-, S-, and P-containing onium salts, protonated or alkylated aza-crown ethers and azacryptands, amidinium and guanidinium cations, etc. [15–18]. Due to the low directionality of the Coulomb force, the successful application of purely ionic interactions in the design of selective anion receptors is rather limited. The shapes and geometries of anions are widely different, and therefore the design of corresponding tailor-made receptors is based mostly on more directional interactions, such as hydrogen bonds. Indeed, an incredible number of neutral receptors bearing amide, sulfonamide, urea, thiourea, pyrrole, or triazole functional groups (to name at least some of them) has appeared during the last two decades [19–21].

Due to well-established functionalisation approaches, calix[4]arenes [22–24] are frequently used as molecular plat-

form in the design of more complex receptor systems. The existence of four basic conformations (*cone*, *partial cone*, *1,3-alternate*, and *1,2-alternate*) offers the combination of a precisely defined 3D structure, with functional groups being introduced at exactly defined mutual positions. This makes calix[4]arenes an ideal molecular scaffold [25,26] for the construction of highly sophisticated molecules, including anionic receptors [27–39].

During our ongoing research on anion complexation, we have reported various calix[4]arene receptors based mainly on amide, urea, or thiourea groups [40,41], some of which are available in different conformations. Although the overwhelming majority of calixarene-based receptors makes use of the *cone* conformer **A** (Figure 1), the corresponding diureidocalix[4]arenes in the *1,3-alternate* conformation **B** showed [42,43] surprisingly good complexation abilities towards selected anions. Especially for chiral anion recognition, contrary to the *cone* receptor, a design based on the *1,3-alternate* conformer enables the introduction of chiral units into the phenolic functions of the inverted aromatic moieties nearby the ureido cavity responsible for the binding, as in **C**. This design can be exemplified by our previously published receptors **C1** based on a calix[4]arene moiety

