FULL PAPER

Preferred Binding of Carboxylates by Chiral Urea Derivatives Containing α-Phenylethyl Group

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An efficient, simple protocol for the synthesis of a new family of chiral ureas **1** – **4** is described. The binding properties of **1** – **4** toward different anion (acetate, benzoate, fluoride, and chloride) have been studied by ^{1}H-NMR titration and have been observed in the case of **4** is a selective receptor for acetate. The theoretical calculation M06/6-311+G(d,p) helped us explain the binding properties observed. The most interesting observation is that this calculated structure is consistent with expected, based on the concept of allylic 1,3-strain ($A^{1,3}$ strain). When chiral caboxylates were studied, urea **1** was the best in discriminating between enantiomers.

Keywords: *Ab initio* calculations, Density functional theory, Hydrogen bonds, Binding constant.

Introduction

Supramolecular chemistry, defined as chemistry beyond the molecule [1], is intrinsically dynamic in view of the reversibility of noncovalent interactions which connect the molecular components into a supramolecular entity. Selective anion recognition plays a critical role in biological processes. A variety of receptors and carriers can be found throughout the natural world, and molecular recognition using synthetic receptors has been extensively studied. The urea moiety plays an important role in the recognition of anions [2] due to its ability to donate two H-bonds to the anion and also because of its pivotal role in biological, environmental, and industrial application [3].

Ureas are frequently used in organocatalysis to activate substrates by H-bonding or to bind anions [2][4]. In this regard, urea complexation with carboxylates has been used in chiral counterion catalysis and in kinetic resolutions [5]. Many artificial carboxylate receptors, such as guanidinium [6], calix[2]arene[2]triazine [7], bis-chromenyl urea [8] among others [9], have been reported. Recognition of carboxylate anions and carboxylic acids by synthetic receptors is of paramount interest due to their presence in a variety of biomolecules, such as amino acids and peptides, which have huge application in pharmaceutical science [10].

The design of selective receptors for anions is based on the geometry of the anion, its size, and basicity. Another feature to take into account is the possible receptor preorganization or its restricted conformation, both of which will reduce the conformational entropy loss that occurs upon guest binding. In this regard, 1,3-disubstitued ureas display a preference for (*Z*,*Z*)-conformation ideal for anion binding which is in sharp contrast to the behavior of thioureas which prefer the (*E*,*Z*)-conformation [11]. This also applies when the receptor has C(3) symmetry [8b][12].

Herein, we would like to report on the binding properties of the urea receptors **1** – **4** with acetate anion. Using ^{1}H-NMR experiments in (D_6)DMSO, it was observed that these molecules are capable of selective anion recognition of carboxylate over halogen ions and they have been investigated as chiral receptors for amino carboxylic acids. Also, the interaction between acetate and urea was modeled by theoretical studies.

Results and Discussion

Synthesis of Receptors **1** – **4**

Urea receptors **1** – **4** were obtained through *Curtius* rearrangement of the corresponding acylazide followed by capture of the isocyanate with (*S*)-phenylethylamine [13]. Urea **1** was prepared through this methodology in 96%

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yield (phenylisocyanate obtained *via* addition of sodium azide to benzoyl chloride). Receptors **2**, **3**, and **4** were obtained from the di- or triacyl chloride in 68%, 57%, and 62% yield, respectively (*Fig. 1*). All compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry.

^{1}H-NMR Titration Studies

In order to investigate the binding properties of receptors **1** – **4** and to obtain the stoichiometry of their adducts with acetate ion, *Job* plots [14] were first performed. (*Fig. 2*) Ureas **1**, **3**, and **4** showed a 1:1 ratio in their

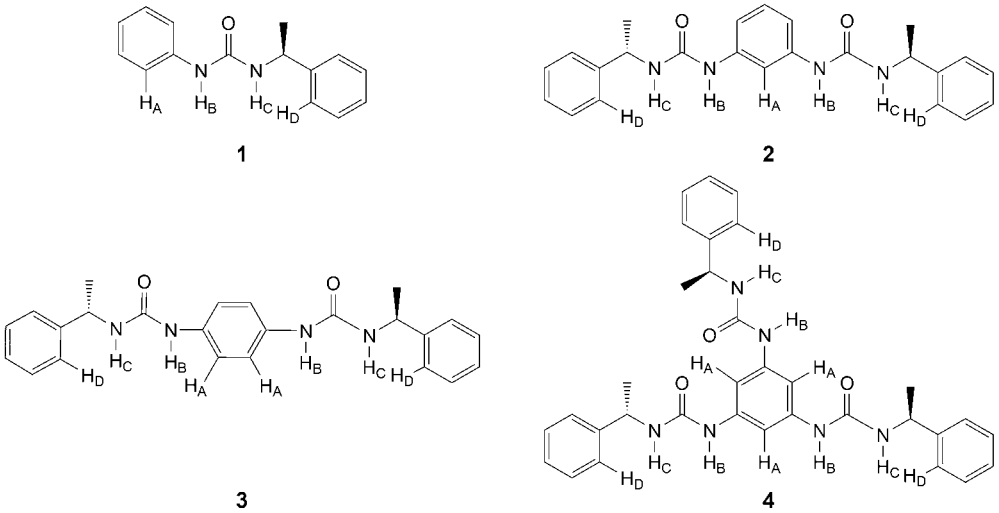

Fig. 1. Ureas **1** – **4** employed in this study.

