28. Molecular Clefts Derived from 9,9′-Spirobi[9*H*-fluorene] for Enantioselective Complexation of Pyranosides and Dicarboxylic Acids

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The molecular clefts (*R*)- and (*S*)-**3**, incorporating 9,9′-spirobi[9*H*-fluorene] as a spacer and two *N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide (CONH(naphthy)) units as H-bonding sites were prepared *via* the bis(succinimid-*N*-yl esters) of (*R*)- and (*S*)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylic acid (**5**). Derivative **6**, with one CONH(naphthy) unit and one succinimid-*N*-yl ester residue allowed easy access to spirobifluorene clefts with two different H-bonding sites, as exemplified by the synthesis of **4**. Binding studies with (*R*)- and (*S*)-**3** and optically active dicarboxylic acids in $CDCl_3$ exhibited differences in free energy of the formed diastereoisomeric complexes ($\Delta(\Delta G°)$) between 0.5 and 1.6 kcal mol^{-1} (T 300 K). Similar enantioselectivities were observed with the spirobifluorene clefts (*R*)- and (*S*)-**1**, bearing two *N*-(6-methylpyridin-2-yl)carboxamide (CONH(py)) H-bonding sites. The thermodynamic quantities $\Delta H°$ and $\Delta S°$ for the recognition processes with (*R*)- and (*S*)-**1** were determined by variable-temperature ^{1}H-NMR titrations and compared to those with (*R*)- and (*S*)-**2**, which have two CONH(py) moieties attached to the 6,6′-positions of a conformationally more flexible 1,1′-binaphthyl cleft. All association processes showed high enthalpic driving forces which are partially compensated by unfavorable changes in entropy. Pyranosides bind to the optically active clefts **1** and **3** in $CDCl_3$ with $-\Delta G° = 3.0$–4.3 kcal mol^{-1}. Diastereoisomeric selectivities up to 1.2 kcal mol^{-1} and enantioselectivities up to 0.4 kcal mol^{-1} were observed. Cleft **4** and *N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)acetamide (**25**) complexed pyranosides **22**–**24** as effectively as **3** indicating that only one CONH(naphthy) site in **3** associates strongly with the sugar derivatives. Based on the X-ray crystal structure of **3**, a computer model for the complex between (*S*)-**3** and pyranoside **22** was constructed. Molecular-dynamics (MD) simulations showed that differential geometrical constraints are at the origin of the high enantioselectivity in the complexation of dicarboxylic acid (*S*)-**7** by (*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**3**.

1. Introduction. – Chiral molecular recognition of small neutral biomolecules with synthetic optically active receptors is a widely pursued goal in supramolecular chemistry. Both molecular clefts [1–6] and cyclophanes [7] [8] have been tested as receptors in a variety of studies which helped establishing two important guidelines for efficient chiral recognition: both *a*) a high degree of preorganization of the receptor and *b*) oriented host-guest interactions such as H-bonding are essential for the selective complexation of one substrate enantiomer over the other [3]. Carbohydrates play a crucial role in important biological recognition processes such as cell-cell and cell-virus recognition [9] [10]. Several X-ray crystal structures of protein-carbohydrate complexes [11] showed that binding occurs *via* an extensive network of H-bonds, that are often ionic, and also by apolar interactions. Carbohydrates currently represent the most challenging class of biosubstrates in synthetic molecular-recognition studies, yet the ability to complex a specific sugar with an artificial receptor is still only poorly developed. *Greenspoon* and *Wachtel* [12] proposed reverse micelles as model systems for carbohydrate-binding proteins and used them to solubilize monosaccharides in apolar solvents. Recognition of

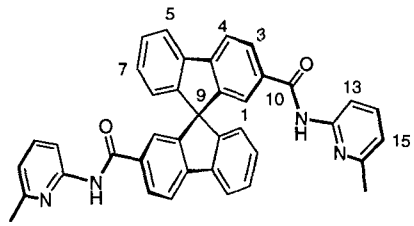
saccharides by derivatives of boronic acids through reversible boronate ester formation was reported by the groups of *Shinkai* and *Aoyama* in various media [13], and *Smith* and coworkers showed that boronic acids facilitate the transport of glucose and glycosides through lipid bilayer membranes [14]. Similar transport processes of saccharide derivatives have also been reported by the groups of *Czarnik* [15] and *Shinbo* [16]. *Savage* and *Gellman* complexed hexosammonium ions selectively in $MeOH/CHCl_3$ mixtures by a macrocycle which incorporates a phosphine-oxide and two sulfoxide residues as H-bond acceptor sites [17]. Complexation of carbohydrates in aqueous solutions [18] remains an even greater challenge. *Penadés* and coworkers showed that cyclodextrin-cyclophane hybrid receptors ('glycophanes') complex nitrophenyl glycosides in H_2O mainly due to apolar interactions [19]. *Aoyama* and coworkers observed weak complexation between sugars and cyclic resorcinol tetramers or β-cyclodextrins [20]. *Poh* and *Tan* reported binding of monomethylated sugars by 'cyclotetrachromotropylene', a cyclophane composed of four bridged 1,8-dihydroxynaphthalene-3,6-disulfonates [21]. *Eliseev* and *Schneider* studied the binding of ribose phosphate by protonated aminocyclodextrins and showed that H-bonds between the receptor and the ribose unit contribute to the association strength [22].

Insight into how selectivity in binding carbohydrates by way of H-bonding can be obtained has been gained mainly in binding studies in $CHCl_3$ with macrocyclic hosts and pyranosides [23] [24]. Diastereo- and enantioselective recognition with a 'cholaphane' receptor, composed of two bridged cholic acids, was reported by *Davis* and coworkers [25]. Enantioselectivity in complexation was also obtained by *Liu* and *Still* in studies with a C_3-symmetrical macrotricyclic receptor which binds its substrates by H-bonding to an array of peptide bonds ($-NHC(=O)-$) that line the rim of the binding cavity [7e]. Despite these advances, general guidelines for designing diastereo- and enantioselective receptors for carbohydrates are still missing, and the efficient binding of the three-dimensional arrangement of OH groups in sugars, as seen in the X-ray crystal structures of protein-sugar complexes [11], has yet to be achieved. Recognition of carbohydrates is further complicated by the formation of intramolecular H-bonds, as *Anslyn* and coworkers showed recently in studies with cyclitols [26].

We have started a program with the goals to develop selective carbohydrate receptors, both of the cleft- and cyclophane-type, to identify in systematic studies the individual contributions of non-ionic and ionic H-bonding and apolar interactions to complexation in various solvents, and ultimately to enable a rational design of carbohydrate binding agents for potential uses in biological studies and therapeutic applications. Here, we present first studies on diastereo- and enantioselective pyranoside binding by simple cleft-type receptors *via* H-bonding in $CHCl_3$, a solvent that does not compete with the binding partners for the H-bonds.

The second class of substrates in this study were derivatives of excitatory amino acids which play an important role in neurochemical recognition processes [27]. A variety of approaches to the complexation of di- and tricarboxylic acids have been developed [4], [28–30] although the receptors employed were mostly achiral. In a preliminary communication of parts of this work [3], we had shown high enantioselectivities in the complexation of derivatives of aspartic acid, glutamic acid, and other dicarboxylic acids by the rigid H-bonding clefts (*R*)- and (*S*)-**1**, and here we present additional results with new, structurally related optically active receptors.

The cleft-type receptors **1**–**4** employed in this study on pyranoside and dicarboxylic-acid binding feature 9,9′-spirobi[9*H*-fluorene] and 1,1′-binaphthyl spacers which had previously been successfully incorporated into crown ethers for chiral recognition of optically active ammonium ions [31] [32]. Receptors **1** and **2** bear two *N*-(6-methylpyridin-2-yl)carboxamide (CONH(py)) moieties as H-bonding sites which had been introduced by *Hamilton* and coworkers for strong complexation of dicarboxylic acids [5] [29]. Compounds **3** and **4** have *N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide (CONH(naphthy)) residues attached, which in the past also served as H-bonding sites in a variety of receptors [33].



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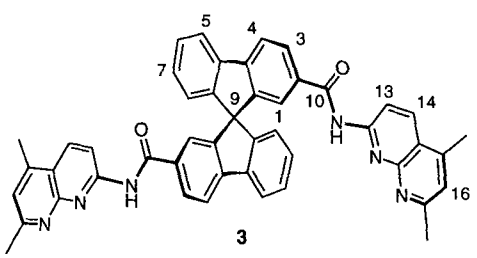

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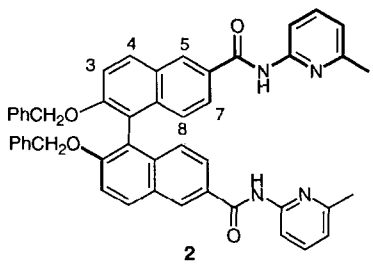

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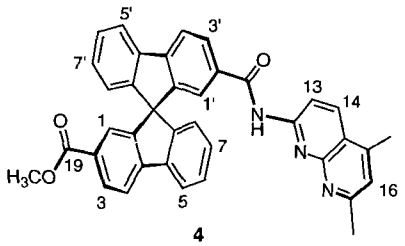

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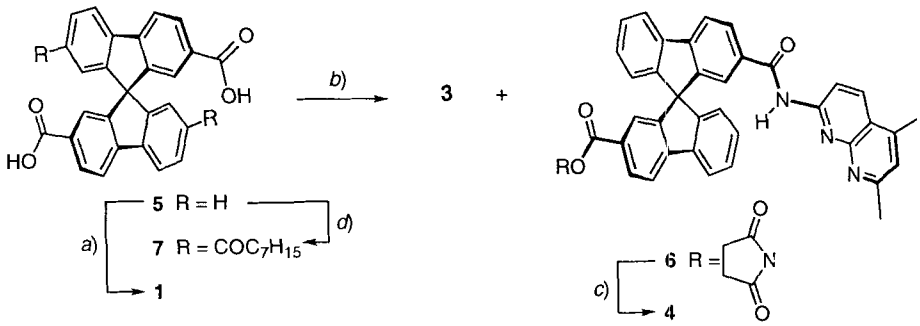
2. Results and Discussion. – 2.1. *Synthesis.* Clefts (*R*)- and (*S*)-**1** were prepared following previously published procedures [30] [34] by reacting the bis(acyl chloride) derivatives of the dicarboxylic acids (*R*)- and (*S*)-**5**, respectively, with 6-methylpyridin-2-amine (*Scheme 1*). For the synthesis of the new receptors (*R*)- and (*S*)-**3**, (*R*)- and (*S*)-**5** were converted to the corresponding bis(succinimid-*N*-yl esters) which reacted with commercial 5,7-dimethyl-1,8-naphthyridin-2-amine to yield (*R*)- and (*S*)-**3**, respectively. Since the displacement of the *N*-hydroxysuccinimide leaving group by this poor nucleophile was slow, (*R*)- and (*S*)-**6** could also be isolated in significant yield. This provided easy access to clefts with two different H-bonding sites as exemplified by the preparation of (*R*)- and (*S*)-**4** simply by reacting (*R*)- and (*S*)-**6**, respectively, with MeOH. The diacid (*S*)-**7** was synthesized by *Friedel-Crafts* reaction from (*S*)-**5**.