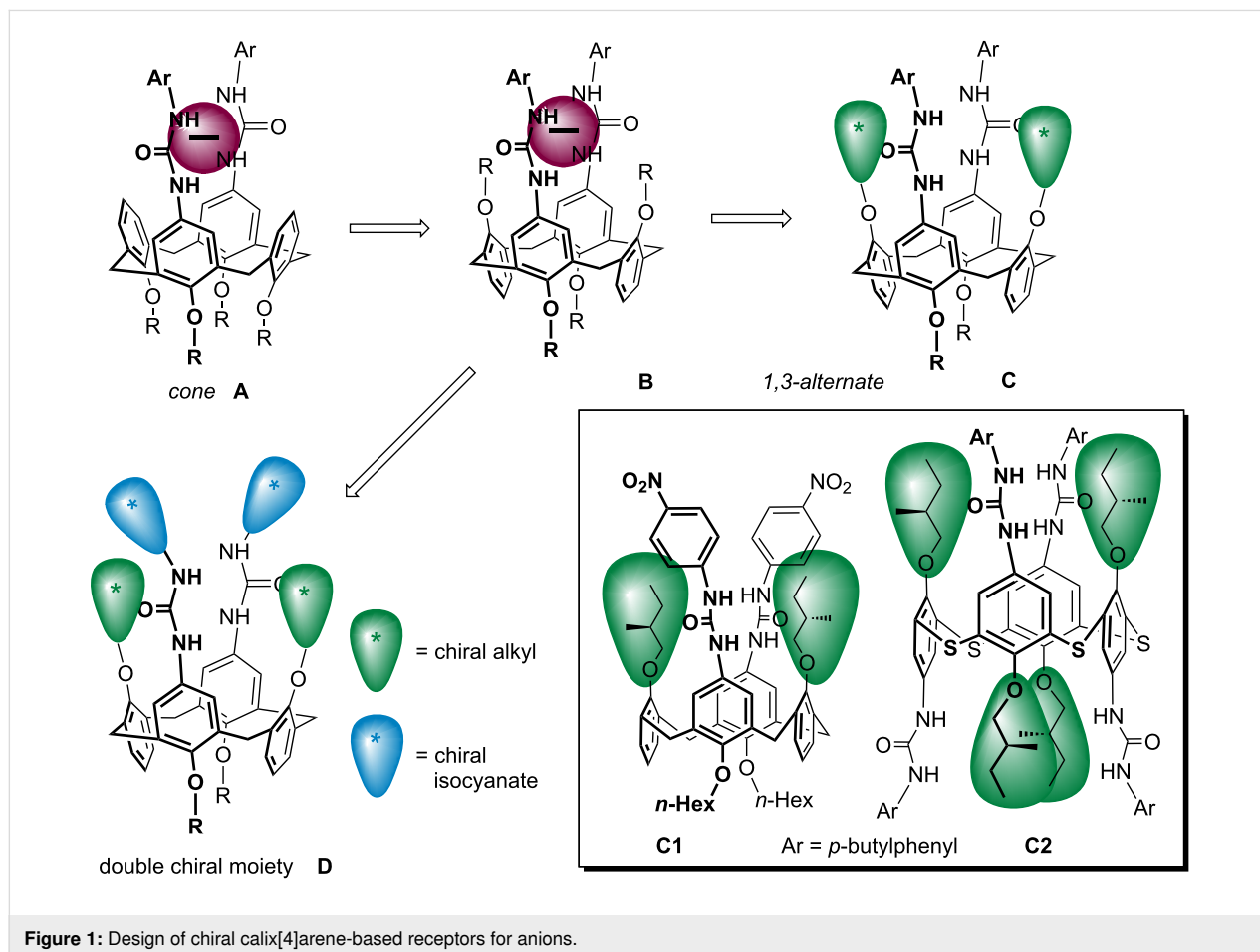


Figure 1: Design of chiral calix[4]arene-based receptors for anions.

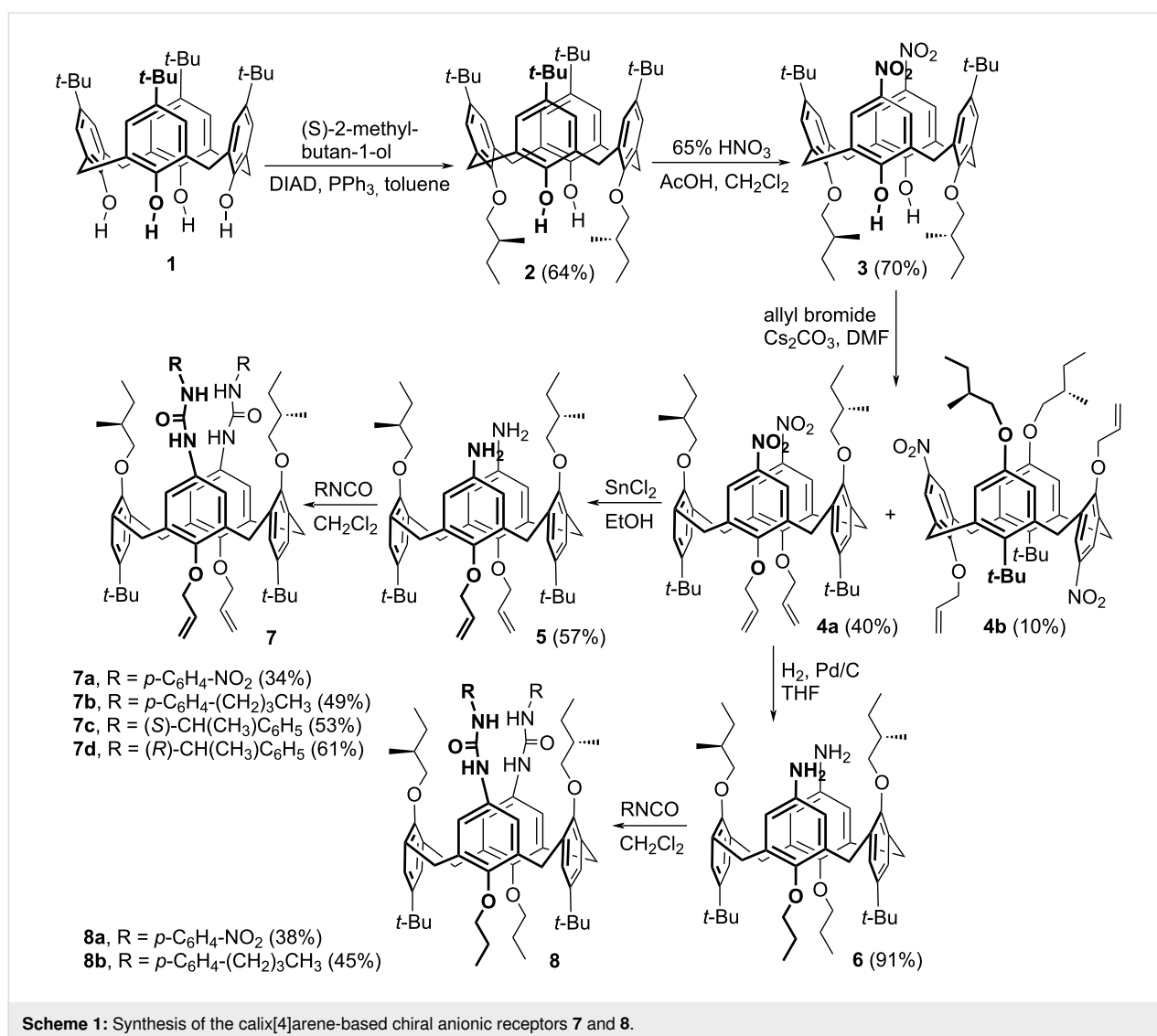
or by **C2** using thiacalix[4]arene as the core scaffold [44,45]. Moreover, the introduction of the *tert*-butyl groups into the *1,3*-alternate conformer should lead to the overall increase rigidity of the molecule, possibly enhancing the interactions within the binding cavity. In this context, we realised that further strengthening of the chiral induction can be reached via the synchronous application of chiral units on the ureido moieties as well, as in **D**. In this paper, we report the preparation and complexation study of the latter type of receptor, bearing double chiral units in the immediate proximity to the preorganised ureido cavity.

