JOC The Journal of Organic Chemistry

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The Impact of Solvent and the Receptor Structure on Chiral Recognition Using Model Acyclic Bisamides Decorated with Glucosamine Pendant Arms

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Cite This: J. Org. Chem. 2020, 85, 11902−11907 Read Online

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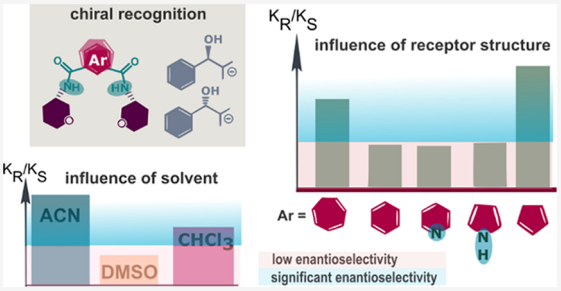
ABSTRACT: We investigated the influence of various factors (including solvent mixtures) on chiral recognition of chiral carboxylates, using the titration method under ^{1}H NMR control. We found that strong binding carboxylates (geometrical matching) is not enough for the satisfactory differentiation of enantiomers. Moreover, solvent mixture studies indicate a significant influence of environment on the formation of diastereomeric complexes and variations among them. Our findings offer insights into the complementarity of chiral recognition processes.



INTRODUCTION

Solving the puzzle of how nature works remains as an unending source of challenges for researchers.[1] One such insufficiently understood problem lies in the subtlest types of selectivity known as chiral recognition.[2] Therefore, current research focuses on aspects such as asymmetric catalysis,[3] molecular recognition,[4] chiral separation,[5] interaction on surfaces,[6] and supramolecular assemblies of chiral molecules in solution.[7]

Chiral recognition phenomena originate from differences in the Gibbs free energy (ΔG_{total}) of diastereomeric complexes formed between chiral molecules.[8] ΔG_{total} depends on the energy of intermolecular interactions (E_{inter}), the energy from conformational changes (ΔE_{intra}), and free solvation energy (ΔG_{solv}). The latter includes the free solvation energy of the complex (ΔG^{HG}_{solv}), free receptor (ΔG^{H}_{solv}), and free guest (ΔG^{G}_{solv}) (Figure 1.).[9]

Differences in interactions between solvent and anionic species and receptors lead to slight differences in ΔG_{solv} and depend on the medium. The solvent's parameters define this distinctiveness. Relative polarity, dielectric constant (ε), and Gutmann numbers[10] are among the criteria describing divergences in solvation (see Table 1). If host−guest interactions are electrostatic and the solvent weakly solvates both, the magnitude of the binding constant is inversely correlated to the dielectric constant of the solvent.[11] Gutmann's Donor Number (DN) defines the donicity of a solvent, meaning its behavior as a Lewis base solvent, while Gutmann's Acceptor Number (AN) reflects a solvent's character as a Lewis acid. Hence, the interactions between a solvent and a charged anion and the H-donor cavity lie along the ion−dipole and dipole−dipole interactions. Analysis of

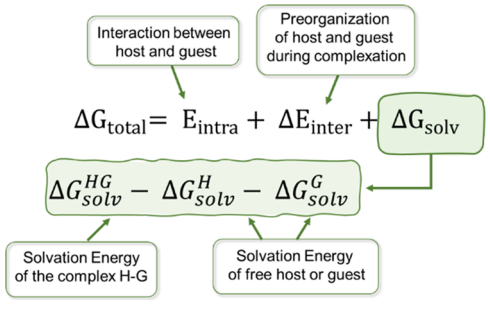


Figure 1. ΔG_{total} equation.

Table 1. Properties of Solvents Used: Gutmann Donor Number (DN) (Kcal Mol^{-1}), Gutmann Acceptor Number (AN) (Kcal Mol^{-1}), Relative Polarity (E_T), and Dielectric Constant (ε)

entry	solvent	DN[12]	AN[12]	E_T[13]	ε[13]
1	CH_3CN	14.1	18.9	0.460	37.5
2	DMSO	29.8	19.3	0.444	46.68
3	$CHCl_3$	4.0	23.1	0.259	4.89
4	H_2O	54.8	18.0	1.000	80.1