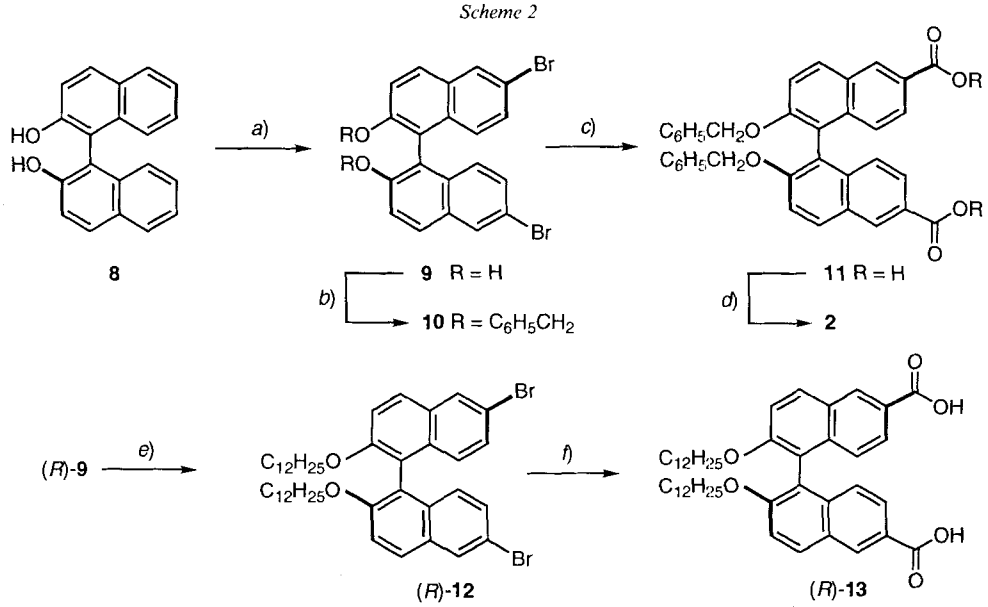
The synthesis of the clefts (*R*)- and (*S*)-**2** started from (*R*)- and (*S*)-1,1′-binaphthyl-2,2′-diol (**8**) [35], respectively, which were brominated to (*R*)- and (*S*)-**9** and converted to (*R*)- and (*S*)-**10** by *Williamson* ether synthesis [36] (*Scheme 2*). Reaction with BuLi followed by CO_2 led to (*R*)- and (*S*)-**11**, which were transformed into (*R*)- and (*S*)-**2**,

Scheme 1



a) 1) $SOCl_2$, pyridine; 2) 6-methylpyridin-2-amine, THF; 79% [30]. *b*) 1) *N*-Hydroxysuccinimide, DCC, THF, *Δ*; 2) 5,7-dimethyl-1,8-naphthyridin-2-amine, $CHCl_3$, *Δ*; 29% (**3**) and 30% (**6**). *c*) MeOH, NEt_3, *Δ*; 80%. *d*) $C_7H_{15}COCl$, $AlCl_3$, CS_2; 68%.

Scheme 2



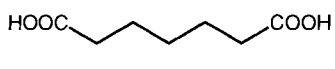
a) Br_2, CH_2Cl_2; 94%. *b*) K_2CO_3, $C_6H_5CH_2Cl$, DMF, *Δ*; 79%. *c*) BuLi, THF, −78°, then CO_2; 88% [30]. *d*) 1) $SOCl_2$; 2) 6-methylpyridin-2-amine, NEt_3, THF; 95% [30]. *e*) K_2CO_3, $C_{12}H_{25}I$, DMF, *Δ*; 66%. *f*) BuLi, THF, −78° then CO_2; 67%.

respectively, *via* corresponding bis(acyl chlorides) [30]. By a similar route, (*R*)-**9** gave (*R*)-**12** and subsequently (*R*)-**13**, one of the guests in the binding studies described in the following.

2.2. *Complexation Studies.* Unless otherwise stated, ^{1}H-NMR binding titrations with one of the binding partners kept at constant concentration were performed at 300 K in dry $CDCl_3$ at fast host-guest exchange. Precautions were taken to keep the conditions

constant since traces of moisture have been shown to strongly influence the results of complexation studies with H-bonding systems in aprotic solvents [37]. Due to the sensitivity of the chemical shift of the amide proton to traces of H_2O and acidic or basic impurities, the complexation-induced changes in chemical shift $\Delta\delta$ of at least one additional, nonacidic proton were evaluated in the titrations. The association constants K_a (1 mol^{-1}) and binding free energies $\Delta G°$ (kcal mol^{-1}) were obtained by nonlinear least-squares curve-fitting of the experimental titration data. *Job* plots [38] were performed on a sufficient number of complexes, so that 1:1 stoichiometry can be assumed for all associations studied. Dilution experiments showed that receptors **3** and **4** do not self-aggregate in the concentration range 0.2–10 mM. Changes in enthalpy $\Delta H°$ (kcal mol^{-1}) and entropy $T\Delta S°$ (kcal mol^{-1}) were determined by *van't Hoff* analysis of variable-temperature ^{1}H-NMR binding titrations between 280 and 318 K. The values of the association constants K_a of all investigated complexes decreased strongly with increasing temperature. The *van't Hoff* plots obtained were all linear, so that changes in heat capacity within the chosen temperature range were considered insignificant.

2.2.1. *Complexation of Dicarboxylic Acids.* The results obtained from dicarboxylic-acid binding by (*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**2** are shown in *Table 1*. Enantioselectivities of 0.9 kcal mol^{-1} and 0.8 kcal mol^{-1} are observed in the complexation of *N*-(benzyloxycarbonyl)-L-aspartic acid (Cbz-Asp; **15**; *Entries 2* and *3*) and *N*-(benzyloxycarbonyl)-L-glutamic acid (Cbz-Glu; **17**; *Entries 6* and *7*), respectively. The relative orientation of the two COOH groups in the glutamic-acid derivatives **17** and **18** with odd-membered chains (= odd number of chain members) differs strongly from that in the aspartic-acid derivatives **15** and **16** with even-membered chains. As a result, the configuration of the host showing the strongest binding is reversed: while (*R*)-**1** forms the strongest complex with the glutamates (*Entries 6* and *8*), (*S*)-**1** is the best binder of aspartates (*Entries 3* and *5*). In general, the association strength is stronger for the glutamic-acid derivatives. Complexes



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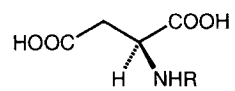
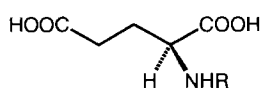
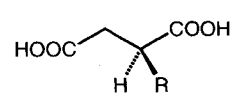


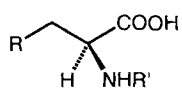
15 R = $C_6H_5CH_2OCO$ (Cbz)
16 R = BuOCO



17 R = Cbz
18 R = BuOCO



19 R = C_6H_5S
20 R = C_6H_5Se



21	**R**	**R'**
a	OH	Cbz
b	C_6H_5	Cbz
c	C_6H_5	C_6H_5NHCO
d	H_2NCOCH_2	Cbz
e	C_6H_5NHCOO	Cbz

Table 1. *Evaluated Host Protons, Association Constants* K_a, *and Binding Free Energies* $\Delta G°$ (uncertainties: ±0.2 kcal mol^{-1}) *of the Complexes Formed between Clefts* (R)- *and* (S)-**1** *and* (R)- *and* (S)-**2** *with Dicarboxylic Acids in* $CDCl_3$ *at 293 K*

Entry	Host	Guest	Evaluated protons ($\Delta\delta_{sat}$[a]); $\Delta\delta_{obs}$[b]))	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
1	**1**	**14**	NH (1.73; 1.52)	1700	−4.3
			H–C(1) (0.02; 0.02)		
2	(*R*)-**1**	**15**	H–C(3) (0.19; 0.14)	820	−3.9
3	(*S*)-**1**	**15**	H–C(3) (0.12; 0.11)	4200	−4.8
4	(*R*)-**1**	**16**	H–C(1) (0.25; 0.20)	1400	−4.2
5	(*S*)-**1**	**16**	H–C(1) (0.13; 0.13)	4800	−4.9
6	(*R*)-**1**	**17**	NH (2.57; 2.50)	14000	−5.6
			H–C(1) (0.24; 0.24)		
7	(*S*)-**1**	**17**	NH (2.20; 2.03)	3900	−4.8
			H–C(1) (0.21; 0.20)		
8	(*R*)-**1**	**18**	H–C(1) (0.24; 0.24)	23000	−5.8
9	(*S*)-**1**	**18**	H–C(1) (0.20; 0.20)	10000	−5.4
10	(*R*)-**1**	**19**	NH (2.82; 1.95)	680	−3.8
			H–C(1) (0.31; 0.21)		
11	(*S*)-**1**	**19**	NH (2.51; 2.28)	3400	−4.7
			H–C(1) (0.18; 0.16)		
12	(*R*)-**1**	**20**	NH (2.51; 1.94)	800	−3.9
			H–C(1) (0.28; 0.20)		
13	(*S*)-**1**	**20**	NH (2.51; 2.18)	2200	−4.5
			H–C(1) (0.21; 0.17)		
14	(*R*)-**1**	**21b**	NH (1.53; 0.99)	420	−3.5
15	(*S*)-**1**	**21b**	NH (1.25; 0.90)	680	−3.8
16	(*R*)-**1**	(*S*)-**7**	NH (1.09; 0.72)	490	−3.6
17	(*S*)-**1**	(*S*)-**7**	NH (1.65; 1.65)	11300	−5.4
			H–C(1) (0.20; 0.20)		
18	**2**	**14**	H–C(5) (0.14; 0.13)	2500	−4.6
19	(*R*)-**2**	**17**	H–C(5) (0.10; 0.10)	20800	−5.8
20	(*S*)-**2**	**17**	H–C(5) (0.10; 0.10)	19400	−5.7
21	(*R*)-**2**	(*R*)-**13**	H–C(5) (0.24; 0.24)	8500	−5.3
22	(*S*)-**2**	(*R*)-**13**	H–C(5) (0.07; 0.07)	7200	−5.2

[a]) Change in chemical shift at saturation binding. [b]) Largest change in chemical shift observed during the titration.

of Cbz and butyloxycarbonyl derivatives show similar binding strength in each case (*Entries 2–9*), which indicates that there are no special aromatic interactions between the Ph rings of the Cbz moieties and the spirobifluorene spacer. High enantioselectivities, up to $\Delta(\Delta G°) = 0.9$ kcal mol^{-1}, are also observed in the complexation of the succinic-acid derivatives **19** and **20** (*Entries 10–13*). Since **19** and **20** have the same configuration as the aspartic-acid derivatives, they undergo the strongest association with the (*S*)-receptor. Monocarboxylic acids **21a–e**, which contain additional H-bonding functionality such as hydroxy, amide, and carbamate residues, only form weak complexes with poor enantioselectivities (*Entries 14* and *15*), which demonstrates that two COOH groups in the substrate are necessary for strong binding and effective chiral recognition.

A particularly high enantioselectivity of $\Delta(\Delta G°) = 1.8$ kcal mol^{-1} is observed in the complexation of 9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylic acid (*S*)-**7**, which is a derivative of (*S*)-**5**, the direct synthetic precursor to the (*S*)-configurated receptor. Diacid (*S*)-**7**

is bound more strongly by the similarly configurated receptor (*S*)-**1** (*Entry 17*) than by the receptor of opposite configuration (*R*)-**1** (*Entry 16*). Since the association strength of the weaker complex is in the range ($K_a \approx 100$–400 l mol^{-1}) of those measured for the recognition between one COOH and one CONH(py) residue [4] [30], it is assumed that, for steric reasons, only one of the two COOH groups in (*S*)-**7** can interact with the H-bonding sites in (*R*)-**1**. This assumption is experimentally supported by the complexation-induced changes in chemical shift at saturation binding ($\Delta\delta_{sat}$) for the averaged resonances of the two receptor NH protons in the diastereoisomeric complexes. Whereas the NH resonance in the (*S*)-**1**·(*S*)-**7** complex is shifted downfield by $\Delta\delta_{sat} = 1.65$ ppm, indicating participation of both CONH(py) moieties in the recognition process, the corresponding downfield shift $\Delta\delta_{sat}$ in the (*R*)-**1**·(*S*)-**7** complex amounts to only 1.09 ppm, in agreement with only one NH proton participating in the H-bonding. Computational studies described below provide support for this analysis of the experimental data.

The findings with the 1,1′-binaphthyl receptors (*R*)- and (*S*)-**2** sharply contrast those with the spirobifluorene system. According to CPK models and computer modeling, the two CONH(py) sites in **1** and **2** can readily adopt similar positions and orientations. Correspondingly, heptanedioic acid (**14**) forms complexes of similar stability with both receptors (*Entries 1* and *18*). However, the binaphthyl receptor does not show enantioselectivity in complexation. Both (*R*)- and (*S*)-**2** form stable diastereoisomeric complexes of nearly identical association strength with Cbz-Glu (**17**) (*Entries 19* and *20*) or with 1,1′-binaphthyl-6,6′-dicarboxylic acid (*R*)-**13** (*Entries 21* and *22*). These experimental findings support in an impressive way that a high degree of receptor preorganization and conformational homogeneity is a requirement for efficient chiral recognition. In contrast to the rigid spirobifluorene cleft, the 1,1′-binaphthyl unit is conformationally flexible and capable of adopting geometries which fit both substrate enantiomers. As a consequence, diastereoisomeric complexes of similar energy are formed.