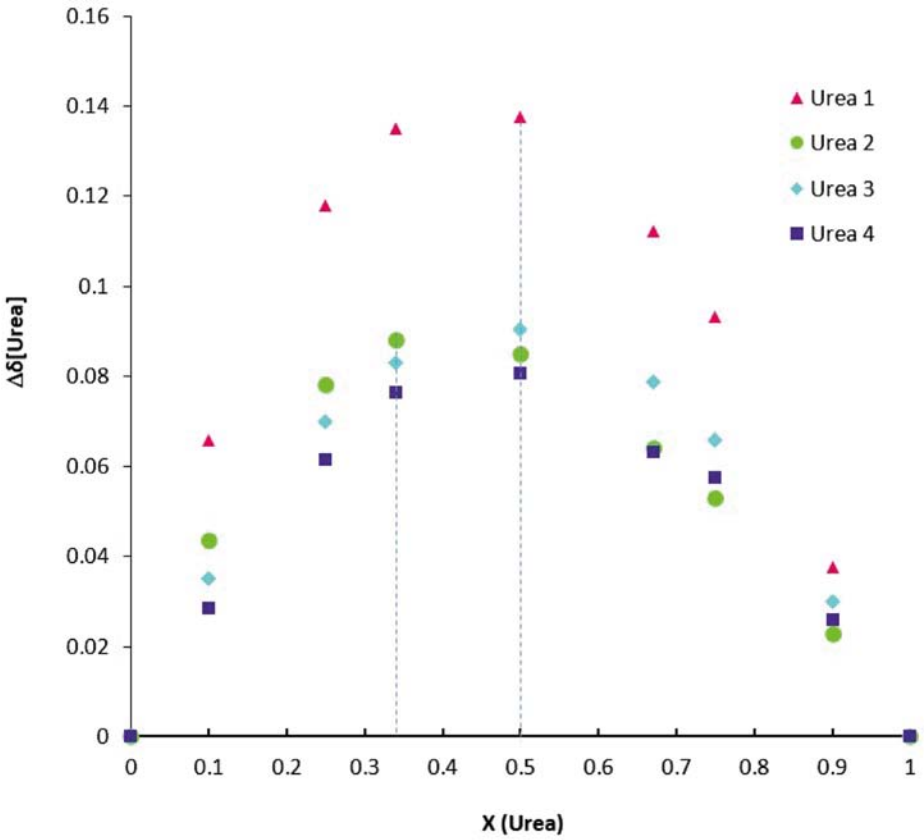

Fig. 2. The *Job*'s plot of receptors **1** – **4** with tetrabutylammonium acetate using ^{1}H-NMR.

Table 1. Association constants of receptors **1**, **2**, **3**, and **4** with tetrabutylammonium anions in (D_6)DMSO from ^{1}H-NMR titration

Receptor + anion	Stoichiometry[a])	K_a (M^{-1})[b])	δ_{end} [ppm]	$\delta_{initial}$ [ppm]	$\Delta\delta$ [ppm]
1 + AcO^-	1:1	213 (7%)[c])	10.3132	8.3715	1.9417
2 + AcO^-	1:2	K_{a1} = 262 (3%) K_{a2} = 39 (10%)[c])	9.6803	8.3328	1.3475
3 + AcO^-	1:1	74 (5%)[c])	10.1986	8.1657	2.0329
4 + AcO^-	1:1	138[d]) (10%)[c])	7.4560	6.4265	1.0295
4 + F^-	1:1	80[d]) (3%)[c])	8.7875	6.42645	2.3610
4 + $C_6H_5COO^-$	1:1	54[d]) (7%)[c])	8.2181	6.4284	1.7897
4 + Cl^-	1:1	27[d]) (15%)[c])	7.1356	6.4270	0.7086

[a]) Stoichiometry was determined from *Job* plots, except for chloride and fluoride anions see *Fig. 2*. [b]) Association constants were calculated by the computer program WINEQNMR [15], which requires the concentration of each component and the observed chemical shift of NHB of the urea. [c]) Estimated error. [d]) K_a's were calculated of NH_C.

interaction with acetate and urea **2** showed a 2:1 stoichiometry with acetate (*Table 1*).

Complexation of ureas **1** – **4** was measured by standard ^{1}H-NMR titration experiments in (D_6)DMSO using constant host concentration (10 mM) and increasing concentration of anions (0.2 – 30 equiv.). The chemical shift data and total concentrations were analyzed by WINEQNMR2 [15] to obtain the binding constant. The addition of tetrabutylammoniun acetate to the solution of receptor **1** in (D_6)DMSO resulted in downfield shifts of 1.94 ppm for both NH of the urea (see *Fig. 3*). This behavior is indicative of a direct interaction between this proton and the anion.

The analysis of binding constants (*Table 1*) showed that urea **1** gave better bonding than ureas **3** and **4,** probably because the need of the carboxylate to interact with other hydrogens which are not at optimal distance in these receptors. Although more H-bonds are made in these cases, these are weaker, and as a result, ureas **3** and **4** have less binding toward acetate. Urea **3** showed a 1:1 stoichiometry with acetate, but lower binding was found (see *Fig. 4*). When interaction of F and Cl anions with receptor **4** was investigated, it was found that fluoride, due to its basic nature was a better guest than chloride, but still not as strong as acetate.