Received: July 16, 2020
Published: August 19, 2020

https://dx.doi.org/10.1021/acs.joc.0c01693
J. Org. Chem. 2020, 85, 11902−11907

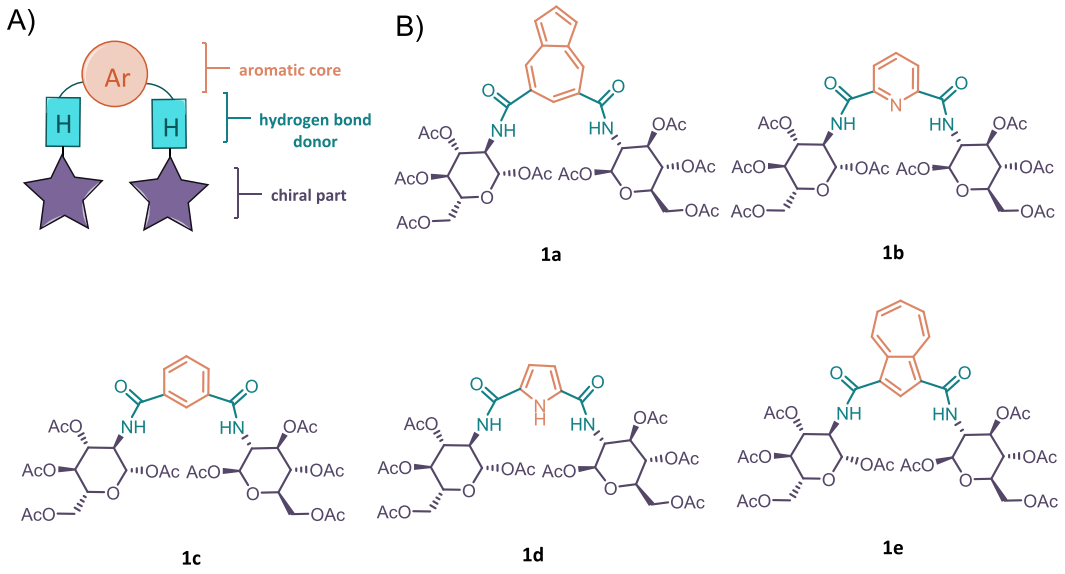


Figure 2. (A) Idea of a chiral receptor structure; (B) chiral receptors **1a**−**1e** investigated in this study.

differences in solvent features indicates that the medium could also be a meaningful factor in chiral recognition. To our knowledge, however, there have been no in-depth studies describing the influence of the medium on chiral recognition of anions.

Another factor is the proper design of the chiral receptor, crucial for binding the anion.[14] Many factors govern the chiral recognition phenomenon, making a prior prediction difficult. The appropriate arrangement of hydrogen bond donors and chiral fragments should ensure enantioselective interactions with chiral anions. Hence, effective chiral recognition of anions requires the synthesis and determination of binding affinities and enantioselectivities of prospective chiral receptors.[15]

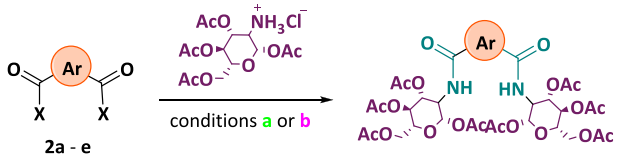
Based on these considerations, we designed a series of chiral receptors (**1a**−**1e**) of various sizes and binding pocket geometries, consequently with different arrangements of hydrogen bonding donors (Figure 2). To achieve this goal, we took the approach of using the covalent attachment of the chiral moiety to an anion binding backbone. Based on our experience[16] showing bisamides to be attractive building blocks for achiral receptors, we applied different simple aromatic platforms (benzene, pyridine, azulene, and pyrrole). As a chiral part, we chose a peracetylated glucosamine derivative,[17] which is a cheap and readily available source of chirality and can be easily functionalized by changing the protecting groups.

RESULTS AND DISCUSSION

First, we synthesized a series of amide-based receptors using per-*O*-acetyl-D-glucosamine hydrochloride with acid dichlorides previously prepared from the corresponding dicarboxylic acid.[18] Due to the high nucleophilicity of the 1- and 3-position of the azulene moiety, we applied HBTU (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) to obtain 5,7-bisamide azulene receptor **1a** (Scheme 1).[19]

We determined the anion binding properties using the ^{1}H NMR titration method. This technique keeps track of the binding process and shows differences in the formation of diastereomeric complexes.[20] Utilizing changes in chemical shifts, we obtained all global stability constants by nonlinear curve fitting to the 1:1 and 1:2 (receptor: anion) binding model[21] using the program HypNMR2008.[22]

Scheme 1. Synthesis of Model Bisamides 1a−1e



2a: X = OH; Ar = 5,7 - azulene; a
2b: X = Cl; Ar = 2,6 - pyridine; b
2c: X = Cl; Ar = 1,3 - benzene; b
2d: X = Cl; Ar = 2,5 - pyrrole; b
2e: X = Cl; Ar = 1,3 - azulene; b

1a (57%)
1b (65%)
1c (75%)
1d (42%)
1e (75%)

conditions **a**: HBTU, TEA, DMF; **b**: TEA, DCM

Hence, as to evaluate the influence of geometry on binding affinity and modes of anion binding by amide-based receptors, we conducted titration experiments with the series of receptors **1a**−**1e** with achiral benzoate anion as tetrabutylammonium salt (TBA). Due to the solubility of receptors (all studied ligands are insoluble in aqueous media), we conducted titration experiments in CD_3CN + 0.5% H_2O. The respective binding constants toward benzoate anion (K_a), the geometrical parameters of the binding pocket, and the maximum chemical shift ($\Delta\delta_{max}$) of the protons in the binding cavity (green H in Figure 3) are presented in Table 2.

In all cases, anion complexation caused a downfield shift of C−H and N−H protons located in the receptor binding pocket. The calculated affinity constants generally increased with the size of the binding cavity. Receptors **1d** and **1e**, based on a five-membered aromatic core, revealed the highest binding affinity toward benzoate anion (binding constants up to 10,000 M^{-1}) and the 1:2 (host:guest) binding model. Dipicolinic acid derivative **1b** binds the anion with the lowest constant K_a = 50 M^{-1} (Figure 4). The repulsive interaction between anion and the electron free pair located on the nitrogen atom may attenuate the formation of hydrogen bonds. Growing changes in chemical shifts of green protons demonstrating weak C−H hydrogen bonds (for **1a**, **1c**, and **1e**) and strong N−H bonds (for **1d**) are in accordance with the calculated affinity constants.