The binding characteristics of the bis(CONH(naphthy))-cleft **3** resemble those of the bis(CONH(py))-cleft **1**. Enantioselectivities of 0.7 kcal mol^{-1} and 0.5 kcal mol^{-1} are measured for Cbz-Glu (**17**) and Cbz-Asp (**15**), respectively, with (*S*)-**3** preferring the aspartate and (*R*)-**3** the glutamate derivative (*Table 2*). Again, the complex (*S*)-**3**·(*S*)-**7** is greatly stabilized ($\Delta(\Delta G°) = 1.6$ kcal mol^{-1}) over the complex (*R*)-**3**·(*S*)-**7**. The compari-

Table 2. *Evaluated Host Protons, Association Constants* K_a, *and Binding Free Energies* $\Delta G°$ (uncertainties: ±0.2 kcal mol^{-1}) *of the Complexes Formed between Clefts* (R)- *and* (S)-**3** *and Dicarboxylic Acids in* $CDCl_3$ *at 300 K*

Host	Guest	Evaluated protons ($\Delta\delta_{sat}$[a]); $\Delta\delta_{obs}$[b]))	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
3	**14**	H–C(1) (0.16; 0.14) H–C(3) (0.10; 0.08)	1350	−4.3
(*R*)-**3**	**15**	H–C(13) (0.12; 0.10)	1100	−4.2
(*S*)-**3**	**15**	H–C(13) (0.10; 0.09)	2600	−4.7
(*R*)-**3**	**17**	H–C(3) (0.10; 0.09)	11650	−5.6
(*S*)-**3**	**17**	H–C(1) (0.16; 0.14) H–C(3) (0.07; 0.06)	3800	−4.9
(*R*)-**3**	(*S*)-**7**	NH (0.45; 0.33)	650	−3.9
(*S*)-**3**	(*S*)-**7**	NH (0.70; 0.61) H–C(1) (0.05; 0.04)	9400	−5.5

[a]) Change in chemical shift at saturation binding. [b]) Largest change in chemical shift observed during the titration.

son of corresponding data in *Tables 1* and *2* shows that changing the H-bonding pattern from CONH(py)· · ·HOOC (in complexes of **1**) to CONH(naphthy)· · ·HOOC (in complexes of **3**) does not significantly alter the free energy and enantioselectivity of complexation. An explanation for this observation can be given by considering two compensating effects. Binding to cleft **3** should be weakened, since the pK_a value (in H_2O) of naphthyridine ($pK_a = 3.39$) [39] is significantly lower than of pyridine ($pK_a = 5.23$) [39], which makes the naphthyridine N-atoms weaker H-bond acceptors. On the other hand, binding to **3** should be strengthened as a result of a more favorable H-bonding pattern (DAA/AD as opposed to DA/AD; A = H-bond acceptor; D = H-bond donor), which should enable the formation of a bifurcated H-bond between the naphthyridine donor sites and the COOH proton (*Fig. 1*). In addition, the DAA/AD pattern should also be more favorable in terms of secondary electrostatic interactions [33a] [40]. *Zimmermann* and *Murray* [41] recently described an enhancement of $\Delta G°$ by 1.4 kcal mol^{-1} under comparable conditions on changing from an AA/DD to an AA/DDD system.

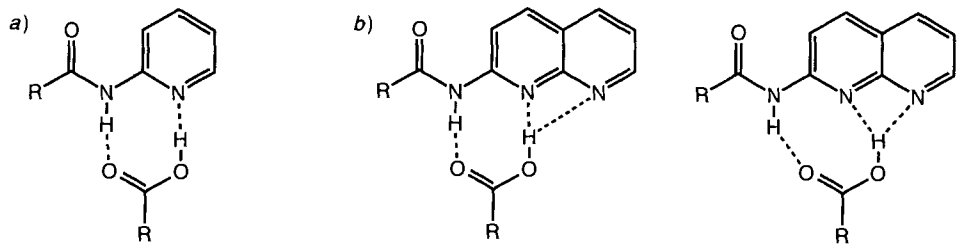


Fig. 1. *Hydrogen-bonding pattern between a COOH residue and* a) *CONH(py) or* b) *CONH(naphthy) moieties*

2.2.2. *Thermodynamic Parameters for Dicarboxylic-Acid Complexation.* The *van't Hoff* analysis of variable-temperature ^{1}H-NMR titrations between 283 and 318 K show that complexation by **1** and **2** in $CDCl_3$ is enthalpically driven (*Table 3*). The enthalpic driving force is partially compensated by an unfavorable change in entropy, which is in agreement with the enthalpy-entropy compensatory effect observed for many biotic and abiotic association processes [42]. Interestingly, the changes in entropy significantly reduce the extent of observable chiral recognition $\Delta(\Delta G°)$. The enthalpic term for the complexation of Cbz-Glu (**17**) by (*R*)-**1** is 2.8 kcal mol^{-1} more favorable than for the association with (*S*)-**1**, whereas the measured enantioselectivity only amounts to $\Delta(\Delta G°) = 0.7$ kcal mol^{-1} (*Table 1*). The enhanced attractive host-guest interactions in the more stable diastereoisomeric complex presumably occur at a much greater expense of frozen bond rotations. The unfavorable role of entropy in reducing the measurable (and usable) degree of chiral recognition $\Delta(\Delta G°)$ is also dramatic for the complexes of the binaphthyl receptors (*S*)- and (*R*)-**2** with **17**. The enthalpic driving force for the formation of the (*R*)-**2**·**17** complex is 1.6 kcal mol^{-1} higher than for the (*S*)-**2**·**17** complex, yet the difference in binding free energy $\Delta(\Delta G°)$ between the two complexes becomes insignificant (*Table 1*).

The thermodynamic characteristics for the complexation of dicarboxylic acid (*S*)-**7** by the enantiomeric spirobifluorene receptors and of diacid (*R*)-**13** by the enantiomeric binaphthyl receptors differ dramatically. Although the free energies for formation of the

most stable complex by (*S*)-**1** and the two diastereoisomeric complexes of (*R*)- and (*S*)-**2** are very similar (*Table 1*), the enthalpic driving force for formation of the binaphthyl complexes is nearly twice as large (*Table 3*). Apparently, the enhanced flexibility of the two binaphthyl components allows for the development of much stronger host-guest H-bonding interactions in the complexes. However, as a result of this 'induced-fit-type' bonding, rotations such as those about the chirality axis in the two binaphthyl components are presumably frozen out, and the resulting unfavorable entropic term compensates all of the enthalpic advantages.

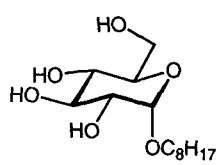
Table 3. *Thermodynamic Parameters for the Complexes of Clefts* **1** *and* **2** *with Dicarboxylic Acids in $CDCl_3$ at 293 K as Calculated from a* van't Hoff *Analysis of Variable-Temperature ^{1}H-NMR Titrations between 283 and 318 K*

Host	Guest	$\Delta H°$[a]) [kcal mol^{-1}]	$T\Delta S°$[a]) [kcal mol^{-1}]
(*R*)-**1**	**17**	−9.3	−3.6
(*S*)-**1**	**17**	−6.5	−1.6
(*R*)-**2**	**17**	−9.2	−3.6
(*S*)-**2**	**17**	−7.6	−2.2
(*R*)-**1**	(*S*)-**7**	−6.3	−2.6
(*S*)-**1**	(*S*)-**7**	−7.3	−1.9
(*R*)-**2**	(*R*)-**13**	−12.1	−6.6
(*S*)-**2**	(*R*)-**13**	−13.8	−8.4

[a]) Uncertainty: ±0.4 kcal mol^{-1}.

Thermodynamic quantities $\Delta H°$ and $T\Delta S°$ for chiral recognition processes were often not reported in the past, and it may be premature to derive too strong conclusions from the data shown here. However, this study seems to suggest that entropic changes, in many cases, reduce the degree of chiral recognition $\Delta(\Delta G°)$ significantly. Therefore, in the design of an enantioselective complexation process, similar attention should be paid to the prevention of losses in rotational entropy as to the development of strong, differential attractive host-guest interactions.

2.2.3. *Complexation of Pyranosides.* The complexation of pyranosides **22**–**24** by the spirobifluorene clefts **1**, **3**, **4**, and naphthyridine **25** was studied by ^{1}H-NMR titrations in $CDCl_3$ (*Table 4*). Preliminary studies with the racemic receptor (±)-**3** showed that diastereoisomeric complexes with differential δ(H) and, hence, differential geometries are



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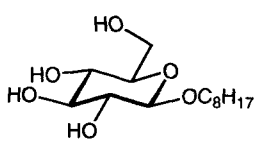

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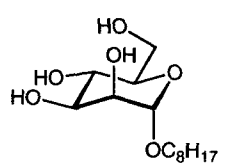

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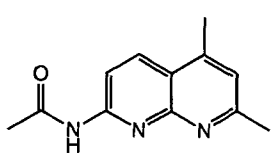

25

formed with pyranoside **22** (*Fig. 2*). The largest complexation-induced downfield shifts were observed for the signals of the aromatic host protons H–C(1), H–C(3), H–(13), and the amide protons, and these signals were monitored and evaluated in the subsequent quantitative binding titrations in which the receptor concentration was held constant (*Table 4*).

Table 4. *Evaluated Host Protons, Association Constants* K_a, *and Binding Free Energies* $\Delta G°$ (uncertainties: ±0.1 kcal mol^{-1}) *of the Complexes Formed between* **1**, **3**, **4**, *and* **25** *and Pyranosides* **11**–**24** *in* $CDCl_3$ *at 300 K*

Entry	Host	Guest	Evaluated protons ($\Delta\delta_{sat}$[a]); $\Delta\delta_{obs}$[b]))	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
1	(*R*)-**1**	**22**	NH (0.21; 0.15) H–C(1) (0.02; 0.02)[c])	160	−3.0
2	(*S*)-**1**	**22**	NH (0.42; 0.31) H–C(1) (0.04; 0.03)[c])	220	−3.2
3	(*R*)-**3**	**22**	NH (0.80; 0.51) H–C(1) (0.14; 0.09) Acetal-H (−0.09; −0.05)[d])	180	−3.1
4	(*S*)-**3**	**22**	NH (0.92; 0.74) H–C(1) (0.12; 0.10) Acetal-H (−0.48; −0.32)[d])	360	−3.5
5	(*R*)-**4**	**22**	NH (0.57; 0.42) H–C(1′) (0.11; 0.08)	240	−3.3
6	(*S*)-**4**	**22**	NH (0.68; 0.51) H–C(1′) (0.13; 0.10)	280	−3.4
7	**25**	**22**	NH (0.79; 0.61) H–C(3) (0.06; 0.05)	270	−3.3
8	(*R*)-**3**	**23**	NH (0.57; 0.44) H–C(1) (0.11; 0.09)	440	−3.6
9	(*S*)-**3**	**23**	NH (0.75; 0.62) H–C(1) (0.09; 0.07)	600	−3.8
10	(*R*)-**4**	**23**	NH (0.32; 0.28) H–C(1′) (0.07; 0.06)	530	−3.7
11	(*S*)-**4**	**23**	NH (0.32; 0.28) H–C(1′) (0.07; 0.06)	550	−3.8
12	**25**	**23**	NH (0.55; 0.48) H–C(3) (0.05; 0.04)	520	−3.7
13	(*R*)-**3**	**24**	NH (0.35; 0.32) H–C(1) (0.06; 0.05)	870	−4.0
14	(*S*)-**3**	**24**	NH (0.45; 0.43) H–C(1) (0.05; 0.04)	1270	−4.3
15	(*R*)-**4**	**24**	NH (0.20; 0.18) H–C(1′) (0.04; 0.04)	940	−4.1
16	(*S*)-**4**	**24**	NH (0.23; 0.21) H–C(1′) (0.05; 0.04)	950	−4.1
17	**25**	**24**	NH (0.58; 0.52) H–C(3) (0.04; 0.04)	780	−4.0

[a]) Change in chemical shift at saturation binding. [b]) Largest change in chemical shift observed during the titration. [c]) The results obtained by evaluation of this proton are in the same range as those derived from NH but have larger errors due to the smaller $\Delta\delta_{sat}$. [d]) The concentration of **22** was kept constant and the host concentration varied.