Computer Modeling

Ab initio calculations showed details of the complexation between ureas **1** – **4** and acetate anion. The conformational

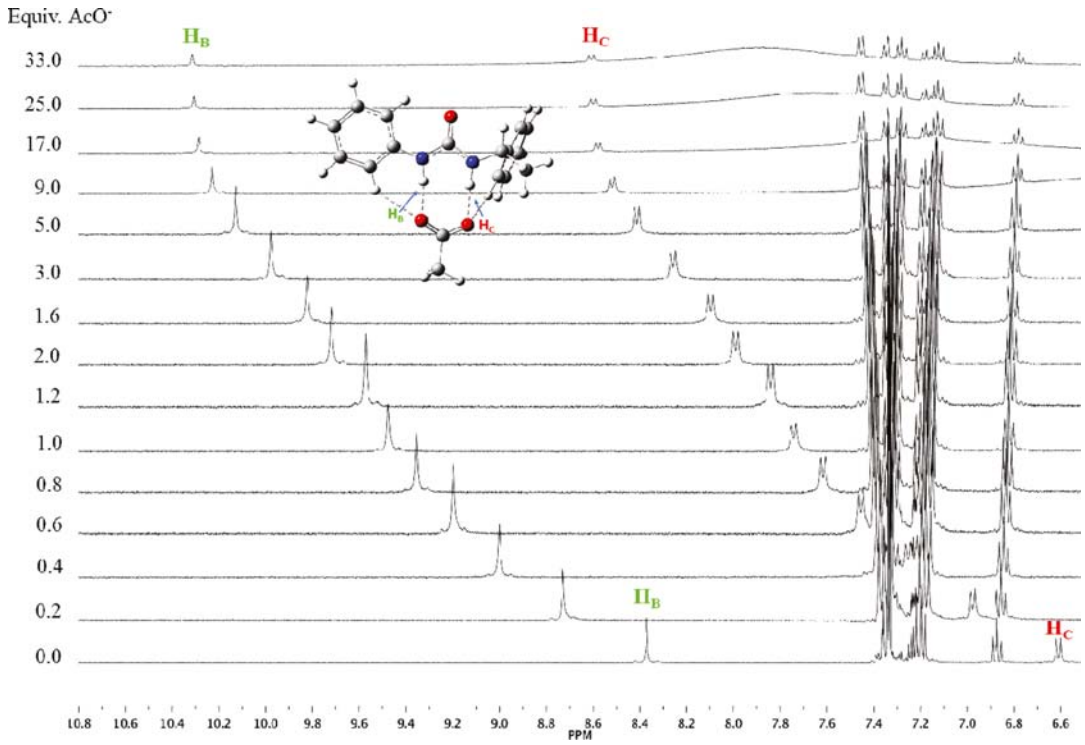

Fig. 3. Stack plot of ^{1}H-NMRs of urea **1** on addition of tetrabutylammonium acetate (0.2 – 33 equiv. in (D_6)DMSO, 400 MHz).

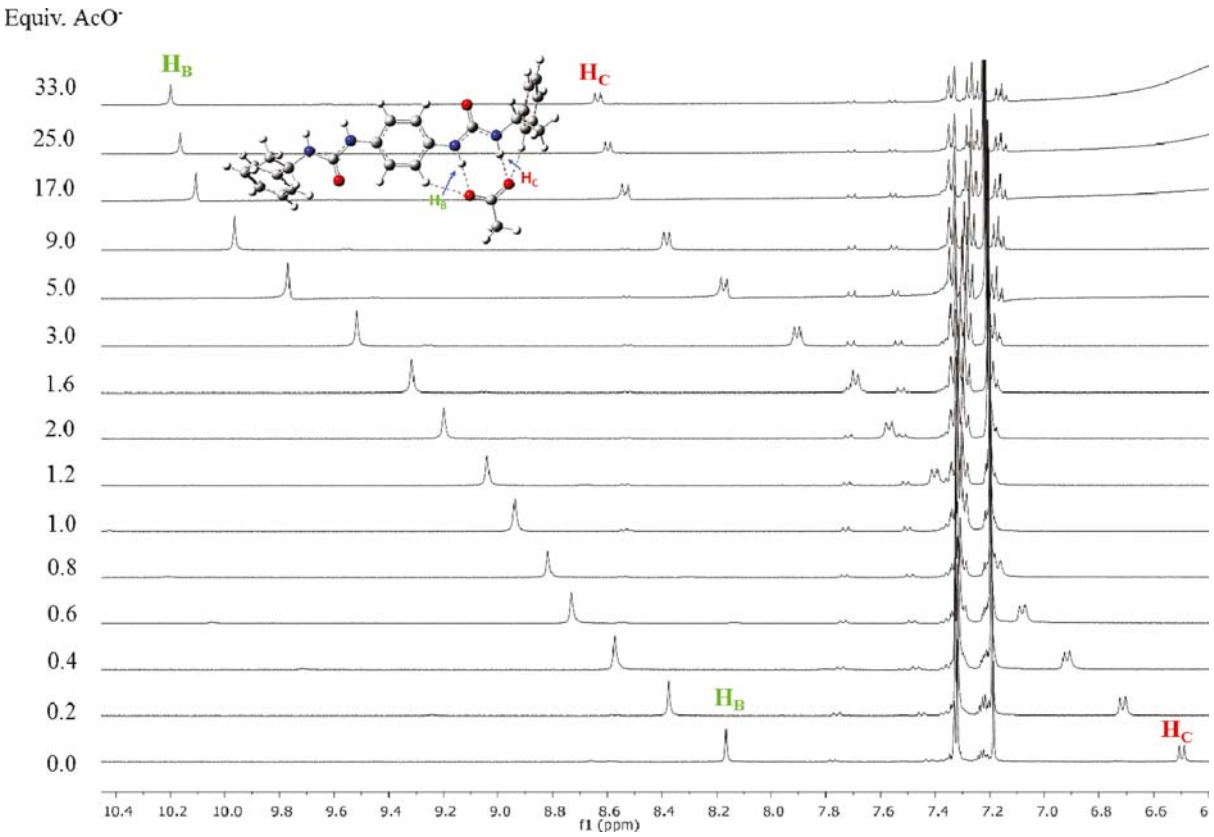

Fig. 4. Stack plot of ^{1}H-NMRs of urea **3** on addition of tetrabutylammonium acetate (0.2 – 33 equiv. in (D_6)DMSO, 400 MHz).

prediction of ureas **1** – **4** was performed using the *Born–Oppenheimer* molecular dynamics with the exchange and correlation functional PBE in combination with the orbital and auxiliary basis sets DZVP and GEN-A2, respectively, as implemented in the program deMonk2k [16]. All the trajectories were recorded at 300 K which was controlled by the canonical BOMD simulations with a *Hoover* chain thermostat. The simulations were started from the equilibrium geometry, with random velocities assigned to the atoms. All systems were sampled for 10 ps with a 1 fs step size. This methodology allows us to find the most stable conformers [17].