https://dx.doi.org/10.1021/acs.joc.0c01693
J. Org. Chem. 2020, 85, 11902−11907

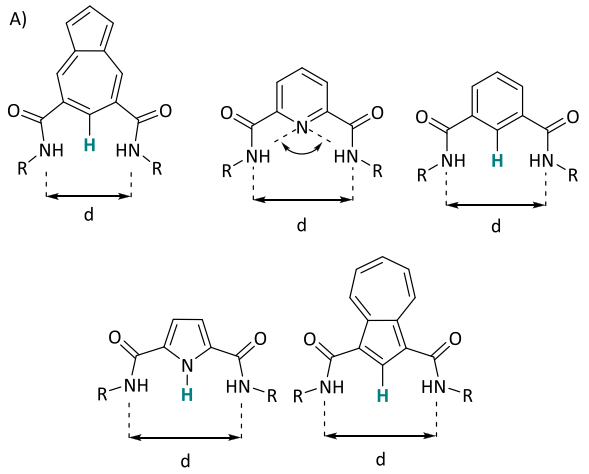


Figure 3. Geometrical parameters presented in Table 2.

Table 2. Comparison of Geometrical Parameters of the Binding Pocket[16] with Binding Constants K_a [M^{-1}][a] for Complexes of Receptors 1a−1e with Benzoate in CD_3CN + 0.5% H_2O[a−c]

receptor	1a	1b	1c	1d	1e
K_a	460	49	1400	>10[4c]	>10[4c]
$\Delta\delta_{max}$ [ppm]	0.33	–	0.77	4.16	1.61
d [Å][b]	4.0	4.6	5.0	5.4	5.6
α [°][b]	117	117	123	139	145

[a]Values determined by ^{1}H NMR spectroscopy titration experiments at T = 303 K; estimated errors <10%; TBA salts were the sources of the anions. [b]Geometrical parameters determined for conformation *syn*−*syn* using X-ray for R = *n*-Bu. [c]Binding model 1:2 (host:guest), $K_{1:2}$ is omitted, for more details see Supporting Information.

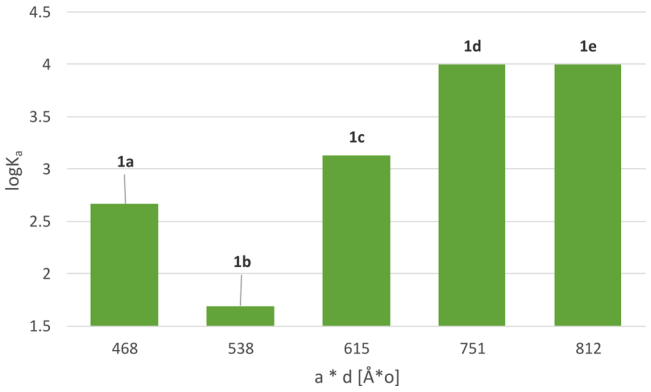


Figure 4. Dependence of logK_a with the size of the binding pocket.

Next, to estimate the receptors' potential for chiral recognition, we evaluated their binding properties with respect to two pairs of enantiomeric carboxylate derivatives: mandelic acid (Man) and *N*-Ac-phenylglycine (*N*-Ac-Phg) (see Figure 5). Given the magnitude of the binding constants with benzoate, we conducted titration experiments in CD_3CN + 0.5% H_2O as a solvent mixture. We used chiral anions as TBA salts. We calculated the association constants (K_R and K_S) determined by separate titration experiments and then compared them. To evaluate the enantioselective properties, we applied thermodynamic selectivity (α), which is a ratio of the binding constants of two diastereomeric complexes (α = K_R/K_S).

Influence of Receptor's Geometry on Chiral Recognition. By analogy to the achiral benzoate anion, we observed that anions formed complexes with respect to receptors with the same stoichiometry (Table 3). Receptors **1b**−**1d** did not exhibit meaningful enantioselective properties toward the investigated chiral pairs of anions (see the Supporting Information, Figure S1). Ligand **1e** recognized the model chiral pair of anion derivatives with α = 3.1 and α = ∼2, respectively, for Man and *N*-Ac-Phg. Receptor **1a** bound the (R) enantiomer more strongly with α = 2.1, with no chiral recognition for Phg derivatives. Comparison analysis of titration curves revealed that the source of the differentiation of chiral mandelic anions for the 5,7-disubstituted azulene derivative **1a** is the difference in binding of the anionic part with amide groups of the receptor (Figure 5c). For receptor **1e** we observed perturbation in chemical shifts both for binding cavity protons and for sugar moieties (Figure 5a). Firstly, this may suggest that the sugar parts adopt a conformation preventing interaction with the side chain of the anions; secondly, it may indicate a close distance of chiral fragments from the binding pocket. Some explanation of origin enantioselective discrimination by **1a** and **1e** we could find in NOESY experiments, where we observe forming hydrogen bonding only by (R)-enantiomers of mandelate with azulene receptors (for more information see Supporting Information). The absence of significant chiral recognition for ligand **1d** and its presence for **1e** shows strong binding of the anion by the chiral receptor is insufficient for successfully recognizing enantiomers.

Impact of the Guest on Chiral Recognition. Model chiral pairs of carboxylates (Man and N-Ac-Phg) exhibit different sizes, acidity, and ability to form hydrogen bonds on the substituent of the α carbon atom. All ligands revealed higher affinity constants toward *N*-Ac-Phg derivatives in comparison to mandalates. We observed enantioselectivity with amino acid derivatives only for receptor **1e**. The results indicate that the guest's structure and complex-forming properties influence the extent of chiral recognition.