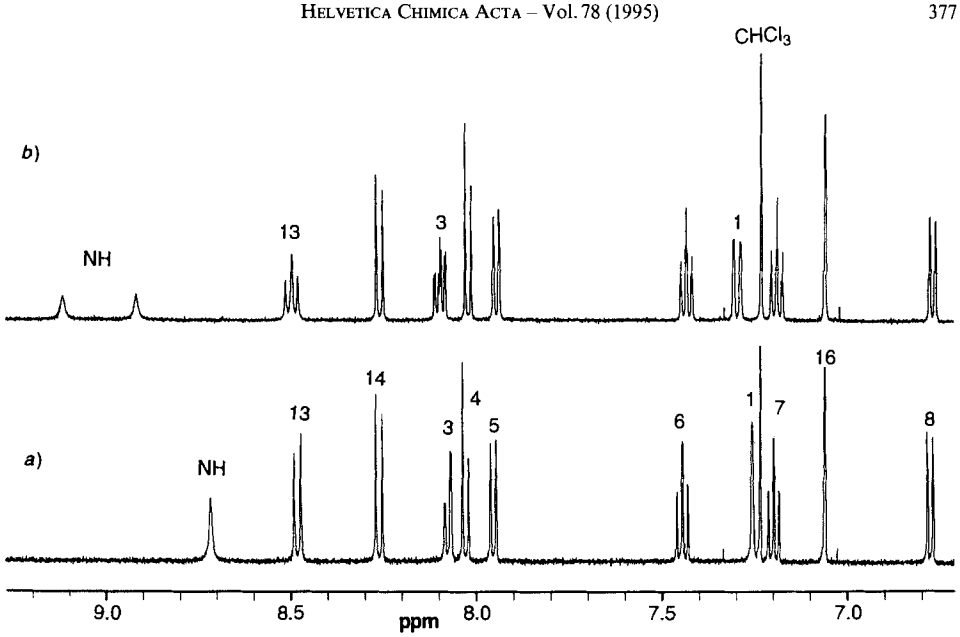

Fig. 2. *Aromatic region in the 500-MHz ^{1}H-NMR spectra* ($CDCl_3$, 300 K) *of* a) *racemic receptor* (±)-**3** (c = 1.0 mM) *and* b) *a mixture of* (±)-**3** (c = 1 mM) *and pyranoside* **22** (c = 2 mM)

Dilution experiments in $CDCl_3$ showed weak self-association of the pyranosides above 1 mM. To confirm that the effect of the self-association on the host-guest binding data is negligible, additional 'inverse' titrations were carried out in which the concentration of glycoside **22** was held constant and that of (*R*)- or (*S*)-**3** varied (*Entries 3* and *4*). In these titrations, the acetal H-atom, which is shifted upfield presumably due to shielding by the spirobifluorene unit, was monitored. The free energies of complexation obtained from these experiments are identical within the limits of uncertainty to those determined from titrations in which the concentration of **3** was held constant and **22** varied, proving that the receptor-pyranoside complexation is much stronger than the self-aggregation of the pyranoside.

Each pyranoside forms complexes of similar association strength with all four receptors (*e.g. Entries 1*, *3*, *5*, and *7*), including the simple naphthyridine **25**, which indicates that the second CONH(py) site in **1** and CONH(naphthy) site in **3** do not contribute significantly to the complex stability. However, in all investigated cases, the complexation-induced change in the averaged chemical shift at saturation binding ($\Delta\delta_{sat}$) of the two NH protons in **3** is larger than in **1** and **4** (*Table 4*), implying that the second NH in **3** is also interacting with the pyranosides.

With all investigated receptors, the association becomes stronger upon changing the pyranoside from **22** to **23** to **24** (*e.g. Entries 4*, *9*, and *14*). Since the three pyranosides form complexes of different stability, it can be assumed that they bind with the edge comprising their structural differences to one CONH(naphthy) unit. This edge in **22**–**24** includes the two OH groups at C(2) and C(3), which should be the relevant H-bonding sites. This binding mode is supported by examinations of CPK models and computer modeling studies (*vide infra*).

Based on the proposed host-guest association mode, the observed pyranoside selectivity can be explained. The intermolecular H-bonds to the naphthyridine moiety in the complexes are formed at the expense of intramolecular H-bonds in the pyranosides. *Anslyn* and coworkers determined the strengths of intramolecular H-bonds between vicinal diols ($CHCl_3$, 295 K) to be 1.9 kcal mol^{-1} for *trans* and 2.2–2.5 kcal mol^{-1} for *cis* diols [26]. The intramolecular H-bonds in the pyranosides that would be affected by complexation (*Fig. 3*) become weaker upon changing from **22**, to **23**, and to **24**. This analysis suggests that pyranosides in which weaker intramolecular H-bonds are disrupted bind more strongly to the receptors.

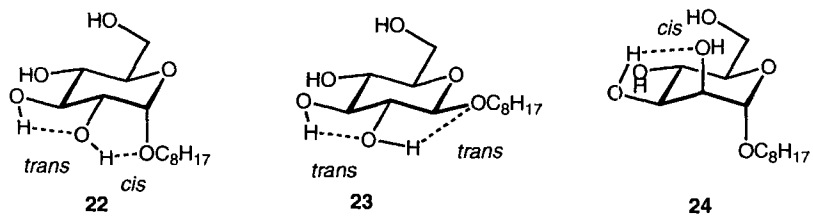

Fig. 3. *Intramolecular H-bonds in* **22–24** *that compete with complexation* via *intermolecular H-bonds as shown in* Fig. 6

The optically active clefts **1**, **3**, and **4** differ in their ability to bind pyranosides enantioselectively. A degree of chiral recognition outside the range of uncertainty ($\Delta(\Delta G°) > 0.2$ kcal mol^{-1}) is only observed with receptor **3**. Enantiomer (*S*)-**3** binds pyranoside **22** by 0.4 kcal mol^{-1} and pyranoside **24** by 0.3 kcal mol^{-1} more strongly than (*R*)-**3** (*Table 4*). The different geometries of the formed diastereoisomeric complexes with pyranoside **22** (*Fig. 2*) are confirmed by nuclear *Overhauser* effect (NOE) difference spectroscopy [43]. In the complex of (*S*)-**3**, the acetal H-atom shows an intermolecular NOE to proton H–C(1) in the cleft, whereas no such NOE is seen in the complex with (*R*)-**3**.

The changes in enthalpy and entropy accompanying the complexation of pyranoside **22** by the receptors (*S*)-**3**, (*S*)-**4**, and **25** (*Table 5*) were determined by *van't Hoff* analysis of variable-temperature ^{1}H-NMR titrations between 280 and 310 K. The formation of all three complexes is strongly enthalpically driven. The $\Delta H°$ and $T\Delta S°$ values are in a similar range, as expected for a similar host-guest association mechanism in all three complexes.

2.4. *X-Ray Crystal Structure of Cleft* **3** *and Computer-Modeling Studies.* Only few X-ray crystal structures of simple 9,9′-spirobi[9*H*-fluorenes] and of 9,9′-spirobi[9*H*-fluo-

Table 5. *Thermodynamic Parameters for the Complexes Formed by* (S)-**3**, (S)-**4**, *and* **25** *with Pyranoside* **22** *in* $CDCl_3$ *at 300 K as Calculated from a* van't Hoff *Analysis of Variable-Temperature* ^{1}*H-NMR Titrations between 280 and 310 K*

Host	$\Delta H°$[a]) [kcal mol^{-1}]	$T\Delta S°$[a]) [kcal mol^{-1}]
(*S*)-**3**	−13.9	−10.4
(*S*)-**4**	−14.9	−11.5
25	−14.9	−11.4

[a]) Uncertainty: ±0.3 kcal mol^{-1}.

rene] crown ethers were reported [32c] [44]. The X-ray crystal structure of **3** as a solvate with 1 equiv. of THF and 2 equiv. of AcOEt and H_2O was determined at 100 K and showed the expected wide open cleft defined by the two CONH(naphthy) moieties in an '*anti*' orientation (*Fig. 4*, *Table 6*). The solid-state structural data subsequently provided

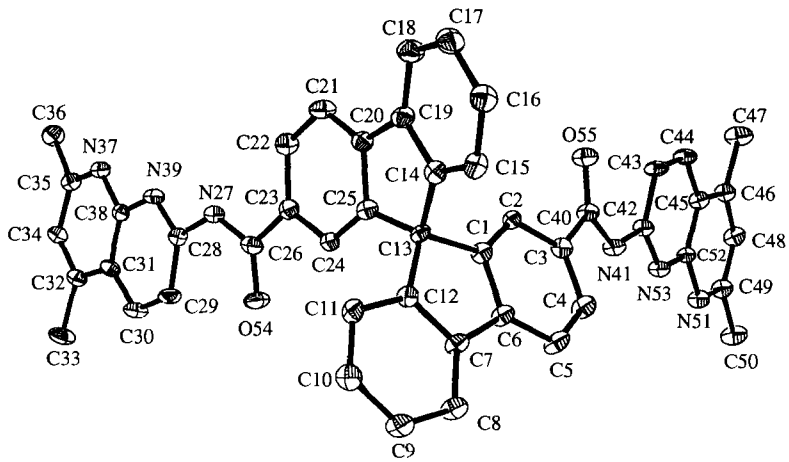

Fig. 4. *ORTEP View of the molecular structure of cleft* **3** *with thermal ellipsoids at 50% probability*

Table 6. *Comparison of the X-Ray Crystal Structure of* **3** *with Gas-Phase Structures Produced by the Original and the Modified* (see *Table 9*) *AMBER* Force Fields.* The numbering is shown in *Fig. 4*.

Selected distances [Å] or angles [°]	X-Ray[a])	AMBER*[b]) (original)	AMBER*[b])[c]) (modified)
C(3)–C(23)	5.85	6.03 (0.18)	6.01 (0.16)
C(40)–C(26)	7.33	7.54 (0.21)	7.49 (0.16)
C(13)–C(25)	1.54	1.53 (−0.01)	1.53 (−0.01)
N(27)–C(28)	1.40	1.40 (0.00)	1.40 (0.00)
C(13)–C(14)–C(15)	127.2	127.5 (0.3)	127.5 (0.3)
C(2)–C(1)–C(13)	129.2	127.5 (−1.7)	127.5 (−1.7)
C(40)–N(41)–C(42)	128.0	121.8 (−6.2)	128.4 (0.4)
C(26)–N(27)–C(28)	127.1	121.9 (−5.2)	128.5 (1.4)
C(3)–C(40)–N(41)	115.9	116.3 (0.4)	117.4 (1.5)
C(23)–C(26)–N(27)	113.8	116.3 (2.5)	117.4 (3.6)
N(41)–C(42)–N(53)	113.5	113.3 (−0.2)	113.2 (−0.3)
N(27)–C(28)–N(39)	113.5	113.5 (0.0)	113.4 (−0.1)
C(2)–C(3)–C(40)–O(55)	0.9	−20.6 (−21.5)	−14.7 (−15.6)
C(24)–C(23)–C(26)–O(54)	−25.2	−20.8 (+4.4)	−14.8 (10.4)
O(55)–C(40)–N(41)–C(42)	0.1	−4.5 (−4.6)	−3.0 (−3.1)
O(54)–C(26)–N(27)–C(28)	−4.2	−4.6 (−0.4)	−2.9 (1.3)
C(40)–N(41)–C(42)–N(53)	174.9	156.8 (−18.1)	177.9 (3.0)
C(26)–N(27)–C(28)–N(39)	176.2	157.0 (−19.2)	177.9 (1.7)

[a]) The standard deviation is ±0.01 Å for the reported distances and ±0.7° for the reported angles. [b]) The numbers in parentheses are the differences between the computed and the X-ray structures. [c]) Modified parameters are given in *Table 9* in the *Exper. Part*.

a good starting point for computer modeling studies of the experimentally investigated recognition processes. Relaxation of the X-ray coordinates of **3** using the AMBER* force field [45] as implemented in MacroModel v. 4.0 [46] with the accompanying BatchMin v. 4.0 [47] led to a C_2-symmetrical structure with almost the same coordinates as the X-ray crystal structure (*Table 6*). Most of the differences between the X-ray and the AMBER* structures can be explained by the distortion from C_2 symmetry in the solid state due to crystal packing forces. This distortion is evident from comparison of distances and angles found in the X-ray structure, which would be equal in a C_2-symmetrical structure. The one difference between solid-state and AMBER* structures which does not seem to be due to packing forces is the tilt of the naphthyridine rings with respect to the plane of the amide. In the solid state, both naphthyridine units are in plane with the amide groups. The fact that the dihedral angles C(40)–N(41)–C(42)–N(53) and C(26)–N(27)–C(28)–N(39) are nearly 180° in a structure where distortions occur necessitated development of new torsional parameters. The new parameters (see *Table 9*, in the *Exper. Part*) are based on *ab initio* calculations on *N*-(pyridin-2-yl)benzamide (Ph-CONH(Py)), a model compound for host **3** [48]. A comparison between selected distances and angles seen in the X-ray and the original and modified AMBER* structures is given in *Table 6*.