The lowest energy conformers found for all ureas (*Fig. 5*) show *syn*-periplanar arrangements between the C–H bond at the α-phenylethyl fragment and the N–C(O) segment, a manifestation of the allylic ^{A1,3} strain [18].

The most stable conformers were selected for each urea and then a local optimization was performed with three functionals: the *Becke*'s three-parameter hybrid functional (B3LYP) [19], the hybrid functional of *Truhlar* and *Zhao* (M06) [20], and the long range-corrected version of wPBE (LC-wPBE) [21]; in all cases, we used the 6-311+G(d,p) orbital basis set for all atoms using the *Gaussian* 09 program (Rev. A 02) (other references related to use of this method see ref. [22]). For all the systems, after optimizing the geometries, the frequencies were calculated to identify local minimum energies using the number of imaginary frequencies (NIMAG = 0). All the geometries were optimized using DMSO medium by PCM method [23]. All calculations, including zero point energy (ZPE) corrections, were also corrected for the BSSE using the counterpoise scheme of *Boys* and *Bernardi* [24]. The electronic energies (ΔE, ΔH, and ΔG) of monomers and complexes are summarized in *Tables S1* and *S2*. Only for carboxylate-urea complexes the theoretical calculations of those energies agree, in the case of halogen-urea complexes these calculated and experimental values did not match. The structures of anion-urea complexes shown correspond to the calculated lowest energy structures. (SI-Coordinates for Optimized Geometries.). The binding energies of gas phase are larger in absolute magnitude compared to those in DMSO as expected from the shielding effect by solvent.

When ureas **1** – **4** were binding to acetate, it was found that not only the NH of the urea participates in the complexation process but also aromatic C–H of the phenylethyl or the aryl ring on the nitrogen. *Fig. 6* shows all the possible H-bonding interaction between acetate and ureas **1** – **4** derived from AIM (atoms molecules) theory [25], and MULTIWFN (version 3.1) [26] was used to study H-bonding interactions.

The green dots in *Fig. 6* represent bond critical points (BCPs). Within this theory, the BCP should connect directly to the pair of atoms (hydrogen and acceptor atom) along the path defined by the electron density gradient. This is one of the most important criteria when

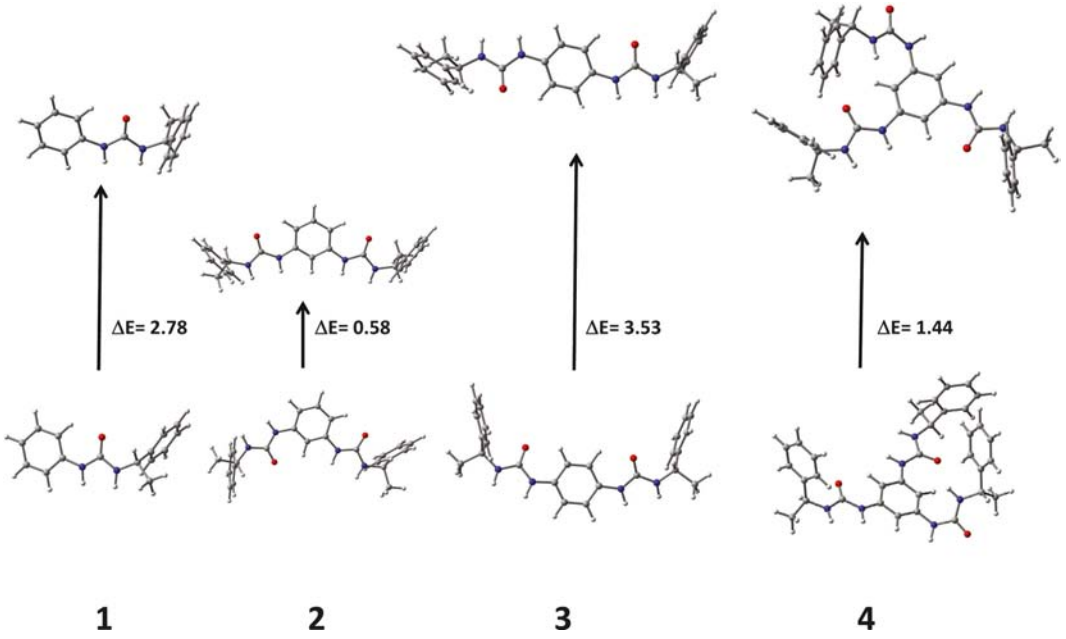

Fig. 5. Lowest-energy conformers for ureas **1** – **4** optimized by M06/6-311+G(d,p) in kcal/mol.