Influence of Solvent on Chiral Recognition. Next, to estimate the influence of the solvent on chiral recognition properties, we conducted titration experiments with receptor **1e** in the presence of model chiral anionic guests, mandelate derivatives, used as TBA salts in various solvent mixtures.

The addition of water into the solvent mixture caused a lowering of the binding constant of receptor **1e** with the anions examined (Table 4, entry 1−6). The admixture of 5% water into CD_3CN changed the affinity toward the (*R*) enantiomer. Experiments conducted in CD_3CN + 5% H_2O and DMSO-d_6 + 0.5% H_2O revealed similar binding affinities. Data fitting showed the considerable chiral recognition ability of receptor **1e** in the CD_3CN + 0.5% H_2O mixture and in chloroform (α = 3.1 and 2.1, Table 4, entry 3 and 4, and 9 and 10, respectively). Comparison of the relative polarity of dimethylsulfoxide and acetonitrile (0.460 and 0.444, respectively, Table 1, entry 1 and 2) indicates the low impact of this parameter on the binding affinity. The higher value of DN points to stronger solvation of the host's binding pocket and simultaneously weakened interaction of guest with the ligand (DN_{DMSO} = 29.8 kcal mol^{-1}, DN_{ACN} = 14.1 kcal mol^{-1}). Similarly, the addition of water (DN = 54.8 kcal mol^{-1}) into the solvent mixture causes an increase in environmental competitiveness.

Comparative analysis of the titration curves of receptor **1e** in the CD_3CN + 0.5% H_2O mixture and in chloroform revealed

https://dx.doi.org/10.1021/acs.joc.0c01693
J. Org. Chem. 2020, 85, 11902−11907

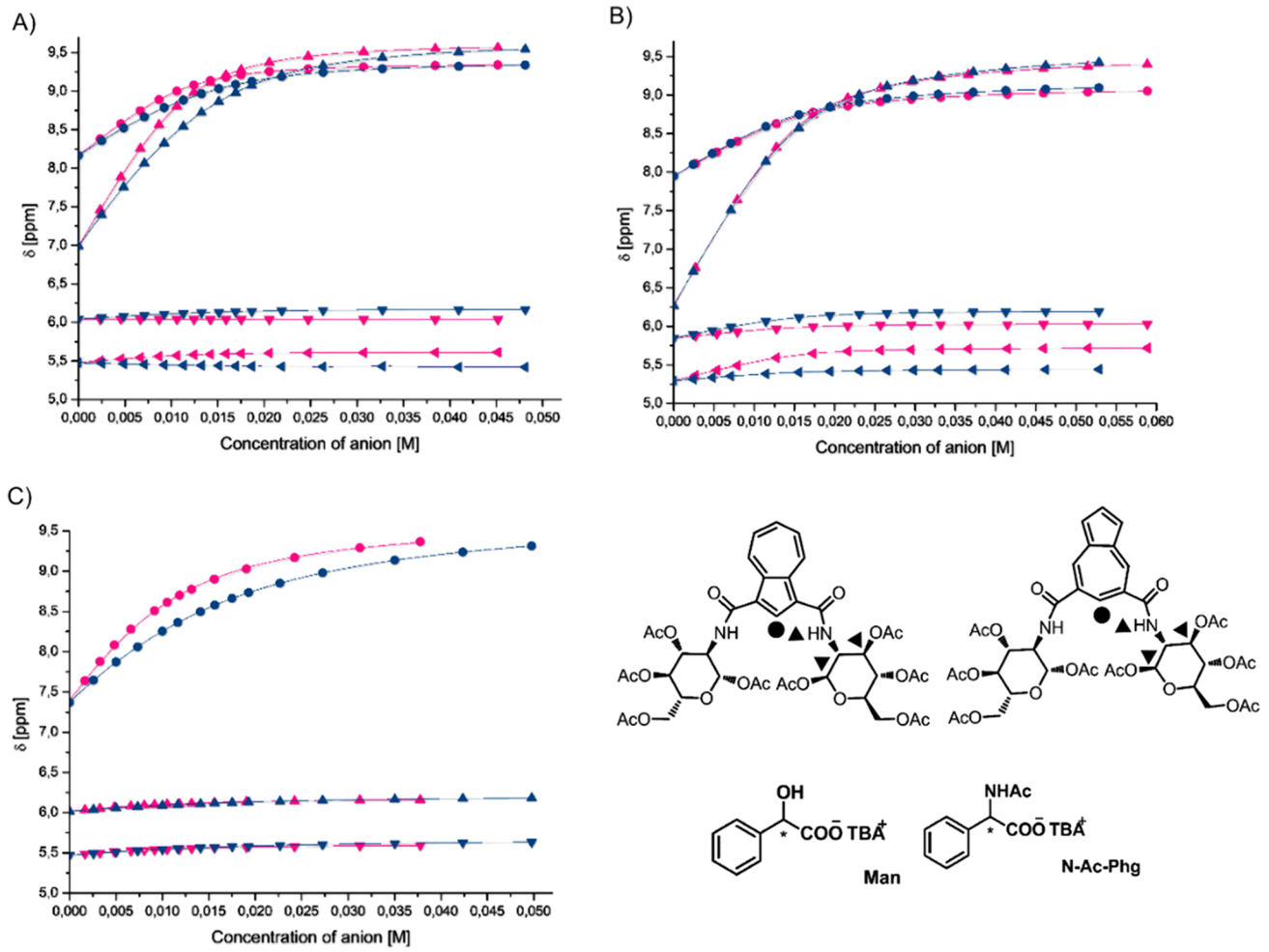


Figure 5. Titration curves of receptor **1e** with Man (*R*, pink; *S*, blue) in (A) CD_3CN + 0.5% H_2O and (B) $CDCl_3$. (C) Receptor **1a** with Man in CD_3CN + 0.5% H_2O.