2.4.1. *Modeling of the 'Self-Recognition' between the Spirobifluorene Derivatives* (*R*)-**1**/(*S*)-**1** *and* (*S*)-**7**. In the preliminary communication of parts of this work, a qualitative model for the 'self-recognition' between the spirobifluorene clefts (*R*)-**1**/(*S*)-**1** and (*S*)-**7**, a derivative of the direct synthetic precursor to (*S*)-**1**, was proposed [3]. It was suggested that the experimentally observed difference of 1.8 kcal mol^{-1} in binding free energy between the two diastereoisomeric complexes (*R*)-**1**·(*S*)-**7** and (*S*)-**1**·(*S*)-**7** is due to the inability of (*S*)-**7** to reach the two CONH(py) units of (*R*)-**1** with both COOH groups because of steric constraints. This proposal found experimental support in the analysis of the complexation-induced changes in ^{1}H-NMR chemical shifts shown in *Section 2.2.1*. To investigate this further, molecular-dynamics (MD) simulations[1]) were carried out at 300 K. Structures were allowed to equilibrate for 50 ps followed by 400 ps of data collection. H-Bond criteria were set such that the D–H···A distance was less than 2.5 Å and the angle was between 150° and 180°. During the simulation, H-bonds *A*, *B*, *C*, and *D* as defined in *Fig. 5* were monitored. On average, the H-bond criteria were met far more often by the (*S*)·(*S*)-complex than by the (*R*)·(*S*)-complex (*Table 7*). Apparently, a steric interaction between H–C(3) and H–C(4) of (*R*)-**1** and the π-surface of (*S*)-**7** (*Fig. 5b*) prevents the formation of strong *C* and *D* H-bonds in complex (*R*)-**1**·(*S*)-**7** thereby explaining the observed enantioselectivity.

2.4.2. *Modeling of a Cleft-Pyranoside Complex*. When proposing a model of complex (*S*)-**3**·**22**, two important factors from NMR experiments were considered. Firstly, the acetal H-atom of the sugar shows a NOE to H–C(1) of the host. Secondly, the downfield shift of the NH protons is greater in the (*S*)-**3**·**22** than in the (*R*)-**3**·**22** complex. From the NMR data, it was concluded that the acetal H-atom must be within 3.5 Å of H–C(1) of the host, and both amide groups of (*S*)-**3** must participate in the complexation.

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[1]) Simulations were carried out with MacroModel v. 4.0 [46] and the accompanying BatchMin v. 4.0 [47]. The SHAKE algorithm was turned on and a timestep of 1.5 fs was used. The simulations were executed with the modified AMBER* forcefield [45] and the GB/SA $CHCl_3$ solvation model [49].

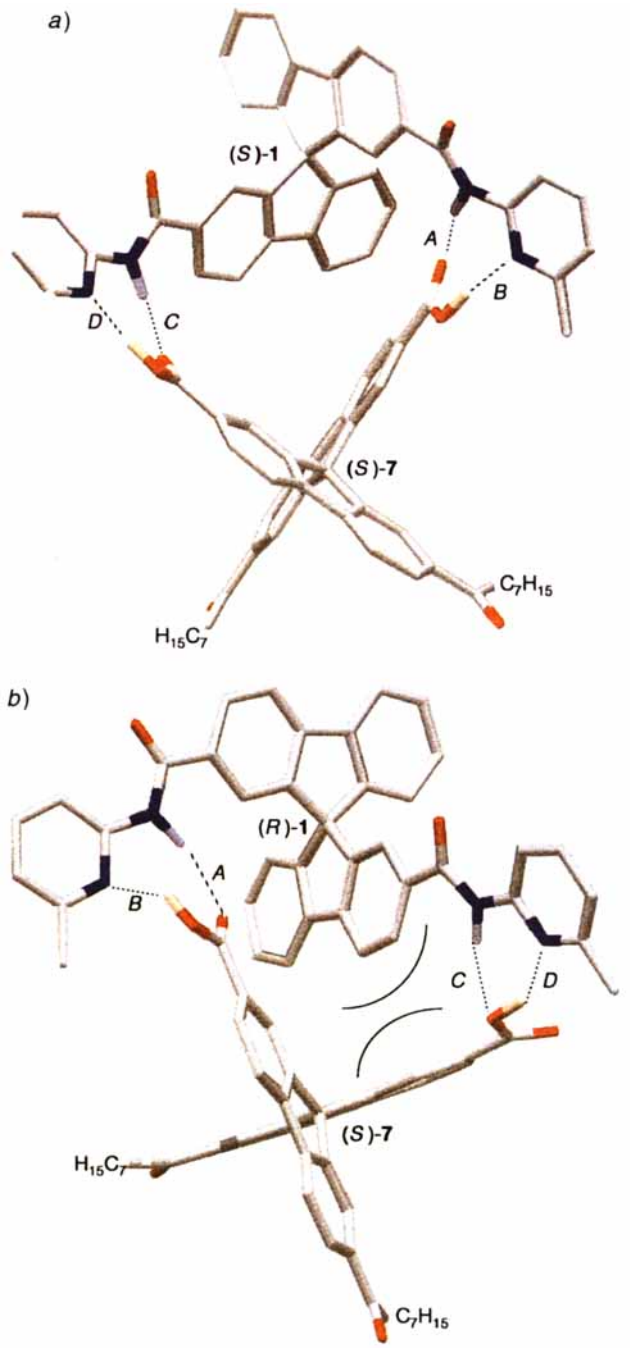

Fig. 5. *Computer-generated models of the 'self-recognition' between spirobifluorene derivatives in the diastereoisomeric complexes* a) (S)-**1**·(S)-**7** *and* b) (R)-**1**·(S)-**7**, *as obtained by molecular-dynamics simulations.* H-Atoms are omitted for clarity.

Table 7. *Average Distances and Angles of H-Bonds in Complexes (S)-**1**·(S)-**7** and (R)-**1**·(S)-**7** from Molecular-Dynamics Simulations and % of Structures Meeting the H-Bond Criteria*[a]). The Numbers in Parentheses are Standard Deviations.

H-Bond	Distance [Å]	D–H···A Angle [°]	% of Structures meeting H-bond criteria
	(*S*)-**1**·(*S*)-**7**		
A	2.28 (0.31)	145 (15)	41
B	1.96 (0.13)	156 (12)	69
C	2.18 (0.26)	147 (12)	43
D	1.99 (0.15)	156 (13)	73
	(*R*)-**1**·(*S*)-**7**		
A	2.80 (0.26)	137 (14)	4
B	2.02 (0.17)	148 (14)	49
C	2.05 (0.17)	141 (12)	22
D	2.28 (0.23)	144 (8)	20

[a]) D–H···A distance less than 2.5 Å and angle between 150° and 180°.

A model resembling the structure shown in *Fig. 6a* was proposed and used as input for a conformational search to find all conformations which fit the experimental data. A 5000-step Monte Carlo (MC) search was conducted with the AMBER* force field and the GB/SA $CHCl_3$ solvation model [49] as implemented in MacroModel v. 4.0. Structures incongruent with the experimentally observed intermolecular NOE between H–C(1) of (*S*)-**3** and the acetal H-atom of **22** were rejected, and the remaining structures that were within 50 kJ mol^{-1} of the global minimum were minimized using the *Polak-Ribière* conjugate-gradient (PRCG) method and the modified torsional parameters. Ten structures were found within 3 kcal mol^{-1} of the global minimum with six showing both amide groups participating in the H-bonding. None showed H-bonds to both naphthyridines. Two representative structures of the six which are in accord with the experimental data are shown in *Fig. 6*. The structure in *Fig. 6a* shows both H–C(1) and H–C(1′) near the acetal H-atom of the sugar and both NH groups of **3** donating H-bonds to the sugar. The OH-group at C(6) of the sugar forms an intramolecular H-bond to O–C(5). *Fig. 6b* shows the minimum-energy structure found which accounts for all the experimental facts since the acetal H-atom is well within 3.5 Å of H–C(1) and one amide NH proton donates a H-bond to the sugar while the other amide accepts a H-bond from the sugar. Both structures show strong interaction with only one of the naphthyridine moieties, which agrees well with the experimental finding that hosts **3**, **4**, and **25** complex pyranosides equally effectively, each with a single naphthyridine unit. Both naphthyridines of **3** do not necessarily accept H-bonds upon complex formation.

3. Conclusion. – The spirobifluorene clefts (*R*)-**1**/(*S*)-**1** and (*R*)-**3**/(*S*)-**3** bind chiral dicarboxylic acids enantioselectively in $CDCl_3$. Enantioselectivities $\Delta(\Delta G°)$ of up to 0.9 kcal mol^{-1} were observed for the recognition of excitatory amino acids and up to 1.8 kcal mol^{-1} for the recognition of 9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylic acid (*S*)-**7**, a derivative of the direct precursor to (*S*)-**1** and (*S*)-**3**. A rational for the high enantioselectivity of the latter association event was obtained by computer modeling. In contrast, the binaphthyl cleft **2** lacks the conformational homogeneity required for efficient chiral recognition, and diastereoisomeric complexes of similar stability were formed with chiral

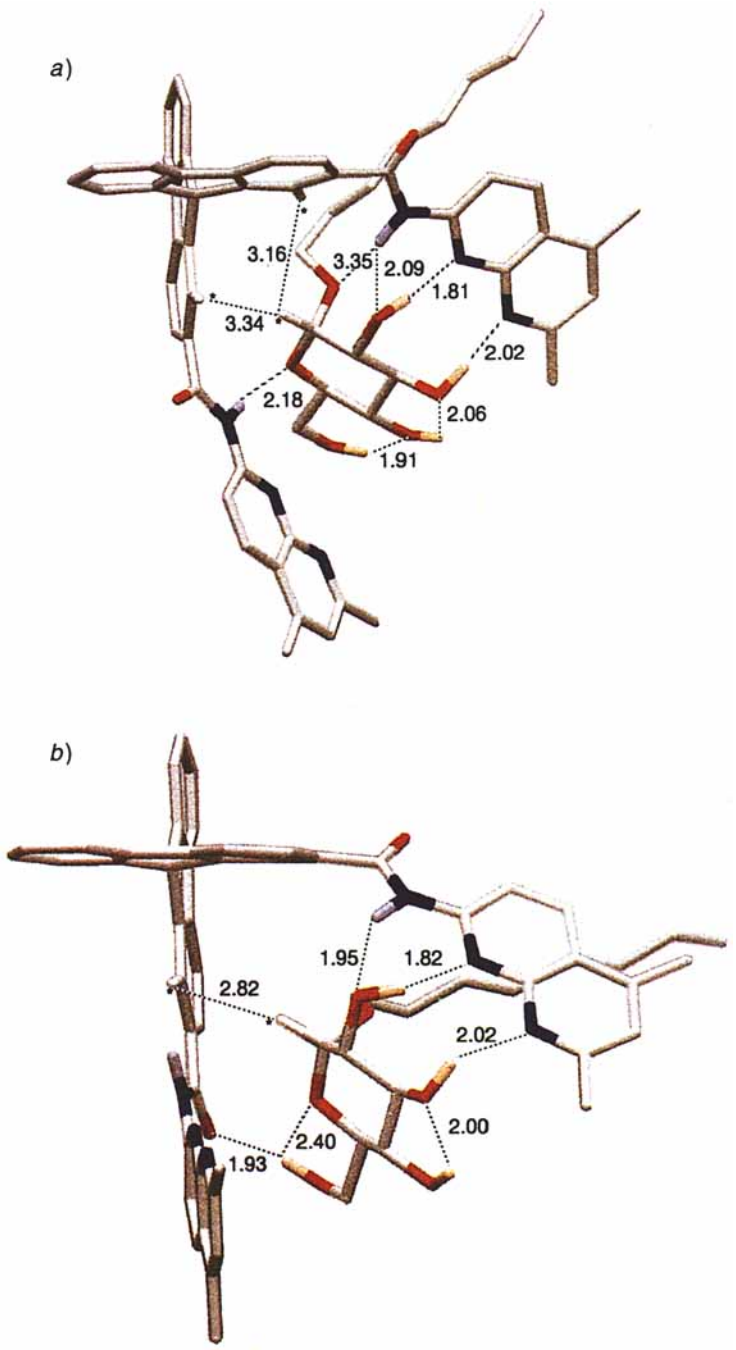

Fig. 6. *Computer-generated models of complex (*S*)-***3***·**22**.* The structure of *Fig. 6b* is the minimum-energy structure found which fits all experimental data. An intermolecular NOE is observed between starred atoms. H-Atoms are omitted for clarity.