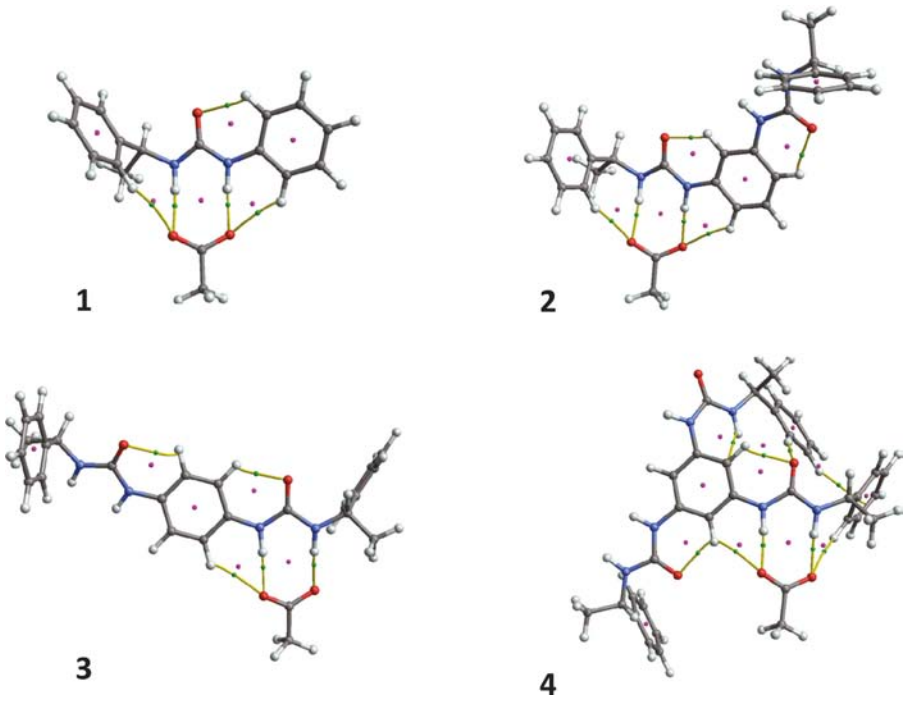

Fig. 6. Detailed description of H-bonding interactions between receptors **1** – **4** and acetate ion.

examining intermolecular interactions. Using this criterion, the number of possible H-bonding interaction between hosts and $MeCO_2^-$ were 4, 4, 3, and 4 for receptors **1**, **2**, **3,** and **4**, respectively, as indicated by either dashed or dotted line in *Fig. 6*. In *Table 2*, H-atoms involved in H-bonding are denoted as H_A, H_B, H_C, and H_D. Relevant physical parameters involving host–guest interaction are listed in *Table 2*. H-bonding is mostly denoted as X–H···B, where X–H is a H-bonding donor and B an acceptor. By analyzing the optimized structures, it is observed that the X–H bond length in X–H···B is larger than that of corresponding free X–H bond. For example, in adduct **1**-OAc N–Hs are elongated by H_B ~0.023 and H_C ~0.021 Å. In addition, aromatic H_A···O and H_D···O (~2.5- 2.8 Å) H-bond interactions are also observed [27].

Table 2. Geometries and charges of receptors **1** – **4** and their AcO^- complex[a])

Host (complex)	**1**	**2**	**3**	**4**	**1** + $MeCOO^-$	**2** + $MeCOO^-$	**3** + $MeCOO^-$	**4** + $MeCOO^-$
Q (H)								
H_A	0.0449	0.0421	0.0475	0.0253	0.0251	0.0236	0.0282	0.0120
H_B	0.1402	0.1403	0.1397	0.1448	0.0794	0.0796	0.0789	0.0803
H_C	0.1361	0.1290	0.1349	0.1399	0.0768	0.0772	0.0764	0.0786
H_D	0.0353	0.0437	0.0356	0.0385	0.0274	0.0248	0.0276	0.0270
Bond length (X–H) [Å]								
H_A–C	1.0874	1.0865	1.0870	1.0870	1.0872	1.0864	1.0868	1.0814
H_B–N	1.0114	1.0113	1.0114	1.0114	1.0344	1.0346	1.0343	1.0361
H_C–N	1.0105	1.0111	1.0108	1.0107	1.0320	1.0322	1.0319	1.0327
H_D–C	1.0875	1.0879	1.0875	1.0875	1.0884	1.0890	1.0883	1.0885
Distance (H···B) [Å]								
H_A···O					2.5125	2.5423	2.5297	2.5613
H_B···O					1.8181	1.8156	1.8183	1.7966
H_C···O					1.8440	1.8439	1.8426	1.8407
H_D···O					2.7684	2.5266	2.9092	2.6868
Distance (X···B) [Å]								
C (ring)···O					3.3824	3.4000	3.3925	3.3930
N_B···O					2.8501	2.8483	2.8503	2.8306
N_C···O					2.8720	2.8706	2.8715	2.8673
C (ring)···O					3.7681	3.5573	3.8643	3.6811
Angle [deg]								
C–H_A···O					136.2	135.1	135.6	133.0
N–H_B···O					175.0	175.6	175.2	175.4
N–H_C···O					173.6	172.5	174.5	172.2
C–H_D···O					152.6	157.5	146.5	151.6
ρ(b)[b])								
H_A···O					0.0086	0.0082	0.0083	0.0079
H_B···O					0.0348	0.0349	0.0348	0.0364
H_C···O					0.0328	0.0330	0.0329	0.0332
H_D···O					0.0052	0.0079	–	0.0061
$\nabla^2\rho$(b)[c])								
H_A···O					0.0331	0.0281	0.0286	0.0274
H_B···O					0.1208	0.1156	0.1152	0.1198
H_C···O					0.1147	0.1105	0.1109	0.1109
H_D···O					0.0268	0.0258	–	0.0197
$E_{H\cdots B}$[d])								
H_A···O					−1.721	−1.635	−1.656	−1.583
H_B···O					−8.796	−8.855	−8.800	−9.414
H_C···O					−8.104	−8.145	−8.122	−8.198
H_D···O					−0.998	−1.5127	–	−1.165

[a]) *Q* is the partial atomic charge derived using *Hirshfeld*. Distances are in angstroms [Å], angles are in degrees [°]. M06/6-311+G** level or theory. [b]) ρ(b) is the electron density at the bond critical point (BCP's). [c]) $\nabla 2\rho$(b) is *Laplacian* electron density at BCP. When two or more equivalents were obtained, overage values are listed. [d]) $E_{H\cdots B}$ is the H-bond energy expressed in kcal/mol.