Table 3. Stability Constants K_a $[M^{-1}]$[a] and Chiral Recognition α for Complexes of Hosts 1a−e with Chiral Anions in CD_3CN + 0.5% H_2O

		1a		1b		1c		1d		1e	
entry	anion	K_a	α	K_a	α	K_a	α	K_a	α[d]	K_a	α[d]
1	*R*-Man	230	2.1	11	1.1	170	1.1	1400[c]	1.2	4400[c]	3.1
2	*S*-Man	110		10		160		1200[c]		1400[c]	
3	L-*N*-Ac-Phg	130	1.1	18	1.1	350	0.9	6900[c]	0.9	$>10^4$[b,c]	[b,c]
4	D-*N*-Ac-Phg	140		20		330		6200[c]		5030[c]	

[a]Values determined by ^{1}H NMR spectroscopy titration experiments at T = 303 K: estimated errors <10%; TBA salts were the sources of the anions. [b]Stability constants above the limit of the ^{1}H NMR titration technique ($K_a > 10^4$); α was estimated. [c]Binding model 1:2 (host:guest), $K_{1:2}$ is omitted, for more details see ESI [d]α given for $K_{R1:1}/K_{S1:1}$.

differences in the formation of diastereomeric complexes, depending on the experimental mixture (Figure 5a,b). In CD_3CN + 0.5% H_2O, we observed disparities in chemical shifts for both the cavity's protons and sugar moieties in relation to the respective enantiomer (Figure 5a). In contrast, similar comparison analysis for chloroform revealed that recognition of stereoisomers occurs by the interaction between the side chain of anion and sugar derivatives with no meaningful difference in chemical shifts of protons in the binding pocket (Figure 5b). These outcomes show that the chosen solvent contributes to the formation of different diastereomeric complexes and to chiral recognition.

CONCLUSIONS

We have reported here the synthesis and anion carboxylate binding properties of a series of chiral receptors bearing glucosamine pendant arms with varied geometries of the binding site. In the course of these studies we discovered the following:

- Comparison of geometric parameters showed that receptors based on a five-membered ring demonstrate the highest affinity toward the carboxylate anion, creating mixed complexes with 1:2 ligand:anion stoichiometry.

https://dx.doi.org/10.1021/acs.joc.0c01693
J. Org. Chem. 2020, 85, 11902−11907

Table 4. Stability Constants K_a $[M^{-1}]$[a] and Chiral Recognition for Complexes of Host 1e with TBA Man in Various Solvent Mixtures

entry	solvent mixture	anion	K_a	α[d]
1	CD_3CN	(*R*)-Man	>10 000[b,c]	[b]
2		(*S*)-Man	>10 000[b,c]	
3	CD_3CN + 0.5% H_2O	(*R*)-Man	4400	3.1
4		(*S*)-Man	1400	
5	CD_3CN + 5% H_2O	(*R*)-Man	11	0.7
6		(*S*)-Man	16	
7	DMSO-d_6 + 0.5% H_2O	(*R*)-Man	11	1.0
8		(*S*)-Man	11	
9	$CDCl_3$	(*R*)-Man	2700	2.1
10		(*S*)-Man	1300	

[a]Values determined by ^{1}H NMR spectroscopy titration experiments at T = 303 K; estimated errors <10%; anions added as TBA salts. [b]Stability constants above the limit of the ^{1}H NMR titration technique ($K_a > 10^4$), α could not be determined. [c]Binding model 1:2 (host:guest), $K_{1:2}$ is omitted, for more details see ESI. [d]α given for $K_{R1:1}/K_{S1:1}$.

- Strong binding of the anion by the chiral receptor is insufficient for successfully recognizing enantiomers; rather, proper conformation is needed to ensure enantioselective interactions.
- The complexation medium has a significant impact on complex formation and on enantiomer differentiation.

Overall, the studies presented above have provided insights into the effects of the geometry and size of the binding cavity on affinity for carboxylate anions and chiral recognition. We evaluated whether the choice of solvent mixture affected the formation of diastereomeric complexes, keeping track of the binding process using the ^{1}H NMR titration technique, and discovered that it does indeed exert an impact. Overall, our findings offer insight into the complementarity of chiral recognition processes.

EXPERIMENTAL SECTION

All precursors for synthesis were obtained from commercial suppliers and were used without further purification. All solvents were of reagent grade quality and were dried under standard conditions. Flash chromatography was carried out using silica gel 60 (63−100 mesh); typically, a 40-fold mass excess of gel was used. TLC analysis was carried out on precoated silica gel plates (60 F254). ^{1}H and ^{13}C NMR spectra were recorded with 400 and 600 MHz NMR instruments. HRMS measurements were performed with ESI ionization and a TOF analyzer.