Results and Discussion

The introduction of the chiral alkyl moiety based on (*S*)-2-methylbutan-1-ol into the starting calix[4]arene **1** was carried out using recently described Mitsunobu reaction conditions [44]. Refluxing the reaction mixture of PPh₃, DIAD, and toluene

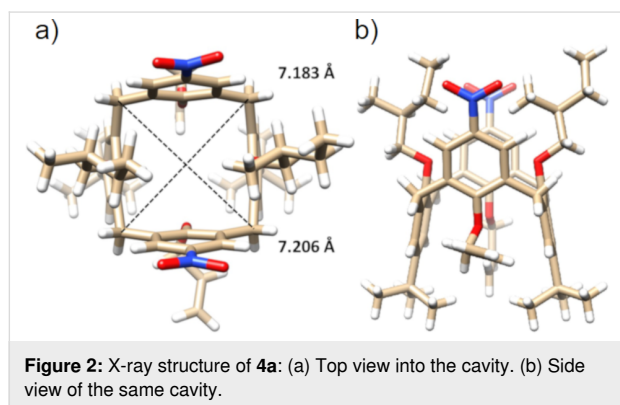
for two days provided the distally dialkylated calixarene **2** in 64% yield (Scheme 1). Compound **2** was regioselectively *ipso*-nitrated with 30 equiv of 65% aq HNO₃ in an AcOH and CH₂Cl₂ mixture, making use of the higher reactivity of the nonalkylated phenolic moieties [45]. The fast reaction afforded the corresponding dinitro derivative **3** within a few minutes with 70% yield.

As we found in our previous attempts [43,45], the alkylation of dinitrocalixarenes to form the *1,3*-alternate conformation is a synthetic challenge. In fact, irrespective of the base or solvent used, the alkylation with appropriate *n*-propyl or *n*-hexyl halides always led to the *partial cone* conformation as the main product. To overcome this problematic step, we used the conditions described by Böhmer et al. [46] for a similar system bearing propyl groups on the lower rim. Indeed, one week of stirring **3** with allyl bromide in the presence of Cs₂CO₃ provided



the expected *1,3-alternate* conformer **4a** in 40% yield accompanied by a small amount of the *partial cone* conformer **4b** (10%).

The unequivocal proof of the structure of the isomer **4a** was provided by single crystal X-ray analysis. The compound crystallised in a tetragonal system, space group $P4_12_12$ as a 1:1 complex with methanol used as a solvent for crystallisation. As shown in Figure 2, the calixarene clearly adopts the *1,3-alternate* conformation with an almost ideal tetragonal shape of the cavity. The lengths of the two main diagonals (the distances between opposite bridging CH₂ moieties) are essentially identical (7.183 Å and 7.206 Å). If the main plane of the molecule is defined by the four bridging C atoms, all phenolic subunits are almost perpendicular to this plane, with the aromatic parts being slightly tilted out of the cavity. The corresponding interplanar angles Φ with the aromatic subunits are 81.55°, 80.78°, 77.08°, and 80.57°, respectively, starting counterclockwise from the upper subunit bearing a nitro group (Figure 2a).