Because host structures are rather rigid and interaction elements are not independent of one another, geometric considerations alone would not be sufficient to determine the relative strengths of H-bonding. Therefore, we also considered electronic properties. Another common feature of H-bonding is the depletion of electron density around the central H-atom. This was found to be the case for all interactions in *Fig. 6*.

The topological criteria of the existence of a H-bond were proposed by *Koch* and *Popelier* [28]. *Rozas* et al. [29] have classified H-bonds applying QTAIM parameters: the *Laplacian* of the electron density at H···O BCP and the total electron energy density at this BCP, designated further in this study as $\nabla^2\rho$(b) and ρ(b), respectively. Weak and medium in strength H-bond show positive values of $\nabla^2\rho$(b) and ρ(b). For strong H-bonds, $\nabla^2\rho$(b) is positive and ρ(b) is negative. For very strong H-bonds, both these values are negative. According to this criteria, as listed in *Table 2*, H_B···O and H_C···O are weak H-bonds for receptors **1**, **2**, **3**, and **4**.

The interaction of aromatic C–H with the acetate was also confirmed experimentally. As shown in *Fig. 7*, the beginning and the end of titration of urea **1** with acetate. It was found that orthohydrogens were shifted to higher chemical shift than the others hydrogens and defined multiplets were found because of a higher organization due to the additional H-bonding.

After the binding studies of ureas with acetate, we set out to explore binding with chiral carboxylates were studied. Therefore, all guest ureas were titrated with salts

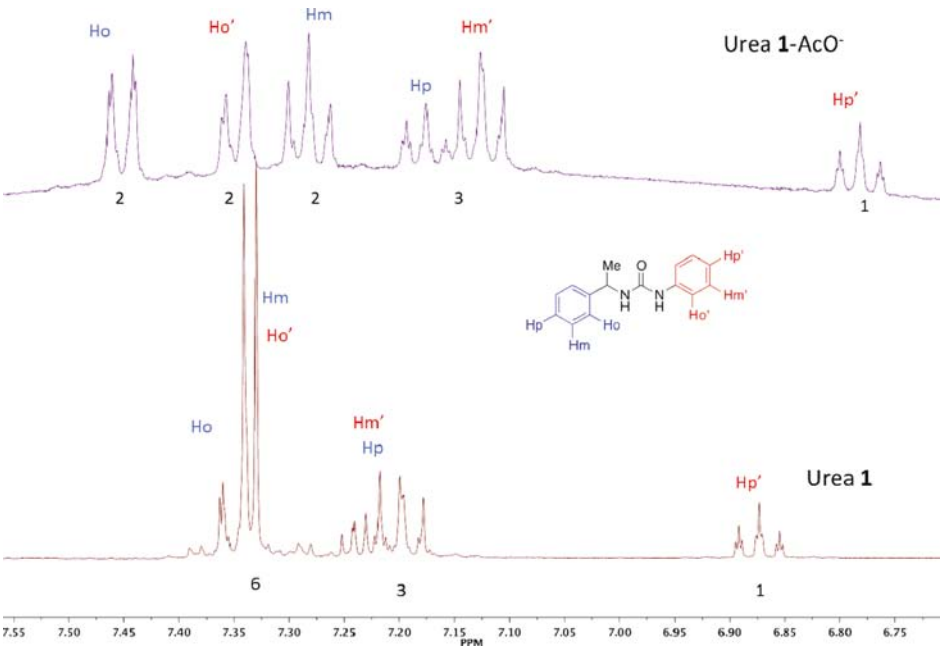

Fig. 7. Comparison of aromatic CH of urea **1** and urea **1** + acetate adduct.

of both enantiomers of mandelic acid. Results showed a lower association compared to that of acetate; this can be explained in terms of a larger steric effect with the substituted carboxylate. The enantiorecognition with these ureas was very low with ureas **3** and **4**, and urea **1** gave the best result in the discrimination of mandelate. Further studies on the association of this urea with other chiral carboxylates found nearly no discrimination of protected aminoacids, phenylglycinate, and alaninate but chiral discrimination was very high towards the (*S*)-enantiomers of *N*-Boc-prolinate and naproxenate (*Table 3*).

Conclusions

In summary, we synthesized a new family of chiral ureas as anion receptors containing the α-phenylethyl group with benzene platforms. ^{1}H-NMR titrations showed that receptor **4** is a selective receptor for acetate, and ureas **1** and **2** showed strong association constant for acetate in polar solvent such as DMSO. In DMSO, acetate was complexed by receptors **1**, **3**, and **4** *via* four types of H-bonding involving urea N_B–H and N_C–H, and aromatic interaction C–H_A and C–H_B. However, only eight types

Table 3. Binding constants[a]) of receptors **1** – **4** with various anions chirals obtained from ^{1}H-NMR titrations in (D_6)DMSO with anions added as TBA salts