dicarboxylic acids. However, thermodynamic studies suggested a high potential for efficient enantioselective dicarboxylic-acid binding, if the binaphthyl receptors are conformationally enforced. Compared to the spirobifluorene clefts (*R*)- and (*S*)-**1**, the enthalpy for complexation by (*R*)- and (*S*)-**2** is much more favorable, but the entropic term is less favorable. To provide strong enthalpic association in one diastereoisomeric complex only and to reduce the unfavorable entropic term, the binaphthyl unit needs to be better preorganized. This objective is currently targeted in our laboratory by bridging the 2,2′-positions at the binaphthyl minor groove [50].

The simple *N*-(naphthyridinyl)acetamide **25** and the spirobifluorene cleft **3** with two CONH(naphthy) moieties formed 1:1 complexes of similar stability with pyranosides in $CDCl_3$, which suggested that the second CONH(naphthy) moiety in **3** is not contributing significantly to the association strength. This was also indicated by a computer model of a pyranoside complex of (*S*)-**3** which fits the observed binding data and NOE. We, therefore, plan to build more refined spirobifluorene receptors with two different binding sites, and compound **6** represents an important intermediate in the development of these unsymmetrical systems. The highest enantioselectivity $\Delta(\Delta G°)$ observed in the pyranoside binding by (*R*)- and (*S*)-**3** was 0.4 kcal mol^{-1}. Pyranoside binding selectivity ($\Delta G°$ between −3.0 and −4.3 kcal mol^{-1}) correlated with the strength of the intramolecular H-bonds which are broken in the sugar derivatives during complex formation: the stronger the intramolecular H-bonds, the weaker the host-guest association. We suggest that artificial receptors, similar to the biological counterparts, should incorporate a large number of H-bonding sites. Intermolecular host-guest H-bonding will compete much better with the intramolecular H-bonding network in carbohydrates if each intramolecular H-bond is replaced by at least two intermolecular H-bonds or if stronger ionic H-bonds are formed. This strategy is currently being pursued.

Experimental Part

General. All reactions were carried out under N_2. Reagent-grade chemicals were purchased from *Fluka* or *Aldrich* and used without further purification unless otherwise stated. THF was freshly distilled from sodium benzophenone ketyl. $CHCl_3$ was purified by washing with H_2O and then distilling over Na_2SO_4. Clefts (*R*)-**1** ($[\alpha]_D^{r.t.} = +177.5$ ($c = 0.435$, $CHCl_3$)) and (*S*)-**1** ($[\alpha]_D^{r.t.} = -180.0$ ($c = 0.570$, $CHCl_3$)) were prepared following the procedure published for the racemic compound [30]. The diacids (*R*)-**11** ($[\alpha]_D^{r.t.} = +38.8$ ($c = 0.70$, MeOH)) and (*S*)-**11** ($[\alpha]_D^{r.t.} = -37.0$ ($c = 0.84$, MeOH)) were prepared from (*R*)- and (*S*)-**10**, respectively, and then converted to (*R*)-**2** ($[\alpha]_D^{r.t.} = -19.4$ ($c = 1.01$, $CHCl_3$)) and (*S*)-**2** ($[\alpha]_D^{r.t.} = +19.3$ ($c = 1.12$, $CHCl_3$)) according to the previously published procedure for the racemates [30]. Thin-layer chromatography: *E. Merck* plates precoated with silica gel F_{254}. Column chromatography: *E. Merck* silica gel *60* (0.040–0.063 mm). M.p.: *Büchi Smp-20*; uncorrected. Optical rotation: *Perkin-Elmer-241* polarimeter; at r.t. (295 ± 1 K). IR Spectra (cm^{-1}): *Perkin Elmer 1600-FTIR*. ^1H- and ^{13}C-NMR Spectra: at 300 K; *Bruker AMX 500* or *Varian Gemini 300* if not stated otherwise; assignments of δ(H) supported by 2D COSY and ROESY experiments [43a]. MS (*m/z*, %): FAB (fast-atom bombardment), 3-nitrobenzyl alcohol as matrix; EI at 70 eV. Elemental analyses: Mikrolabor des Laboratoriums für Organische Chemie at ETHZ.

Complexation Studies. For binding studies, the diacids **14**, **15**, **17**, **21a**, **21b**, and **21d** were purchased from *Sigma* and the pyranosides **22** and **23** from *Fluka*. Pyranoside **24** [51], amide **25** [52], and acid **21c** [53] were prepared according to the published procedures. Compounds **16** ($[\alpha]_D^{r.t.} = +48.1$ ($c = 0.413$, MeOH)) [54] and **19** ($[\alpha]_D^{r.t.} = +125.9$ ($c = 0.340$, $CHCl_3$)) [55] were synthesized following published procedures for the racemic compounds.

All ^1H-NMR titration data were acquired on a *Bruker* 500-MHz NMR spectrometer thermostated to ±0.1 K at 300 K if not mentioned otherwise. The $CDCl_3$ used for diacid binding was dried over molecular sieves (4 Å). For the binding of pyranosides, dry $CDCl_3$ (from a fresh bottle) was used in a first run. The binding results with

pyranosides were reproduced in duplicate runs with $CDCl_3$ that was passed through basic alumina (act. I) immediately prior to use. Binding studies with receptors **1** and **2** were carried out as previously described [30]. Clefts **3**, **4**, and **25** were dried at 80°/0.05 Torr for 12 h and stored moisture-free. Commercially available guests were used withouth further treatment. For each binding study, ten titration samples were prepared with *Gilson Pipetman* (200 µl and 1000 µl) pipettors from sonicated stock solns. which were obtained by weighing the compounds into 2-ml or 5-ml volumetric flasks on a *Mettler AT20* microbalance. If not mentioned otherwise, the host concentration was kept constant at 0.5 mM or 1.0 mM, and the concentration of the guest was varied to reach saturation values up to 70–90%. The complexation-induced change in chemical shift $\Delta\delta$ of host protons was plotted against the guest concentration. Quantitative binding data (K_a, $\Delta G°$, $\Delta\delta_{sat}$) were obtained by using a nonlinear least-squares curve-fitting program [56]. The K_a and $\Delta G°$ values reported are averages calculated from the complexation-induced changes in chemical shift of all observed protons of multiple runs. *Job* plots were performed by keeping the sum of host and guest concentration at 1.0 mM [38]. *Job* plots of receptors **1** and **2** with several diacids were previously performed and confirmed the 1:1 stoichiometry for complexes of this type [30]. *Job* plots of receptors **3**, **4**, and **25** with pyranoside **22** proved the 1:1 stoichiometry so that this was assumed for all other investigated pyranoside complexes. Self-association was checked by varying the concentration of the pyranosides between 0.2 and 10 mM. The impact of this process and any further equilibria on the observed binding data was not considered and remains to be explored.

(R)-N,N'-Bis(5,7-dimethyl-1,8-naphthyridin-2-yl)-9,9'-spirobi[9H-fluorene]-2,2'-dicarboxamide ((*R*)-**3**) *and 2,5-Dioxopyrrolidin-1-yl (R)-2'-[(5,7-dimethyl-1,8-naphthyridin-2-yl)carbamoyl]-9,9'-spirobi[9H-fluorene]-2-carboxylate* ((*R*)-**6**). Diacid (*R*)-**5** (400 mg, 1.0 mmol) [34] and *N*-hydroxysuccinimide (230 mg, 2.0 mmol) were mixed in THF (5 ml), and dicyclohexylcarbodiimide (DCC; 450 mg, 2.2 mmol) in THF (2.5 ml) was added. After refluxing for 4 h, the precipitated dicyclohexylurea was filtered off and the solvent evaporated. The crude bis(succinimid-*N*-yl ester) was dissolved in $CHCl_3$ (10 ml), and 5,7-dimethyl-1,8-naphthyridine-2-amine (340 mg, 2.0 mmol) was added as a solid. The mixture was refluxed for 2 d, the solvent evaporated, and the residue chromatographed (AcOEt→AcOEt/THF 1:1) to give two main products. Recrystallization of the compound with the lower R_f value (0.40; AcOEt/THF 1:1) from $CHCl_3$/hexane and drying (12 h, 80°/0.05 Torr) afforded (*R*)-**3** (215 mg, 29%). White crystals. M.p. 265–267° (dec.). $[\alpha]_D^{r.t.} = +291.0$ ($c = 0.460$, $CHCl_3$). IR (KBr): 3424*w*, 1676*w*, 1599*s*, 1508*s*, 1406*m*, 1310*s*, 804*w*, 748*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.60 (*s*, 6H); 2.64 (*s*, 6H); 6.78 (*d*, $J = 7.5$, 2H); 7.06 (*s*, 2H); 7.20 (*dd*, $J = 7.5, 7.5$, 2H); 7.26 (*d*, $J \approx 1.4$, 2H); 7.45 (*dd*, $J = 7.6, 7.5$, 2H); 7.97 (*d*, $J = 7.6$, 2H); 8.04 (*d*, $J = 8.0$, 2H); 8.09 (*dd*, $J = 8.0, 1,4$, 2H); 8.28 (*d*, $J = 9.0$, 2H); 8.50 (*d*, $J = 9.0$, 2H); 8.71 (br. *s*, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 17.97; 25.44; 65.76; 113.35; 118.62, 120.89; 121.33; 122.18; 122.54; 124.17; 128.21; 128.53; 129.36; 133.07; 135.58; 140.52; 145.11; 146.29; 148.62; 148.64; 152.93; 154.61; 162.94; 165.22. FAB-MS: 715.2 ($[M + H]^+$). Anal. calc. for $C_{47}H_{34}N_6O_2 \cdot 1.5\ H_2O$ (741.85): C 76.10, H 5.03, N 11.33; found: C 76.35, H 5.07, N 11.29.

Drying the product with the higher R_f value (0.57; AcOEt/THF 1:1) for 12 h at 80°/0.05 Torr afforded (*R*)-**6** (200 mg, 30%). White, crystalline solid. M.p. 235–237° (dec.). $[\alpha]_D^{r.t.} = +181.7$ ($c = 0.545$, $CHCl_3$). IR (KBr): 3364*w*, 1764*s*, 1732*s*, 1682*m*, 1599*s*, 1507*s*, 1406*m*, 1310*m*, 1207*s*, 1152*w*, 1072*s*, 1014*m*, 844*w*, 804*w*, 750*s*, 638*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.62 (*s*, 3H); 2.67 (*s*, 3H); 2.82 (br. *s*, 4H); 6.78 (*d*, $J = 7.7$, 1H); 6.79 (*d*, $J = 7.6$, 1H); 7.08 (*s*, 1H); 7.21–7.26 (*m*, 2H); 7.28 (*d*, $J \approx 1.4$, 1H); 7.43–7.49 (*m*, 2H); 7.46 (*d*, $J = 1.5$, 1H); 7.94 (*d*, $J = 7.6$, 1H); 7.99–8.03 (*m*, 3H); 8.10 (*dd*, $J = 8.0, 1.4$, 1H); 8.24 (*dd*, $J = 8.1, 1.5$, 1H); 8.30 (*d*, $J = 9.0$, 1H); 8.55 (*d*, $J = 9.0$, 1H); 8.82 (br. *s*, 1H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 17.98; 25.42; 25.56; 65.69; 113.43; 118.61; 120.61; 120.69; 121.13; 121.71; 122.20; 122.66; 124.09; 124.17; 124.31; 126.17; 128.29; 128.50; 128.60; 129.41; 129.97; 131.27; 133.16; 135.58; 140.03; 140.48; 145.16; 146.12; 148.22; 148.24; 148.27; 148.58; 149.02; 152.98; 154.57; 161.58; 162.90; 165.13; 169.14. HR-FAB-MS: 657.2134 ($[M + H]^+$, $C_{41}H_{29}N_4O_5^+$, calc. 657.2138).