The *1,3-alternate* isomer **4a** represents quite an interesting synthetic intermediate as the presence of the allyl groups immobilizes the required conformation and at the same time enables the potential incorporation of the macrocycle into a polymeric matrix. Consequently, the subsequent reduction step was carried out in two alternative ways: (i) exclusive reduction of the nitro groups or (ii) concomitant reduction of the nitro groups and the allyl moieties. Thus, the reaction of **4a** with SnCl₂·2H₂O in ethanol gave the corresponding amine **5** in 57% yield after column chromatography on alumina. On the other hand, the four-day stirring of **4a** with Pd/C under a H₂ atmosphere (5 atm) in an autoclave at room temperature provided compound **6** in 91% yield.

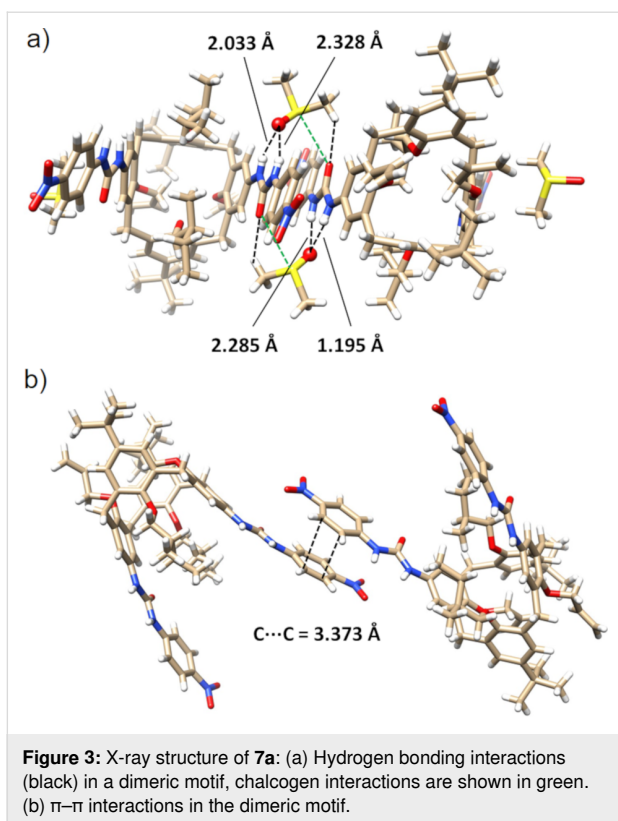
The starting compound **5** was then reacted with commercially available isocyanates comprising *p*-nitrophenyl isocyanate, *p*-*n*-butylphenyl isocyanate, (*S*)- α -methylbenzyl isocyanate, and (*R*)- α -methylbenzyl isocyanate. The reactions were carried out at room temperature in anhydrous dichloromethane, and the

products **7a–d** were isolated in 40–60% yields. Similarly, the propyl-substituted analogues **8a** and **8b** were obtained from the reaction of **6** with the corresponding isocyanates in 38% and 45% yield, respectively.

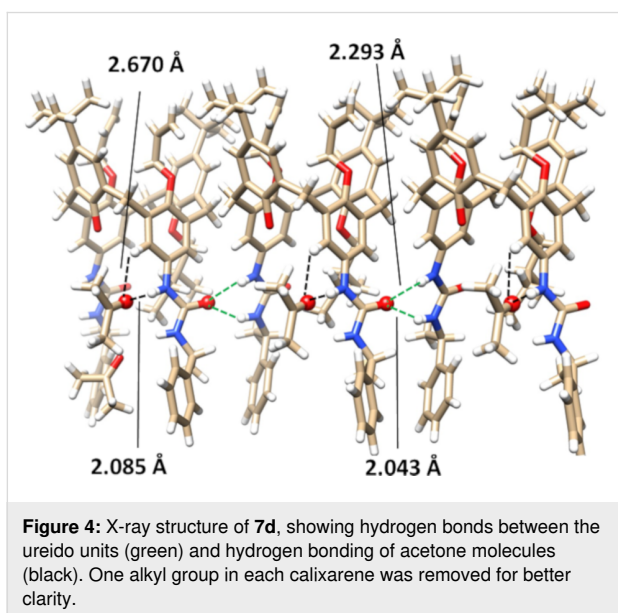
The structures of final receptors **7a–d** and **8a,b** were confirmed by means of HRMS and NMR techniques. Thus, the HRESIMS (positive mode) analysis of **8** showed signals at $m/z = 1141.59784$ and 1157.57129 , which is in a good agreement with the $[M + Na]^+$ (1141.59846 Da) and $[M + K]^+$ (1157.57240 Da) ions predicted for the product. The splitting pattern and multiplicity of the signals in the ¹H NMR spectrum fully corresponded to the expected *1,3-alternate* conformation (see Supporting Information File 1). Thus, the two doublets with typical *ortho* substituent coupling constants ($J = 7.3$ Hz) at 7.64 and 8.14 ppm support the presence of *p*-nitrophenyl groups. At the same time, the singlets at 8.36 and 9.37 ppm reflected the ureido NH protons (DMSO-*d*₆, 400 MHz, 298 K).