Receptor + anion	K_a (M^{-1}) (%)[b])	δ_{end} [ppm]	$\delta_{initial}$ [ppm]	$\Delta\delta$ [ppm]	Selectivity factor $K_{(S)}/K_{(R)}$
1 + (*S*)-Mandelate	26 (3)	11.006	8.3667	2.6393	2.1[c])
1 + (*R*)-Mandelate	54 (4)	10.4459	8.3634	2.0825	
2 + (*S*)-Mandelate	31 (6)	9.6565	8.3259	1.3306	1.6
2 + (*R*)-Mandelate	19 (5)	9.8295	8.3114	1.5181	
3 + (*S*)-Mandelate	16 (6)	10.1055	8.1696	1.9359	1.0
3 + (*R*)-Mandelate	16 (7)	10.0034	8.1700	1.8334	
4 + (*S*)-Mandelate	20 (8)	9.2030	8.2875	0.9155	1.2
4 + (*R*)-Mandelate	17 (6)	9.1165	8.286	0.8305	
1 + Boc-(*S*)-Alaninate	98 (2)	10.5829	8.3649	2.218	1.1
1 + Boc-(*R*)-Alaninate	92 (6)	10.6060	8.3624	2.2436	
1 + CBz-(*S*)-Phenylglycinate	32 (6)	10.5105	8.3758	2.1347	1.1
1 + CBz-(*R*)-Phenylglycinate	29 (10)	10.9415	8.3748	2.5667	
1 + Boc-(*S*)-Prolinate	402 (2)	11.1835	8.3622	2.8213	6.8[c])
1 + Boc-(*R*)-Prolinate	59 (2)	10.1757	8.3614	1.8143	
1 + (*S*)-Naproxenate	417 (3)	11.1479	8.3622	2.7857	5.0[c])
1 + (*R*)-Naproxenate	83 (3)	10.7599	8.3638	2.3961	

[a]) Binding constants were calculated by the computer program WINEQNMR, considering a stoichiometric receptor: anion (1:1) using the chemical shift of NH_B. [b]) Selectivity factor $K_{(R)}/K_{(S)}$. [c]) Estimated error.

of H-bonding were expected for receptor **2**. Theoretical calculation let to the identification of an additional H-bonding element. When chiral carboxylates were studied, the simplest urea **1** was the most effective towards binding and discrimination of enantiomers.

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Supporting Information

Supporting Information for this article is available on the www under http://dx.doi.org./10.1002/hlca201500177.

Experimental Part

General

All reagents for the synthesis were purchased from *Sigma–Aldrich* (St. Louis, MO, USA). Organic solvents were dried by standard procedures. M.p.: *Büchi Melting Point B-540* apparatus (*Büchi Switzerland*); uncorrected. Optical rotations were measured at 20 °C on a *PerkinElmer 341 Polarimeter* (Waltham, MS, USA) at 589 nm (Na D line) in a 1.0 dm cell with a total volume of 1 ml. IR Spectra: *PerkinElmer* FT-IR spectrometer; reported in terms on frequency of absorption (cm^{-1}). ^{1}H-NMR Spectra: *Varian VNMR 400* spectrometer (*Agilent Technologies*, CA, USA), operating at 400 MHz at 19 °C using (D_6)DMSO as a solvent purchased from *Sigma–Aldrich*; all chemical shift values (δ) are reported ppm, using the reference residual solvent signal (2.50) for (D_6)DMSO solns. Elemental analyses: *PerkinElmer 2400 Elemental Analyzer* instrument.

General Procedure for the Synthesis of Chiral Ureas (**1** – **4**)

In a 25 ml round-bottomed flask containing a magnetic stirring bar was placed 1 equiv. of the corresponding acyl chloride in 3 ml of dimethylformamide as solvent, followed by the addition of 2 – 6 equiv. of sodium azide. The resulting solution was stirred at r.t. at 1.5 – 2 h. Then the reaction mixture was diluted with 30 ml AcOEt, washed with H_2O (2 × 30 ml) and brine (2 × 30 ml). The organic phase was collected, dried (Na_2SO_4), filtered, and the solvents were vacuum removed (the temperature is maintained not over 25 °C). The acyl azide was used without further purification and diluted with 15 ml of dry toluene under nitrogen in a 50 ml round-bottomed flask containing a magnetic stirring bar. The resulting solution was allowed to react for 1.5 – 3 h at 80 °C before addition of 1.1 – 3.3 equiv. of (–)-(*S*)-α-phenylethylamine. The resulting mixture was then stirred at 80 °C overnight. The precipitate that formed was filtered, and in all cases, crude product was purified by recrystallization using AcOEt to afford the final product.

Synthesis of 1-Phenyl-3-[(1*S*)-1-phenylethyl]urea (**1**). Benzoyl chloride (0.50 ml, 4.31 mmol) and sodium azide (0.561 g, 8.62 mmol) were allowed to react according to the *General Procedure* for 80 min to give the benzoyl azide. This product was left stirring at 80 °C for 90 min to obtain the isocyanate. Then (–)-(*S*)-α-phenylethylamine (0.6 ml, 4.70 mmol) was added and the reaction mixture was stirred overnight at 80 °C to afford 0.870 g (84% yield) of **1** as a white solid (M.p. 149 – 150 °C). $[\alpha]_D^{20}$ = −12.0 (*c* = 1, $CHCl_3$). IR (KBr) 3315, 1554 (N–H), 1633 (C=O). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.39 (*d*, 3 H, *J* = 7.0); 4.83 (*m*, 1 H); 6.63 (*d*, 1 H, *J* = 7.9); 6.88 (*tt*, 1 H, *J* = 1.2, 7.3); 7.19 – 7.23 (*m*, 3 H); 7.33 – 7.35 (*m*, 4 H); 7.38 (*m*, 2 H); 8.40 (*s*, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 23.1; 48.6; 117.54; 121.08; 125.8; 126.7; 128.4; 128.7; 140.4; 145.2; 154.4. Anal. Calcd. $C_{15}H_{16}N_2O$ (240.30): C 74.97, H 6.71, N 11.66; found C 74.97, H 6.87, N 11.66. These data are similar to those reported previously by *Feng et al.* [30].