(*S*)-**3** ($[\alpha]_D^{r.t.} = -295.9$ ($c = 0.433$, $CHCl_3$)) and (*S*)-**6** ($[\alpha]_D^{r.t.} = -183.4$ ($c = 0.589$, $CHCl_3$)) were prepared in the same manner from (*S*)-**5** [34].

Methyl (R)-2'-[(5,7-Dimethyl-1,8-naphthyridin-2-yl)carbamoyl]-9,9'-spirobi[9H-fluorene]-2-carboxylate ((*R*)-**4**). A mixture of (*R*)-**6** (100 mg, 0.15 mmol) and NEt_3 (0.1 ml, 3.6 mmol) in MeOH (5 ml) in the presence of molecular sieves (4 Å) was stirred under reflux for 12 h. The solvent was evaporated (water-aspirator pressure) and the crude product chromatographed on a short column (AcOEt, R_f 0.28) and recrystallized (AcOEt) to yield, after drying (12 h, 80°/0.05 Torr), (*R*)-**4** (70 mg, 80%). White, crystalline solid. M.p. 203–205° (dec.). $[\alpha]_D^{r.t.} = +136.7$ ($c = 0.418$, $CHCl_3$). IR (KBr): 3037*w*, 1722*s*, 1667*s*, 1602*s*, 1511*s*, 1434*m*, 1406*m*, 1312*m*, 1225*m*, 802*w*, 751s, 638*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.64 (*s*, 3H); 2.68 (*s*, 3H); 3.80 (*s*, 3H); 6.76 (*d*, $J = 7.7$, 1H); 6.77 (*d*, $J = 7.6$, 1H); 7.10 (*s*, 1H); 7.19–7.23 (*m*, 2H); 7.24 (*s*, 1H); 7.40 (*s*, 1H); 7.45 (*dd*, $J = 7.6, 7.4$, 2H); 7.95–7.98 (*m*, 3H); 8.02 (*d*, $J = 8.1$, 1H); 8.09 (*d*, $J = 8.0$, 1H); 8.15 (*d*, $J = 8.1$, 1H); 8.31 (*d*, $J = 9.0$, 1H); 8.52 (*d*, $J = 9.0$, 1H); 8.71 (br. *s*,

1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 18.05; 25.45; 51.96; 65.70; 113.33; 118.64; 120.21; 120.67; 121.07; 121.30; 122.24; 122.44; 124.05; 124.25; 125.23; 128.13; 128.29; 128.43; 129.24; 129.25; 129.60; 130.19; 133.06; 135.64; 140.48; 140.61; 145.19; 146.20; 146.53; 147.74; 148.68; 148.88; 148.90; 152.90; 154.58; 162.99; 165.33; 166.79. FAB-MS: 574.2 ($[M + H]^+$). Anal. calc. for $C_{38}H_{27}N_3O_3 \cdot 1.5\ H_2O$ (600.68): C 75.98, H 5.03, N 7.00; found: C 76.13, H 5.18, N 7.01.

(*S*)-**4** ($[\alpha]_D^{r.t.} = -140.6$ ($c = 0.377$, $CHCl_3$)) was prepared in the same manner from (*S*)-**6**.

(S)-7,7'-Di(octanoyl)-9,9'-spirobi[9H-fluorene]-2,2'-dicarboxylic Acid ((*S*)-**7**). To a soln. of octanoyl chloride (0.39 ml, 380 mg, 2.3 mmol) and $AlCl_3$ (960 mg, 7.2 mmol) in CS_2 (2.6 ml) was added (*S*)-**5** (300 mg, 0.74 mmol), and the mixture was stirred for 12 h. After cooling in an ice-bath, 2M aq. HCl (10 ml) was added and the product extracted with Et_2O. Drying ($MgSO_4$) followed by evaporation yielded crude product which was recrystallized from MeOH: (*S*)-**7** (330 mg, 68%). Colorless solid. M.p. 270°. $[\alpha]_D^{r.t.} = +3.1$ ($c = 0.450$, acetone). IR (KBr): 2927*m*, 1724*m*, 1682*s*, 1605*m*, 1433*m*, 1409*m*, 1297*m*, 1232*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.81 (*t*, $J = 7.1$, 6H); 1.19–1.30 (*m*, 16H); 1.58 (*m*, 4H); 2.78 (*t*, $J = 7.3$, 4H); 7.26 (br. *s*, 2H); 7.31 (br. *s*, 2H); 7.96 (*d*, $J = 8.1$, 2H); 7.97 (*d*, $J = 8.1$, 2H); 8.02 (*dd*, $J = 8.1$, 1.4, 2H); 8.13 (*dd*, $J = 8.1$, 1.3, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.00; 22.52; 24.16; 29.04; 29.18; 31.59; 38.68; 65.52; 121.16; 121.31; 123.64; 125.88; 129.09; 129.61; 131.03; 137.86; 144.70; 145.95; 148.37; 148.51; 171.21; 199.62. EI-MS: 656.4 (20, M^+), 572.2 (53), 446.2 (100), 313.3 (66). Anal. calc. for $C_{43}H_{44}O_6 \cdot 0.5\ H_2O$ (665.83): C 77.57, H 6.81; found: C 77.50, H 6.72.

(S)-6,6'-Dibromo-1,1'-binaphthyl-2,2'-diol ((*S*)-**9**). Br_2 (7.0 ml, 21.8 g, 140 mmol) in CH_2Cl_2 (40 ml) was added to (*S*)-**8** (12.7 g, 44.4 mmol) in CH_2Cl_2 (400 ml) at −78°. After stirring for 3 h at r.t., the excess Br_2 was destroyed by addition of 10% aq. $Na_2S_2O_5$ soln. (200 ml). The phases were separated, and the aq. phase was extracted with AcOEt. The combined org. phases were dried ($MgSO_4$) and evaporated. Recrystallization from AcOEt/cyclohexane afforded (*S*)-**9** (18.5 g, 94%). White product. M.p. 198.0–199.5°. $[\alpha]_D^{r.t.} = +98.0$ ($c = 1.05$, $CHCl_3$). IR (KBr): 3453, 1586, 825. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.02 (*s*, 2H); 6.97 (*d*, $J = 9.0$, 2H); 7.38 (*dd*, $J = 9.0$, 2.5, 2H); 7.40 (*d*, $J = 9.0$, 2H); 7.91 (*d*, $J = 9.0$, 2H); 8.06 (*d*, $J = 2.5$, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 110.78; 117.96; 118.98; 125.88; 130.41; 130.53; 130.61; 130.81; 131.91; 152.96. FAB-MS: 444 (M^+, $C_{20}H_{12}{}^{79}Br^{81}BrO_2^+$). Anal. calc. for $C_{20}H_{12}Br_2O_2$ (444.13): C 54.09, H 2.72, Br 35.98; found: C 54.26, H 2.48, Br 35.75.

(*R*)-**9** ($[\alpha]_D = -97.8$ ($c = 0.997$, $CHCl_3$)) was prepared in the same manner.

(S)-2,2'-Bis(benzyloxy)-6,6'-dibromo-1,1'-binaphthyl ((*S*)-**10**). K_2CO_3 (26.0 g, 190 mmol) and benzyl chloride (18.0 ml, 19.8 g, 156 mmol) were added to a soln. of (*S*)-**9** (32.4 g, 73 mmol) in DMF (500 ml). After stirring for 24 h at 70°, the solvent was evaporated and 3M aq. HCl (500 ml) added. Extraction with AcOEt, drying ($MgSO_4$), and evaporation followed by recrystallization from THF/cyclohexane yielded (*S*)-**10** (36.0 g, 79%). M.p. 99–100°. $[\alpha]_D^{r.t.} = -28.0$ ($c = 1.00$, $CHCl_3$). IR (KBr): 1580, 1222. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.05 (*s*, 4H); 6.95 (*d*, $J = 7.1$, 4H); 6.99 (*d*, $J = 9.0$, 2H); 7.09–7.15 (*m*, 6H); 7.27 (*dd*, $J = 9.0$, 2.5, 2H); 7.42 (*d*, $J = 9.0$, 2H); 7.83 (*d*, $J = 9.0$, 2H); 8.02 (*d*, $J = 2.5$, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 71.04, 116.73; 117.66; 120.24; 126.68; 127.21; 127.54; 128.29; 128.68; 129.79; 129.94; 130.46; 132.61; 137.16; 154.40. FAB-MS 624 (M^+, $C_{34}H_{24}{}^{79}Br^{81}BrO_2^+$). Anal. calc. for $C_{34}H_{24}Br_2O_2$ (624.38): C 65.41, H 3.87, Br 25.60; found: C 65.81, H 3.82, Br 25.26.

(*R*)-**10** ($[\alpha]_D = +27.4$ ($c = 1.00$, $CHCl_3$)) was prepared in the same manner.

(R)-6,6'-Dibromo-2,2'-bis(dodecyloxy)-1,1'-binaphthyl ((*R*)-**12**). K_2CO_3 (560 mg, 4.0 mmol) and dodecyl iodide (0.4 ml, 480 mg, 1.6 mmol) were added to a soln. of (*R*)-**9** (300 mg, 0.66 mmol) in DMF (15 ml). The mixture was stirred at 100° for 12 h, then the solvent evaporated, and H_2O added. Extraction with Et_2O, drying ($MgSO_4$), and evaporation, followed by chromatography (hexane/CH_2Cl_2 9:1) yielded (*R*)-**12** (340 mg, 66%). M.p. 81–82°. $[\alpha]_D^{r.t.} = +21.6$ ($c = 1.01$, $CHCl_3$). IR (KBr): 2922*s*, 2851*m*, 1581*m*, 1492*m*, 1468*m*, 1340*m*, 1264*m*, 1076*w*, 871*w*, 815*w*, 790*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.90 (*t*, $J = 7.0$, 6H); 0.90–1.40 (*m*, 40H); 3.93 (*m*, 4H); 6.98 (*d*, $J = 9.0$, 2H); 7.25 (*dd*, $J = 9.0$, 2.1, 2H); 7.41 (*d*, $J = 9.0$, 2H); 7.84 (*d*, $J = 9.0$, 2H); 8.00 (*d*, $J = 2.1$, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.11; 22.69; 25.63; 29.11; 29.27; 29.36; 29.47; 29.50; 29.64; 29.66; 31.92; 69.53; 116.40; 117.19; 120.03; 127.10; 128.34; 129.41; 129.73; 130.17; 132.55; 154.74. EI-MS: 780.1 (100, M^+, $C_{44}H_{60}{}^{81}Br^{79}BrO_2^+$), 442.8 (49). HR-EI-MS: 778.2965 (M^+, $C_{44}H_{60}{}^{79}Br_2O_2^+$, calc. 778.2960).