The structures of the selected receptors **7a** and **7d** were further proven by single crystal X-ray studies. The calixarene **7a** crystallised in a monoclinic system, space group C_2 , and the unit cell contained two receptors with four molecules of DMSO used as the crystallisation solvent (7·2DMSO complex). Both calixarene molecules exhibited an almost ideal square shape of the cavity, with the lengths of the main diagonals being 7.322 Å × 7.122 Å and 7.323 Å × 7.137 Å, respectively. Every ureido group held one molecule of DMSO via synchronous hydrogen bonding interactions between the two NH protons and a sulfoxide oxygen atom (Figure 3a). The S=O⋯H–N distances were 1.995, 2.285, 2.033, and 2.328 Å, indicating strong interactions in the solid state. At the same time, the carbonyl groups from the neighbouring receptor urea moieties interacted with the C–H bonds of the DMSO methyl group (the C=O⋯H–C distances were 2.486 and 2.452 Å), thus forming the calixarene dimer with a head-to-tail mutual orientation. The overall supramolecular binding motif was completed by the close contacts between carbonyl oxygen atoms (of the urea group) and S atoms (of DMSO), indicating possible chalcogen interactions [47,48], and the C=O⋯S=O distances were 3.269 and 3.308 Å (Figure 3a). The molecular packing was further strengthened by the π – π interactions of the *p*-nitrophenyl moieties, exhibiting several close C_{Ar}⋯C_{Ar} contacts at a 3.373 Å distance (Figure 3b).

The receptor **7d** crystallised in a triclinic system, space group P_1 , as a 1:3 complex with acetone (used as solvent for crystallisation). The main packing motive (see Figure 4) was represented by an infinite chain of calixarene molecules joined together by intermolecular hydrogen bonds between the ureido groups (the C=O⋯H–N distances were 2.293 and 2.048 Å).



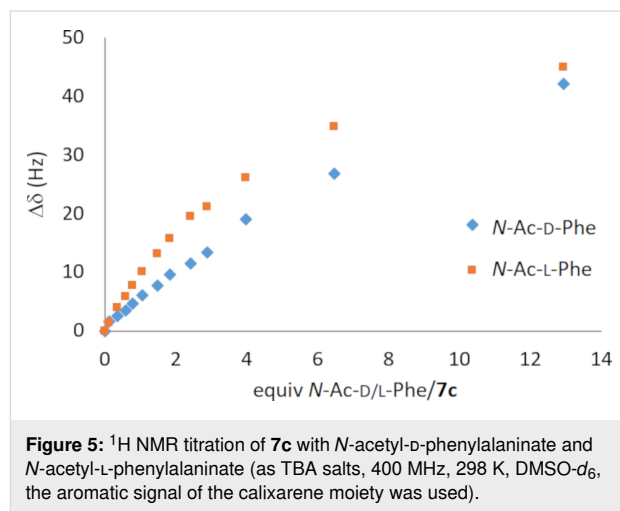
One of the ureido functions in the macrocycle also held acetone via a $C=O\cdots H-N$ hydrogen bond (2.085 Å) and via a $C=O\cdots H-C$ bond (2.670 Å) from the *meta*-position of the adjacent aromatic moiety (Figure 4).



