An artificial receptor for the intermolecular and enantioselective formation of peptide sheets

Frank Eblinger and Hans-Jörg Schneider*†

FR Organische Chemie, Universität des Saarlandes, D 66041 Saarbrücken, Germany

Received (in Cambridge, UK) 22nd July 1998, Accepted 7th September 1998

Peptide strands coupled at the C terminus to bis[*p*-(aminomethyl)phenyl] ether allow in $CHCl_3$ solution association of lipophilic N-protected peptides with hydrogen bonds in the mode of antiparallel β-sheets; the enantioselectivity observed with a phenylalanine derivative is characterized by a binding constant ratio of around 15.

The formation of β-sheets in peptide strands is an important part of protein folding and is of general interest with respect to peptide recognition. Models showing typical β-sheet patterns have until now invariably been formed between *covalently* bound peptide strands with *intramolecular* hydrogen bonds. For the construction of β-sheet patterns Feigel *et al*. used amino acid fragments within macrocycles,[1] whereas in the models of Kemp *et al*.,[2] Kelly *et al*.,[3] Nowick *et al*.,[4] Gellman *et al*.[5] and Ogawa *et al*.,[6] special scaffolds between peptide chains secure a possible intramolecular binding in such hairpin-type structures. In line with our earlier analyses of energetic contributions of hydrogen bonds in such amide-type structures[7] we wanted to measure association constants between separate peptide strands; at the same time we were looking for biomimetic receptors which could distinguish enantiomers on the basis of hydrogen bonds between peptide strands.

Computer aided molecular modelling suggested two peptide strands coupled *via* the *para* positions to a diphenyl ether spacer (or diphenylamine, or diphenylmethane) as suitable host. Such an entity could bind a single strand peptide in the fashion of an antiparallel β-sheet, *e.g*. with two hydrogen bonds per amino acid at each side of the guest molecule (see Fig. 1). In order to avoid steric interference with the spacer the N-terminus of the guest peptide had to bear a formyl group, whereas the C-terminus can in principle take up any amine (or amino acid sequence). The semi-open structure makes this type of receptor a promising starting point for the building-up of longer β-sheets.

As in most other studies[8] relying on hydrogen bonds for complex formation, both host and guest compounds had to be soluble in hydrophobic media such as $CHCl_3$. We tried to achieve this first by introduction of long alkyl chains at the end of the peptide strands. The corresponding derivatives (*e.g*. with R = $C_{15}H_{31}$), however, turned out to be sparingly soluble in $CDCl_3$. Only introduction of the more bulky and spherical adamantyl groups avoid lattice stabilization in the solid state *via* parallel aligned n-alkane chains, and provided materials soluble in $CHCl_3$. Scheme 1 shows the synthesis of the host and guest derivatives; the cleft compound **1** was obtained in 10% overall yield, with $[\alpha]_D^{25}$ = −67.3 (*c* 0.2 M in EtOH) and only one set of ^1H and ^{13}C NMR signals at 400 and 100 MHz, respectively, indicating the absence of racemization. The enantiomers D-**2** and L-**2**, synthesized from commercially available amino acids, show $[\alpha]_D^{25}$ values of −14.7 and +15.2, respectively (*c* 0.2 M in EtOH).

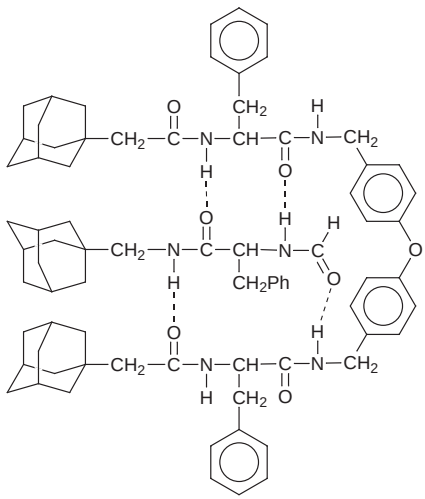
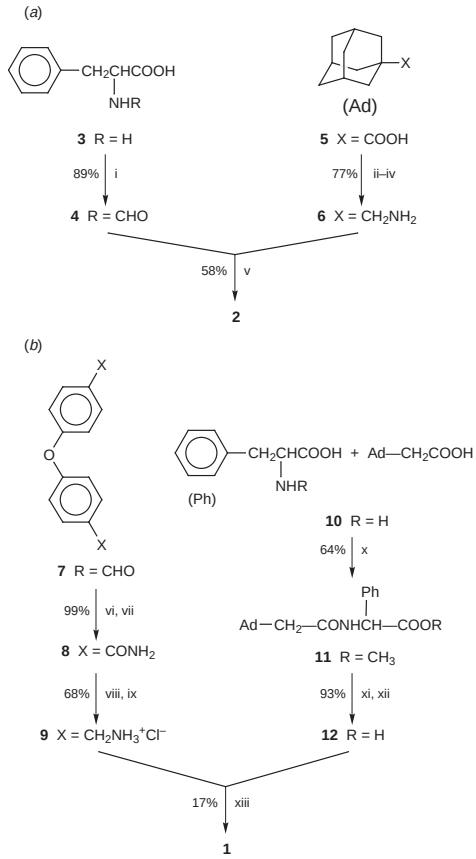


Fig. 1 Antiparallel β-sheet structure of host **1** and guest **2**.