(R)-2,2'-Bis(dodecyloxy)-1,1'-binaphthyl-6,6'-dicarboxylic Acid ((*R*)-**13**). A soln. of (*R*)-**12** (330 mg, 0.42 mmol) in THF (1 ml) was added dropwise to 2M BuLi in hexane (0.8 ml, 1.6 mmol) in THF (10 ml) at −78°. After stirring for 10 min, dry ice was added and the yellow soln. allowed to warm up to r.t. The solvent was evaporated and the crude product partitioned between AcOEt and H_2O. The aq. layer was acidified with 2M aq. HCl and the precipitated product isolated by filtration and dried: (*R*)-**13** (200 mg, 67%). M.p. 140–142°. $[\alpha]_D^{r.t.} = +14.7$ ($c = 0.231$, $CHCl_3$). IR (KBr): 2922*s*, 2856*m*, 1682*s*, 1619*m*, 1464*m*, 1277*m*, 804*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87 (*t*, $J = 6.9$, 6H); 0.92–1.43 (*m*, 40H); 4.00 (*m*, 4H); 7.17 (*d*, $J = 8.9$, 2H); 7.48 (*d*, $J = 9.1$, 2H); 7.83 (*dd*, $J = 8.9$, 1.7, 2H); 8.09 (*d*, $J = 9.1$, 2H); 8.72 (*d*, $J = 1.7$, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.08; 22.67; 25.60; 29.07; 29.16; 29.35; 29.46; 29.47; 29.62; 29.63; 31.90; 69.23; 115.60; 119.55; 123.81; 125.42; 125.75; 127.88; 131.22;

132.38; 136.78; 156.76; 170.69. EI-MS: 710.3 (M^+). Anal. calc. for $C_{46}H_{62}O_6 \cdot H_2O$ (729.02): C 75.79, H 8.85; found: C 75.64, H 8.68.

N-(Butoxycarbonyl)-L-glutamic Acid (**18**). A mixture of L-glutamic acid (1.47 g, 1.0 mmol), KOH (1.12 g, 2.0 mmol), Na_2CO_3 (2.12 g, 2.0 mmol), and butyl chloroformate (1.30 ml, 1.37 g, 1.0 mmol) in H_2O (50 ml) was stirred at r.t. for 12 h. Acidification with 2M aq. HCl, extraction with Et_2O, drying ($MgSO_4$), and evaporation gave **18** (2.00 g, 81%). M.p. 65–66°. $[\alpha]_D^{r.t.} = +19.42$ ($c = 0.345$, $CHCl_3$). IR (KBr): 3306*m*, 2961*m*, 1704*s*, 1548*m*, 1425*m*, 1266*s*, 1066*w*. ^{1}H-NMR (300 MHz, CD_3OD): 0.94 (*t*, $J = 7.3$, 3H); 1.41 (*m*, 2H); 1.61 (*m*, 2H); 1.91 (*m*, 1H); 2.14 (*m*, 1H); 2.40 (*t*, $J = 7.6$, 2H); 4.04 (*t*, $J = 6.5$, 2H); 4.18 (*m*, 1H). ^{13}C-NMR (75.5 MHz, CD_3OD): 14.11; 20.14; 28.00; 31.24; 32.29; 54.61; 65.97; 159.11; 175.51; 176.43. FAB-MS: 248.1 ($[M + H]^+$). Anal. calc. for $C_{10}H_{17}NO_6$ (247.25): C 48.58, H 6.93, N 5.67; found: C 48.56, H 6.93, N 5.50.

(S)-2-(Phenylseleno)succinic Acid (**20**). $NaBH_4$ (260 mg, 6.86 mmol) was added to diphenyl diselenide (1.02 g, 3.38 mmol) in EtOH (15 ml). After addition of the disodium salt of L-2-chlorosuccinic acid [57] (1.06 g, 6.56 mmol) in H_2O (15 ml), the mixture was stirred at r.t. for 12 h. The soln. was washed with hexane and acidified with 2M aq. HCl. The filtered precipitate was dried to give **20** (300 mg, 23%), $[\alpha]_D^{r.t.} = +66.1$ ($c = 0.516$, $CHCl_3$), which had previously been reported as a racemate [58].

N-(Benzyloxycarbonyl)-O-(phenylaminocarbonyl)-L-serine (**21e**). *N*-(Benzyloxycarbonyl)-L-serine (240 mg, 1.0 mmol) and phenyl isocyanate (120 mg, 0.11 ml, 1.0 mmol) were refluxed in AcOEt (5 ml) for 1 h. After evaporation, the residue was recrystallized from $CHCl_3$/hexane: **21e** (240 mg, 67%). M.p. 120–121°. $[\alpha]_D^{r.t.} = +10.06$ ($c = 0.634$, MeOH). IR (KBr): 3392*m*, 1716*s*, 1659*m*, 1524*m*, 1445*m*, 1269*m*, 1225*m*, 1196*m*, 1072*m*, 755*w*, 696*w*. ^{1}H-NMR (300 MHz, CD_3OD): 4.39–4.56 (*m*, 3H); 5.08 (*d*, $J = 12.6$, 1H); 5.13 (*d*, $J = 12.6$, 1H); 7.01 (*t*, $J = 7.4$, 1H); 7.22–7.41 (*m*, 9H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 56.07; 66.24; 68.77; 120.87; 125.15; 129.82; 129.99; 130.45; 130.80; 139.10; 140.98; 156.30; 159.49; 173.75. FAB-MS: 359.1 ($[M + H]^+$). Anal. calc. for $C_{18}H_{18}N_2O_6$ (358.35): C 60.33, H 5.06, N 7.82; found: C 60.28, H 5.16, N 7.91.

X-Ray Crystal Structure of **3**. Crystal data at 100 K for $(C_{47}H_{34}N_6O_2) \cdot (C_4H_8O) \cdot 2(C_4H_8O_2) \cdot 2(H_2O)$, M_r 999.1: monoclinic, space group *C*2 (No. 5), $\rho_{calc.} = 1.30$ g cm^{-3}, $Z = 4$, $a = 22.442$ (2), $b = 14.119$ (2), $c = 17.729$ (2) Å, $\beta = 114.92$ (2)°, $V = 5094.6$ (1.1) Å^3. *Enraf-Nonius-CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å. Single crystals were obtained by slow evaporation of an AcOEt/THF soln. The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL PLUS), using an isotropic extinction correction and experimental weights. Final $R(F) = 0.068$, $wR(F) = 0.094$ for 713 variables and 4607 observed reflexions with $F > 6\sigma F$ and $\theta < 74°$ (heavy atoms, anisotropic; H-atoms, isotropic; H positions based on stereochemical considerations). The molecular geometry is given in *Table 8*. Further details of the crystal structure investigations are available on request from the Director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK.

Table 8. *Selected Bond Lengths* [Å] *and Bond Angles* [°] *of* **3**

C(1)–C(2)	1.383 (7)	C(1)–C(6)	1.414 (7)
C(1)–C(13)	1.522 (7)	C(2)–C(3)	1.425 (8)
C(3)–C(4)	1.402 (12)	C(3)–C(40)	1.486 (9)
C(4)–C(5)	1.390 (9)	C(5)–C(6)	1.402 (8)
C(6)–C(7)	1.451 (8)	C(7)–C(8)	1.400 (11)
C(7)–C(12)	1.407 (10)	C(8)–C(9)	1.373 (8)
C(9)–C(10)	1.400 (11)	C(10)–C(11)	1.400 (12)
C(11)–C(12)	1.368 (7)	C(12)–C(13)	1.521 (10)
C(13)–C(14)	1.513 (11)	C(13)–C(25)	1.538 (10)
C(40)–N(41)	1.374 (8)	C(40)–O(55)	1.237 (11)
N(41)–C(42)	1.384 (7)	C(42)–C(43)	1.425 (11)
C(42)–N(53)	1.323 (9)	C(43)–C(44)	1.372 (8)
C(44)–C(45)	1.410 (10)	C(45)–C(46)	1.412 (7)
C(45)–C(52)	1.432 (11)	C(46)–C(47)	1.519 (11)
C(46)–C(48)	1.375 (10)	C(48)–C(49)	1.419 (11)
C(49)–C(50)	1.513 (10)	C(49)–N(51)	1.287 (7)
N(51)–C(52)	1.368 (9)	C(52)–N(53)	1.357 (7)
C(23)–C(26)	1.501 (11)	C(26)–N(27)	1.383 (10)
C(26)–O(54)	1.214 (10)	N(27)–C(28)	1.398 (10)

Table 8 (cont.)

C(2)–C(1)–C(13)	129.2 (4)	C(6)–C(1)–C(13)	109.8 (4)
C(2)–C(3)–C(40)	116.6 (7)	C(4)–C(3)–C(40)	124.0 (5)
C(1)–C(6)–C(7)	108.6 (5)	C(6)–C(7)–C(12)	108.7 (6)
C(7)–C(12)–C(13)	110.1 (5)	C(11)–C(12)–C(13)	128.9 (7)
C(1)–C(13)–C(12)	101.4 (5)	C(1)–C(13)–C(14)	118.3 (5)
C(12)–C(13)–C(14)	115.4 (5)	C(1)–C(13)–C(25)	109.5 (5)
C(12)–C(13)–C(25)	111.3 (5)	C(14)–C(13)–C(25)	101.1 (6)
C(13)–C(14)–C(15)	127.2 (7)	C(13)–C(14)–C(19)	111.5 (6)
C(3)–C(40)–N(41)	115.9 (7)	C(3)–C(40)–O(55)	120.9 (5)
N(41)–C(40)–O(55)	123.2 (6)	C(40)–N(41)–C(42)	128.0 (7)
N(41)–C(42)–C(43)	123.8 (6)	N(41)–C(42)–N(53)	113.5 (7)
C(43)–C(42)–N(53)	122.7 (5)	C(42)–C(43)–C(44)	118.5 (6)
C(43)–C(44)–C(45)	120.9 (7)	C(44)–C(45)–C(46)	125.5 (7)
C(44)–C(45)–C(52)	116.1 (5)	C(46)–C(45)–C(52)	118.3 (6)
C(45)–C(46)–C(47)	120.7 (6)	C(45)–C(46)–C(48)	118.0 (7)
C(47)–C(46)–C(48)	121.3 (5)	C(46)–C(48)–C(49)	119.7 (5)
C(48)–C(49)–C(50)	119.3 (5)	C(48)–C(49)–N(51)	123.4 (7)
C(50)–C(49)–N(51)	117.3 (7)	C(49)–N(51)–C(52)	119.3 (7)
C(45)–C(52)–N(51)	121.2 (5)	C(45)–C(52)–N(53)	123.0 (6)
N(51)–C(52)–N(53)	115.7 (7)	C(42)–N(53)–C(52)	118.8 (7)
C(23)–C(26)–N(27)	113.8 (7)	N(27)–C(28)–N(39)	113.5 (7)

Computer Modeling: Modified Torsional Parameters for Amidopyridines and Amidonaphthyridines. The low quality $C(sp^2)$–$N(sp^2)$–$C(sp^2)$ equilibrium bond angle was changed from 110 to 120° to reproduce the geometry of **3** as well as 26 other amidopyridines retrieved from the *Cambridge Crystal Structure Data Base*. The $V_2/2$ torsional parameters affecting rotation about the Ar–CO and N–(naphthy) bonds of **3** as well as the amide bond were then varied to reproduce the relative energies of seven stationary points of a model for **3**, *N*-(pyridin-2-yl)benzamide; (BA), which were calculated using local density functional theory (LDFT) as implemented in the program DGauss which is part of the UniChem package of programs running on the *Cray Y-MP* of the ETH-Zürich [59]. A double zeta plus polarization (DGauss notation: DZVP2/A2) basis set optimized for use in DFT calculations was employed. Initially, relative energies of stationary points having the pyridine N-atom of BA in a *trans* orientation to the amide NH group were not reproduced during the parameterization. Following the example of *MacDonald* and *Still* [60], a remote torsional interaction which accounts for some of the dipole-dipole repulsion between the carbonyl O-atom and the pyridine N-atom was introduced. The final parameter set used in the calculations on **3** and its complexes is given in *Table 9*.

Table 9. *Modified AMBER* Parameters*

	Original AMBER*	Modified AMBER*
Bend	Equilibrium angle [°]	Equilibrium angle [°]
CU–N2–CU	110.0	120.0
Torsion	$V_2/2$ [kcal mol^{-1}]	$V_2/2$ [kcal mol^{-1}]
O=C–N–$C(sp^2)$	1.500	1.779
$C(sp^2)$*$C(sp^2)$–C(=O)–N	0.650	1.071
$C(sp^2)$*$C(sp^2)$–C=O	0.650	1.071
$C(sp^2)$*$C(sp^2)$–$N(sp^2)$–X	1.000	1.283
$C(sp^2)$–$N(sp^2)$	1.325	1.790
Remote torsion	$V_1/2$ [kcal mol^{-1}]	$V_1/2$ [kcal mol^{-1}]
O=C···$C(sp^2)$*$N(sp^2)$	0.000	3.519

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