The complexation ability of the novel receptors towards selected chiral anions was studied using standard 1H NMR titra-

tion experiments. There are several reasons why $DMSO-d_6$ was selected as the solvent for the complexation studies: (i) it dissolves all anionic species tested, (ii) prevents the receptor molecule from self-association, and (iii) reduces the complexation constants to values easily measurable by 1H NMR titrations.

A solution of an anion was gradually added to a solution of **7** or **8** in $DMSO-d_6$ to obtain various calixarene/anion ratios of 1:0.3–1:15. Upon the addition of anions in the form of TBA salts, significant downfield shifts of the ureido NH signals were observed, indicating the complexation under fast exchange conditions [49]. The corresponding complexation constants were calculated based on the analysis of the binding isotherms obtained from the complexation-induced chemical shift (CIS) values of urea NH protons or aromatic CH signals (Figure 5) [50–52]. The nonlinear curve-fitting of the experimental data was performed using the freely available software Bindfit [53]. The stoichiometry of the complexes was determined based on the Bindfit output, where the 1:1 model provided the best fit among all tested stoichiometries (1:1, 1:2, and 2:1).



The results summarised in Table 1 and Table 2 revealed that the complexation properties of the receptors do not depend significantly on the lower-rim substitution of the calixarene. Comparing the complexation constants for the otherwise identical receptors (**7a** vs **8a** or **7b** vs **8b**), it is obvious that the presence of allyl vs propyl substituents does not impose much difference in terms of absolute K values and selectivity.

As expected, the nitro-substituted receptors **7a** and **8a** exhibited complexation constants higher than the butyl-substituted analogues **7b** and **8b** for all anions – compare **7a** (Table 1, run 5, $K = 660 M^{-1}$) vs **7b** (Table 2, run 15, $K = 90 M^{-1}$). On the other hand, despite the differences in the K values, the enantioselect-

Table 1: Binding constants of the receptors **7a** and **8a** towards selected anions (¹H NMR titration, 400 MHz, DMSO-*d*₆, 298 K).

run ^a	anion	<i>K</i> (M ⁻¹) of 7a	<i>s</i> ^b	<i>K</i> (M ⁻¹) of 8a	<i>s</i> ^b
1	<i>N</i> -acetyl-D-phenylalaninate	279	1.18	290	1.10
2	<i>N</i> -acetyl-L-phenylalaninate	330	(for L)	320	(for L)
3	<i>N</i> -acetyl-D-leucinate	140	1.33	150	1.46
4	<i>N</i> -acetyl-L-leucinate	190	(for L)	220	(for L)
5	D-phenylalaninate	660	1.06	580	1.05
6	L-phenylalaninate	700	(for L)	610	(for L)
7	D-leucinate	480	1.02	320	1.12
8	L-leucinate	490	(for L)	360	(for L)
9	(<i>R</i>)-mandelate	260	1.03	250	1.04
10	(<i>S</i>)-mandelate	270	(for L)	260	(for L)

^aRuns 1–10: tetrabutylammonium (TBA) salts. ^bSelectivity factor: $s = K_D/K_L$ or K_L/K_D to obtain $s \geq 1$.

Table 2: Binding constants of the receptors **7b** and **8b** towards selected anions (¹H NMR titration, 400 MHz, DMSO-*d*₆, 298 K).

run ^a	anion	<i>K</i> (M ⁻¹) of 7b	<i>s</i> ^b	<i>K</i> (M ⁻¹) of 8b	<i>s</i> ^b
11	<i>N</i> -acetyl-D-phenylalaninate	180	1.11	200	1.10
12	<i>N</i> -acetyl-L-phenylalaninate	200	(for L)	220	(for L)
13	<i>N</i> -acetyl-D-leucinate	20	2.00	16	1.87
14	<i>N</i> -acetyl-L-leucinate	40	(for L)	30	(for L)
15	D-phenylalaninate	90	1.11	105	1.04
16	L-phenylalaninate	100	(for L)	110	(for L)
17	D-leucinate	90	1.20	95	1.10
18	L-leucinate	108	(for L)	105	(for L)
19	(<i>R</i>)-mandelate	160	1.06	140	1.14
20	(<i>S</i>)-mandelate	170	(for L)	160	(for L)

^aRuns 11–20: TBA salts. ^bSelectivity factor: $s = K_D/K_L$ or K_L/K_D to obtain $s \geq 1$.

tivity remained almost the same in both receptor series. Thus, the selectivity factor $s = K_L/K_D$ for phenylalaninate was 1.06 for **7a** and 1.11 for **7b**, and similar values were also obtained for **8a** (1.05) and **8b** (1.04), using the L-enantiomer in each case. The highest chiral discrimination (for an L-enantiomer) was achieved for *N*-acetyl-L-leucinate, with a selectivity factor of $s = 2.0$ and 1.87 for **7b** and **8b**, respectively.