General Procedure for the Preparation of Diamide Derivatives 1b−1e. The reaction was carried out under argon conditions. To the solution of dichloride acid (1.1 mmol) in dry dichloromethane (100 mL), triethylamine (4.4 mmol) was slowly added. After 5 min of stirring, per-*O*-Ac-glucosamine hydrochloride (2.2 mmol), obtained according to the literature procedure,[17] was added and the reaction mixture was stirred overnight. Afterward, the reaction mixture was washed with 0.1 M HCl (2 × 50ml), saturated $NaHCO_3$ (2 × 50ml), and water (1 × 50ml). Then, the organic phase was separated and was dried over $MgSO_4$, and then filtrated and evaporated under vacuum. The crude product was purified using silica gel column chromatography with mixtures of dichlomethane and metanol (200:1 > 30:1, v/v] as eluents. The product was crystallized from a dichloromethane:hexane (1:3 v/v) mixture, yielding as solid.

Receptor 1a. The reaction was carried out under argon conditions. To the solution of diacid **2a** (216 mg, 1 mmol) (obtained according to the literature procedure)[19] in dry DMF (100 mL) , triethylamine (1.4 mL, 10 mmol) was slowly added followed with HBTU (1.5 g, 4 mmol). After 10 min of stirring, per-*O*-Ac-glucosamine hydrochloride (1.5 g, 4 mmol), obtained according to the literature procedure,[17] was added and the reaction mixture was stirred overnight. Afterward, the mixture was concentrated on a rotary evaporator to 1/3 of the starting volume and water (10 mL) was added and the precipitate was washed with water. The crude product was purified by column chromatography on silica gel with the dichloromethane:methanol (99:1, v/v) mixture as an eluent. The product was crystallized from the dichloromethane:hexane (1:3, v/v) mixture yielding **1a** (0.5 g, 57%) as blue solid. Mp: 124−127 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.88 (d, J = 8.9 Hz, 2H), 8.75 (d, J = 1.7 Hz, 2H), 8.47 (s, 1H), 8.07 (t, J = 3.8 Hz, 1H), 7.73 (d, J = 3.8 Hz, 2H), 5.95 (d, J = 8.8 Hz, 2H), 5.41 (t, J = 9.9 Hz, 2H), 5.02 (t, J = 9.6 Hz, 2H), 4.30−4.20 (m, 4H), 4.08−4.01 (m, 4H), 2.05 (s, 6H), 2.04 (s, 6H), 2.01 (s, 6H), 1.92 (s, 6H). ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ = 170.0, 169.7, 169.2, 168.9, 168.9, 138.7, 137.2, 136.4, 135.5, 127.4, 124.4, 91.8, 72.4, 71.7, 68.0, 61.5, 53.4, 45.8, 20.5, 20.4, 20.3. HRMS (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{40}H_{46}N_2O_{20}Na$, 897.2542; found, 897.2523. Anal. Calcd for $C_{40}H_{46}N_2O_{20}$: C, 54.92; H, 5.30; N, 3.20. Found: C, 54.81; H, 5.40; N, 3.25.

Receptor 1b. Receptor **1b** was prepared according to the general procedure using commercially available 2,6-pyridinedicarbonyl dichloride (0.51 g, 2.5 mmol) yielding the product (1.35 g, 65%) as white powder. Mp: 196−197 °C. ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ = 8.32 (d, J = 9.4 Hz, 2H), 8.21−8.16 (m, 2H), 8.11 (dd, J = 8.6, 6.7 Hz, 1H), 6.03 (d, J = 8.7 Hz, 2H), 5.62−5.54 (m, 2H), 5.19 (t, J = 9.8 Hz, 2H), 4.27 (dt, J = 13.5, 5.8 Hz, 4H), 4.12 (dd, J = 12.4, 2.2 Hz, 2H), 3.99 (ddd, J = 10.0, 4.7, 2.3 Hz, 2H), 2.04 (s, 6H), 2.04 (s, 6H), 1.99 (s, 6H), 1.87 (s, 6H). ^{13}C{H} NMR (100 MHz DMSO-d_6): δ = 172.1, 171.3, 170.5, 170.1, 164.6, 149.2, 140.8, 125.6, 93.4, 73.8, 73.2, 68.9, 62.7, 54.5, 21.0, 21.0, 20.9, 20.9. HRMS (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{35}H_{43}N_3O_{20}Na$, 847.2385; found, 847.2356. Anal. Calcd for $C_{35}H_{43}N_3O_{20}$: C, 50.91; H, 5.25; N, 5.09. Found: C, 50.89; H, 5.30; N, 5.13.

Receptor 1c. Receptor **1c** was prepared according to the general procedure using commercially available isophthaloyl dichloride (0.5 g, 2.5 mmol) yielding the product (1.5 g, 75%) as white powder. Mp: 117−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.74 (d, J = 9.0 Hz, 2H), 8.17 (s, 1H), 7.87 (d, J = 6.7 Hz, 2H), 7.60 (t, J = 7.7 Hz, 1H), 5.91 (d, J = 8.7 Hz, 2H), 5.37 (t, J = 9.9 Hz, 2H), 4.99 (t, J = 9.6 Hz, 2H), 4.24 (m, J = 10.2 Hz, 4H), 4.01 (m, J = 11.3 Hz, 4H), 2.03 (s, 6H), 2.00 (s, 6H), 2.00 (s, 6H), 1.86 (s, 6H). ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ = 170.0, 169.6, 169.2, 168.8, 165.8, 134.2, 129.8, 128.6, 126.2, 91.8, 72.4, 71.7, 68.0, 61.5, 52.7, 20.5, 20.4, 20.4, 20.2. HRMS (ESI−TOF) m/z: $[M + Na]^+$ calcd for: $C_{36}H_{44}N_2O_{20}Na$, 847.2385; found, 847.2356. Anal. Calcd for $C_{36}H_{44}N_2O_{20}\cdot 0.5\ H_2O$: C, 51.86; H, 5.44; N, 3.36. Found: C, 51.57; H, 5.54, N, 3.36.