Synthesis of 1,1′-Benzene-1,3-diylbis{3-[(1*S*)-1-phenylethyl]urea} (**2**). Isophthaloyl chloride (0.500 g, 2.46 mmol) and sodium azide (0.640 g, 9.85 mmol) were allowed to react according to the *General Procedure* for 120 min to give the isophthaloyl azide. This product was left stirring at 80 °C for 2 h to obtain the isocyanate. Then (–)-(*S*)-α-phenylethylamine (0.69 ml, 5.42 mmol) was added and the reaction mixture was stirred overnight at 80 °C to afford 0.614 g (62% yield) as a white solid (M.p. > 300 °C). $[\alpha]_D^{20}$ = −44.7 (*c* = 1, DMSO). IR (KBr) 3300, 1562 (N–H), 1635 (C=O). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.37 (*d*, 6 H, *J* = 7.0); 4.79 (*m*, 2 H); 6.53 (*d*, 2 H, *J* = 7.9); 6.91 – 6.93 (*m*, 2 H); 7.02 (*dd*, 1 H, *J* = 1.6, 7.0); 7.20 – 7.26 (*m*, 2 H); 7.32 – 7.33 (*m*, 8 H); 7.44 (*t*, 1 H, *J* = 7.9); 8.35 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 23.1; 48.6; 106.7; 110.5; 125.8; 126.7; 128.4; 128.9; 140.7; 145.2; 154.3. Anal. Calcd. $C_{24}H_{26}N_4O_2$ (402.49): C 71.62, H 6.51, N 13.92; found C 71.49, H 6.48, N 13.68.

Synthesis of 1,1′-Benzene-1,4-diylbis{3-[(1*S*)-1-phenylethyl]urea} (**3**). Terephthaloyl chloride (0.510 g, 2.51 mmol) and sodium azide (0.653 g, 10.04 mmol) were allowed to react according to the *General Procedure* for 120 min to give the terephthaloyl azide. This product was left stirring at 80 °C for 2 h to obtain the isocyanate. Then (–)-(*S*)-α-phenylethylamine (0.70 ml, 5.53 mmol) was added and the reaction mixture was stirred overnight at 80 °C to afford 0.506 g (50% yield) as a white solid (M.p. > 300 °C). $[\alpha]_D^{20}$ = −68.6 (*c* = 1, DMSO). IR (KBr) 3332, 1575 (N–H), 1640 (C=O). ^{1}H-NMR (400 MHz, (D_6) DMSO): 1.37 (*d*, 6 H, *J* = 7.0); 4.80 (*m*, 2 H); 6.54 (*d*, 2 H, *J* = 7.9); 7.21 (*s*, 4 H); 7.23 (*t*, 1 H, *J* = 4.3); 7.32 (*m*, 8 H); 8.22 (*s*, 2H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 23.2; 48.6; 118.3; 125.8; 126.6; 128.4; 134.2; 145.4; 154.6. Anal. Calcd. $C_{24}H_{26}N_4O_2$ (402.49): C 71.62, H 6.51, N 13.92; found C 71.59, H 6.51, N 13.70.

Synthesis of 1,1′,1″-Benzene-1,3,5-triyltris{3-[(1*S*)-1-phenylethyl]urea} (**4**). 1,3,5-benzenetricarbonyl trichloride (0.300 g, 1.13 mmol) and sodium azide (0.441 g, 6.78 mmol) were allowed to react according to the *General Procedure* for 120 min to give the product corresponding. Then benzene-1,3,5-tricarbonyl azide was left stirring at 80 °C for 3 h to obtain the isocyanate. Then (–)-(*S*)-α-phenylethylamine (0.47 ml, 3.73 mmol) was added and the reaction mixture was stirred overnight at 80 °C to afford 0.255 g (40% yield) as a white solid (M.p. > 300 °C). $[\alpha]_D^{20} = -39.2$ (c = 1, DMSO). IR (KBr) 3299, 1552 (N–H), 1641 (C=O). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.36 (*d*, 9 H, J = 6.9); 4.78 (*m*, 3 H); 6.43 (*d*, 3 H, J = 7.8); 7.06 (*s*, 3 H); 7.20 – 7.24 (*m*, 3 H); 7.31 – 7.32 (*m*, 12 H); 8.29 (*s*, 3 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 23.5; 48.9; 100.4; 126.2; 127.1; 128.7; 141.2; 145.6; 154.7. Anal. Calcd. $C_{33}H_{36}N_6O_3$ (564.68): C 70.19, H 6.43, N 14.88; found C 69.92, H 6.45, N 14.57.

General Procedure for ^{1}H-NMR Titrations

In a NMR tube, 0.005 mmol of the urea was dissolved in 0.5 ml of (D_6)DMSO. A ^{1}H-NMR spectrum was acquired and the signals in the chemical shift of NH accounted as free urea. The titrations were carried out by the consecutive additions of tetrabutylammonium salts (NBu_4+X^-; X^-=CH_3COO^-,$C_6H_5COO^-$, F^-, Cl^-) stock solution until the chemical shift of the H_B or H_C reached steady values which was accounted as the urea-anion adduct. With the data of concentration and chemical shifts during the titration the binding constants with WINEQNMR2 [15] were obtained. The stock solution of carboxylate of tetrabutylammonium was prepared with 0.2 mmol of AcOH in 2 ml of tetrabutylammonium hydroxide (0.1M in iPrOH and MeOH), this mixture was placed in an ultrasonic bath for 25 min, the solvents were reduced to dryness before addition of 1 ml of (D_6)DMSO.

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