The above-mentioned results indicate that the binding cavity composed of two preorganised ureido groups and chiral alkyl substituents in the near proximity possesses some ability of enantioselective recognition. In fact, this assumption was already established by our previous receptors **C1** and **C2** (Figure 1) [44,45], although the direct comparison with our novel results is rather difficult due to the different types of derivatives (**C1** has a cavity without *tert*-butyl groups, and **C2** is based on thiacalix[4]arene). Nevertheless, the simultaneous introduction of chiral isocyanate to form chiral urea moieties has not been accomplished yet.

The formation of another chiral centre within the derivatives **7c** and **7d** led to the expected decrease [42] of the complexation constant values (by approximately one order of magnitude) due to the presence of alkyl instead of aryl urea receptors (Table 3). Thus, going from **7a** to **7c**, the complexation constant *K* for D-leucinate decreased from 480 to 50 (run 7, Table 1 vs run 27, Table 3), and the appropriate values for D-phenylalaninate are 660 vs 40 (run 5, Table 1 vs run 25, Table 3).

On the other hand, the chiral recognition properties of the receptors **7c** and **7d** are accentuated compared to **7a** and **8a** or **7b** and **8b**. The introduction of another chiral centre leads to higher selectivity factors in almost all the cases. The stereodiscrimination of **7c** (bearing an (*S*)- α -methylbenzyl moiety on the urea group) for *N*-acetylphenylalaninates represents the maximum value achieved ($s = 3.33$ for L). Interestingly, the diastereomeric isomer **7d**, possessing an (*R*)-chiral centre, prefers the D-isomer, with a selectivity factor of $s = 1.75$, and the same holds for *N*-acetyl-D-leucinate ($s = 1.34$). These results indicate

Table 3: Binding constants of the receptors **7c** and **7d** towards selected anions (¹H NMR titration, 400 MHz, DMSO-*d*₆, 298 K).

run ^a	anion	<i>K</i> (M ⁻¹) of 7c	<i>s</i> ^b	<i>K</i> (M ⁻¹) of 7d	<i>s</i> ^b
21	<i>N</i> -acetyl-D-phenylalaninate	15	3.33	35	1.75
22	<i>N</i> -acetyl-L-phenylalaninate	50	(for L)	20	(for D)
23	<i>N</i> -acetyl-D-leucinate	20	2.50	31	1.34
24	<i>N</i> -acetyl-L-leucinate	50	(for L)	23	(for D)
25	D-phenylalaninate	40	1.37	25	1.28
26	L-phenylalaninate	55	(for L)	32	(for D)
27	D-leucinate	50	1.20	27	1.11
28	L-leucinate	60	(for L)	30	(for D)
29	(<i>R</i>)-mandelate	20	1.75	11	1.37
30	(<i>S</i>)-mandelate	35	(for L)	8	(for D)

^aRuns 21–30: TBA salts. ^bSelectivity factor: $s = K_D/K_L$ or K_L/K_D to obtain $s \geq 1$.

that both chiral moieties (the alkyl group on the calixarene and the chiral centre on the urea moiety) function synergistically, and a proper choice of both substituents can lead to an even better stereoselectivity.

Conclusion

In conclusion, the introduction of chiral alkyl groups into the lower rim of calix[4]arene immobilised in the *1,3-alternate* conformation resulted in a macrocycle with a preorganised ureido cavity bearing chiral alkyl substituents in the near proximity. As shown by ¹H NMR titration experiments, these compounds function as receptors for chiral anions in DMSO-*d*₆. The chiral recognition ability can further be strengthened by the introduction of another chiral moiety directly to the urea nitrogen atoms. The systems with double chiral units located around the binding ureido cavity showed a better stereodiscrimination, with the highest selectivity factor being 3.33 (for L) achieved for *N*-acetylphenylalaninate.

Supporting Information

Supporting Information File 1

Experimental details and characterisation data (including X-ray data for **4a**, **7a**, and **7d**, NMR, IR, and HRMS) as well as NMR titration data.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-249-S1.pdf>]

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