Receptor 1d. Receptor **1d** was prepared according to the general procedure using acid dichloride obtained according to the literature procedure[18] (0.155 g, 1 mmol) yielding the product (320 g, 42%) as white powder. Mp: 231−234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.82 (s, 1H), 8.40 (d, J = 8.6 Hz, 2H), 6.67 (s, 2H), 5.85 (d, J = 8.8 Hz, 2H), 5.30 (t, J = 10.1 Hz, 2H), 4.96 (t, J = 9.7 Hz, 2H), 4.28−4.09 (m, 4H), 4.03 (t, J = 11.1 Hz, 4H), 2.02 (s, 6H), 2.00 (s, 6H), 1.99 (s, 6H), 1.86 (s, 6H).^{13}C{H} NMR (100 MHz, DMSO-d_6): δ = 170.0, 169.5, 169.2, 168.8, 159.6, 128.4, 111.9, 91.8, 72.2, 71.5, 68.1, 61.5, 52.1, 20.5, 20.5, 20.4, 20.3. HRMS (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{34}H_{43}N_3O_{20}Na$, 836.2338; found, 836.2349. Anal. Calcd for $C_{34}H_{43}N_3O_{20}\cdot H_2O$: C, 49.10; H, 5.45; N, 5.05. Found: C, 49.13; H, 5.26; N, 5.02.

Receptor 1e. Receptor **1e** was prepared according to the general procedure using acid dichloride obtained according to the literature procedure[16] (0.380 g, 1.5 mmol) yielding the product (750 g, 75%) as purple powder. Mp: 223−226 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, J = 9.6 Hz, 2H), 8.45 (d, J = 8.7 Hz, 2H), 8.33 (s, 1H), 8.06 (t, J = 9.2 Hz, 1H), 7.72 (t, J = 9.7 Hz, 2H), 5.96 (d, J = 8.7 Hz, 2H), 5.44 (t, J = 9.9 Hz, 2H), 5.00 (t, J = 9.4 Hz, 2H), 4.30 (dd, J = 36.2, 9.4 Hz, 4H), 4.04 (d, J = 11.7 Hz, 4H), 2.04 (s, 12H), 2.00 (s, 6H), 1.87 (s, 6H). ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ = 170.0, 169.7, 169.2, 168.9, 165.0, 141.4, 140.3, 138.8, 135.8, 128.7, 119.8, 92.0,

https://dx.doi.org/10.1021/acs.joc.0c01693
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72.6, 71.6, 68.2, 61.5, 52.2, 20.6, 20.5, 20.4, 20.3. HRMS (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{40}H_{46}N_2O_{20}Na$, 897.2542; found, 897.2515. Anal. Calcd for $C_{40}H_{46}N_2O_{20}$: C, 54.92; H, 5.30; N, 3.20. Found: C, 54.86; H, 5.44; N, 3.15.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01693.

Details concerning the determination of binding constants, TBA salt preparation, titration curves, changes in ^1H NMR spectra, and copies of ^1H and ^{13}C spectra (PDG)

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The manuscript was written through contributions of both authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to acknowledge Poland's National Science Centre (2016/21/B/ST5/03352) for the financial support.

■ REFERENCES

(1) Luisi, P. L. *The Emergence of Life: From Chemical Origins to Synthetic Biology*; Cambridge Univ. Press: 2006.

(2) (a) Guijarro, A.; Yus, M. *The Origin of Chirality in the Molecules of Life: A Revision from Awareness to the Current Theories and Perspectives of this Unsolved Problem*; Royal Society of Chemistry: 2009; (b) Wagnière, G. H. *On Chirality and the Universal Asymmetry: Reflections on Image and Mirror Image*; John Wiley & Sons: 2007, DOI: 10.1002/9783906390598.

(3) Steppeler, F.; Iwan, D.; Wojaczyńska, E.; Wojaczyński, J. Chiral thioureas-preparation and significance in asymmetric synthesis and medicinal chemistry. *Molecules* **2020**, *25*, 401.

(4) (a) Wang, Q.; Zhong, Y.; Miller, D. P.; Lu, X.; Tang, Q.; Lu, Z.-L.; Zurek, E.; Liu, R.; Gong, B. Self-Assembly and Molecular Recognition in Water: Tubular Stacking and Guest-Templated Discrete Assembly of Water-Soluble, Shape-Persistent Macrocycles. *J. Am. Chem. Soc.* **2020**, *142*, 2915−2924. (b) Taylor, M. S. Anion recognition based on halogen, chalcogen, pnictogen and tetrel bonding. *Coord. Chem. Rev.* **2020**, *413*, 213270.

(5) Berthod, A. *Chiral Recognition in Separation Methods. Mechanisms and Applications*; Springer-Verlag: Berlin Heidelberg, 2010; *XIV*, 337.