Scheme 1 *Reagents and conditions*: i, HCO_2H, Ac_2O, 278 K; ii, PCl_5; iii, NH_3; iv, BH_3·THF; v, DCC, room temp.; vi, $SOCl_2$; vii, aq, NH_3; viii, BH_3·THF; ix, MeOH, HCl; x, carbonyldiimidazole; xi, NaOH; xii, HCl; xiii, carbonyldiimidazole.

Fig. 2 shows titration curves with host **1** and the enantiomeric guest compounds D-**2** and L-**2**. Whereas the complex with the L-isomer is strong enough to be evaluated *via* non-linear least-squares fitting of the N–H NMR shift change, the complexation constant for the D-isomer can only be obtained from the

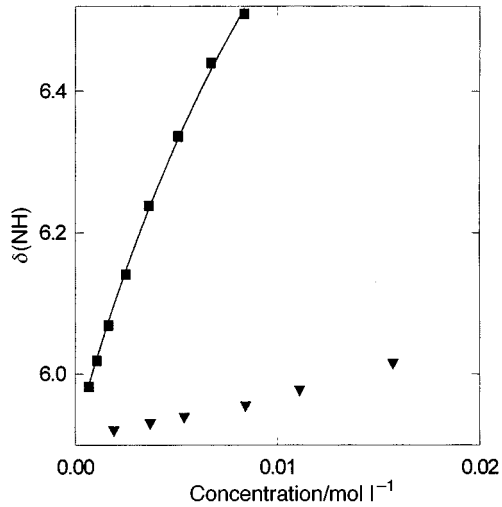


Fig. 2 Titration curves of host **1** with guests (■) L-**2** and (▼) D-**2** in $CDCl_3$ at 298 K. The line represents the best fit.

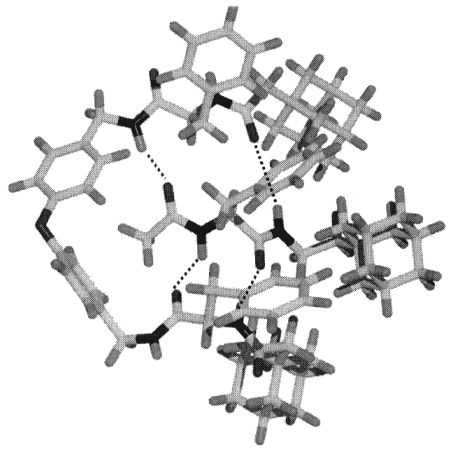


Fig. 3 Quanta/CHARMm minimized structures of the complex of host **1** and guest L-**2**. Hydrogen bonds are marked as dashed bonds.

Table 1 NMR titration results of host **1** and guests D-**2** and L-**2** in $CDCl_3$ at 298 K (The data represent the mean values of two observed N–H signals)

Complex	K/M^{-1}	ΔG/kJ mol^{-1}	CIS (ppm)
1·L-**2**	80 ± 6%	−10.8	1.79
1·D-**2 D**	5 ± 10%	−4.1	(1.79)

observed two N–H shifts of host compound **1** in comparison to the CIS value of 1.8 ppm which is expected for a 100% complex formation. The corresponding CIS for the L-enantiomer complex calculated from the least-squares fit is close to the N–H shielding effects observed in related amide-type associations,[7b] in line with the structure proposed in Fig. 1. The expected downfield shifts of the CH(α) protons could not be evaluated due to small shift changes and/or overlapping with other signals during the titration. Control experiments with related peptide derivatives, also bearing adamantyl groups for solubility reason, showed no self-association in $CHCl_3$; this supports the suggestion that an effective recognition requires hydrogen bonds from *two* sides of the guest as depictet in Fig. 1.

The total binding free energy ΔG (Table 1) for the 'best' isomer L-**2** (11 kJ mol^{-1}) is relatively small in comparison with values observed with related systems, which for $CHCl_3$ as solvent predict up to 5 kJ mol^{-1} per hydrogen bond.[7] The reason for the relatively weak binding might be due to some geometric mismatch, but must be seen primarily as a consequence of unfavourable secondary interactions between donor and acceptor groups. These have been elucidated by Jorgensen *et al*.,[9] and were found to be as large as *e.g*. 2.8 kJ mol^{-1} by systematic analysis of many amide-type associations in $CHCl_3$.[7b]

The degree of chiral discrimination ($\Delta\Delta G \approx 7$ kJ mol^{-1}) compares favourably with the few enantioselective peptide receptors hitherto available.[8a,10] Molecular mechanics calculations (gas phase, $\varepsilon = 3$) using CHARMm[11] shed light on the origin of the observed stereoselectivity: only with the L-isomer does one obtain after energy minimization a structure with the four hydrogen bonds, as depicted in Fig. 3. Minimizations with the D-isomer invariably lead to structures without hydrogen bonds: Unfavourable interactions of the guest (D-**2**) and host benzyl groups lead to deformation of the backbone, preventing the formation of hydrogen bonds. As is often the case, the observed stereoselectivity of association is a consequence of repulsion between groups which are not involved in the formation of non-covalent bonds, and which are remote from the actual binding sites.

Notes and references

† E-mail: ch12hs@rz.uni-sb.de

1 V. Brandmeier, W. H. B. Sauer and M. Feigel, *Helv. Chim. Acta*, 1994, 77, 70; C. Gailer and M. Feigel, *J. Comput. Aided Mol. Des*., 1997, **11**, 273 and references cited therein.
2 D. S. Kemp, B. R. Bowen and C. C. Muendel, *J. Org. Chem*., 1990, **55**, 4650; D. S. Kemp and Z. Q. Li, *Tetrahedron Lett*., 1995, **36**, 4175 and 4179 and references cited therein.
3 J. P. Schneider and J. W. Kelly, *Chem. Rev*., 1995, **95**, 2169; C. L. Nesloney and J. W. Kelly, *J. Am. Chem. Soc*., 1996, **118**, 5836 and references cited therein.
4 J. S. Nowick, E. M. Smith and M. Pairish, *Chem. Soc. Rev*., 1996, **25**, 401; D. L. Holmes, E. M. Smith and J. S. Nowick, *J. Am. Chem. Soc*., 1997, **119**, 7665; J. S. Nowick, M. Pairish, I. Q. Lee, D. L. Holmes and J. W. Ziller, *J. Am. Chem. Soc*., 1997, **119**, 5413; J. S. Nowick and S. Insaf, *J. Am. Chem. Soc*., 1997, **119**, 10903 and references cited therein.
5 R. R. Gardner, L. A. Christianson and S. H. Gellman, *J. Am. Chem. Soc*., 1997, **119**, 5041; H. E. Stanger and S. H. Gellman, *J. Am. Chem. Soc*., 1998, **120**, 4236 and references cited therein.
6 A. B. Gretchikhine and M. Y. Ogawa, *J. Am. Chem. Soc*., 1996, **118**, 1543 and references cited therein.
7 (*a*) H.-J. Schneider, R. K. Juneja and S. Simova, *Chem. Ber*., 1989, **112**, 1211; (*b*) J. Sartorius and H.-J. Schneider, *Chem. Eur. J*., 1996, **2**, 1446; H.-J. Schneider, *Chem. Soc. Rev*., 1994, **22**, 227.
8 (*a*) For a short review see: H.-J. Schneider, *Angew. Chem., Int. Ed. Engl*., 1993, **32**, 848; *Angew. Chem*., 1993, **105**, 890; (*b*) M. Famulok, K. S. Jeong, D. Deslongchamps and J. Jr. Rebek, *Angew. Chem*., 1991, **103**, 880; (*c*) R. Liu and W. C. Still, *Tetrahedron Lett*., 1993, **34**, 2573; (*d*) A. Borchardt and W. C. Still, *J. Am. Chem. Soc*., 1994, **116**, 373; (*e*) J. Dowden, P. D. Edwards and J. D. Kilburn, *Tetrahedron Lett*., 1997, **38**, 1095; (*f*) E. Martinborough, T. M. Denti, P. P. Castro, T. B. Wyman, C. B. Knobler and F. Diederich, *Helv. Chim. Acta*, 1995, **78**, 1037; (*g*) A. Casnati, E. Di Modugno, M. Fabbi, M. Pelizzi, A. Pochini, F. Sansone, G. Tarzia and R. Ungaro, *Bioorg. Med. Chem. Lett*., 1996, **6**, 2699; (*h*) M. Crego, A. Partearroyo, C. Raposo, M. L. Mussons, J. L. Lopez, V. Alcazar and J. R. Moran, *Tetrahedron Lett*., 1994, **35**, 1435 and references cited therein.
9 W. Jorgensen and J. Pranata, *J. Am. Chem. Soc*., 1990, **112**, 2008.
10 S. S. Yoon and C. W. Still, *Tetrahedron Lett*., 1994, **35**, 8557; *J. Am. Chem. Soc*., 1993, **115**, 823 and references cited therein.
11 B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan and M. Karplus, *J. Comput. Chem*., 1983, **4**, 187; C. L. Brooks and M. Karplus, *Methods Enzymol*., 1986, **127**, 369; A.T. Brünger and M. Karplus, *Acc. Chem. Res*., 1991, **24**, 54.

Communication 8/05720F