(6) (a) Kühnle, A.; Linderoth, T. R.; Hammer, B.; Besenbacher, F. Chiral recognition in dimerization of adsorbed cysteine observed by scanning tunnelling microscopy. *Nature* **2002**, *415*, 891−893. (b) De Cat, I.; Guo, Z.; George, S. J.; Meijer, E. W.; Schenning, A. P. H. J.; De Feyter, S. Induction of Chirality in an Achiral Monolayer at the Liquid/Solid Interface by a Supramolecular Chiral Auxiliary. *J. Am. Chem. Soc.* **2012**, *134*, 3171−3177.

(7) (a) Gaeta, M.; Sortino, G.; Randazzo, R.; Pisagatti, I.; Notti, A.; Fragalá, M. E.; Parisi, M. F.; D'Urso, A.; Purrello, R. Long-Range Chiral Induction by a Fully Noncovalent Approach in Supramolecular Porphyrin-Calixarene Assemblies. *Chem. − Eur. J.* **2020**, *26*, 3515−3518. (b) Lawrence, D. S.; Jiang, T.; Levett, M. Self-Assembling Supramolecular Complexes. *Chem. Rev.* **1995**, *95*, 2229−2260.

(8) Hembury, G. A.; Borovkov, V. V.; Inoue, Y. Chirality-Sensing Supramolecular Systems. *Chem. Rev.* **2008**, *108*, 1−73.

(9) Cai, W.; Yu, Y.; Shao, X. Chiral recognition of aromatic compounds by β-cyclodextrin based on bimodal complexation. *J. Mol. Mod.* **2005**, *11*, 186−193.

(10) Krygowski, T. M.; Fawcett, W. R. Complementary Lewis acid-base description of solvent effects. I. Ion-ion and ion-dipole interactions. *J. Am. Chem. Soc.* **1975**, *97*, 2143−2148.

(11) Izatt, R. M.; Wang, T.; Hathaway, J. K.; Zhang, X. X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C. Y.; Huszthy, P. Factors influencing enantiomeric recognition of primary alkylammonium salts by pyridino-18-crown-6 type ligands. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 157−175.

(12) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*; Fourth Edition; John Wiley & Sons: 2010.

(13) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Third Edition; John Wiley & Sons: 2003.

(14) (a) Dabrowa, K.; Ulatowski, F.; Lichosyt, D.; Jurczak, J. Catching the chloride: searching for non-Hofmeister selectivity behavior in systematically varied polyamide macrocyclic receptors. *Org. Biomol. Chem.* **2017**, *15*, 5927−5943. (b) Cholewiak, A.; Stepniak, P.; Jurczak, J. Linear Neutral Receptors for Anions: Synthesis, Structure and Applications. *Synthesis* **2018**, *50*, 4555−4568.

(15) (a) Lichosyt, D.; Wasiłek, S.; Jurczak, J. Exploring the Chiral Recognition of Carboxylates by C_2-Symmetric Receptors Bearing Glucosamine Pendant Arms. *J. Org. Chem.* **2016**, *81*, 7342−7348. (b) Stibor, I.; Zlatušková, P. Chiral Recognition of Anions. In *Anion Sensing*; Stibor, I., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2005; 31−63. (c) Granda, J. M.; Jurczak, J. Exploration of the Chiral Recognition of Sugar-Based Diindolylmethane Receptors: Anion and Receptor Structures. *Chem. - Eur. J.* **2015**, *21*, 16585−16592.

(16) Zieliński, T.; Kędziorek, M.; Jurczak, J. Bisamides Derived from Azulene-1,3- and −5,7-dicarboxylic Acids as New Building Blocks for Anion Receptors. *Chem. − Eur. J.* **2008**, *14*, 838−846.

(17) Krishnamurthy, V. R.; Dougherty, A.; Kamat, M.; Song, X.; Cummings, R. D.; Chaikof, E. L. Synthesis of an Fmoc-threonine bearing core-2 glycan: A building block for PSGL-1 via Fmoc-assisted solid-phase peptide synthesis. *Carbohydr. Res.* **2010**, *345*, 1541−1547.

(18) Zieliński, T.; Jurczak, J. Thioamides versus amides in anion binding. *Tetrahedron* **2005**, *61*, 4081−4089.

(19) Lichosyt, D.; Dydio, P.; Jurczak, J. Azulene-Based Macrocyclic Receptors for Recognition and Sensing of Phosphate Anions. *Chem. − Eur. J.* **2016**, *22*, 17673−17680.

(20) Thordarson, P. Determining association constants from titration experiments in supramolecular chemistry. *Chem. Soc. Rev.* **2011**, *40*, 1305−1323.

(21) (a) Ulatowski, F.; Dąbrowa, K.; Bałakier, T.; Jurczak, J. Recognizing the Limited Applicability of Job Plots in Studying Host−Guest Interactions in Supramolecular Chemistry. *J. Org. Chem.* **2016**, *81*, 1746−1756. (b) Brynn Hibbert, D.; Thordarson, P. The death of the Job plot, transparency, open science and online tools, uncertainty estimation methods and other developments in supramolecular chemistry data analysis. *Chem. Comm.* **2016**, *52*, 12792−12805.

(22) Frassineti, C.; Ghelli, S.; Gans, P.; Sabatini, A.; Moruzzi, M. S.; Vacca, A. Nuclear Magnetic Resonance as a Tool for Determining Protonation Constants of Natural Polyprotic Bases in Solution. *Anal. Biochem.* **1995**, *231*, 374−382.