Tetrahedron: Asymmetry Vol. 1, No.6, pp.367-370, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Intramolecular Host-Guest Complexes Of D- And L-Mono-6 Phenylalanyl-Amino-6-Deoxy Cyclomalto-Heptaoses.

Hélène Parrot-Lopez [a], Hervé Galons [a], Anthony W. Coleman [b]
Florence Djedaini [c], Nelly Keller [c] and Bruno Perly [c*]

a- Laboratoire de Chimie Organiqtte 3, Université de Paris V, 75006 Paris (France)
b- Unité Associée CNRS 496, Université de Paris XI. 922% Chatenay Malabry (France)
c- Service de Chimie Moléculaire, Centre d'Etudes Nucléaires de Saclay, 91191 Gif sur Yvette (France)

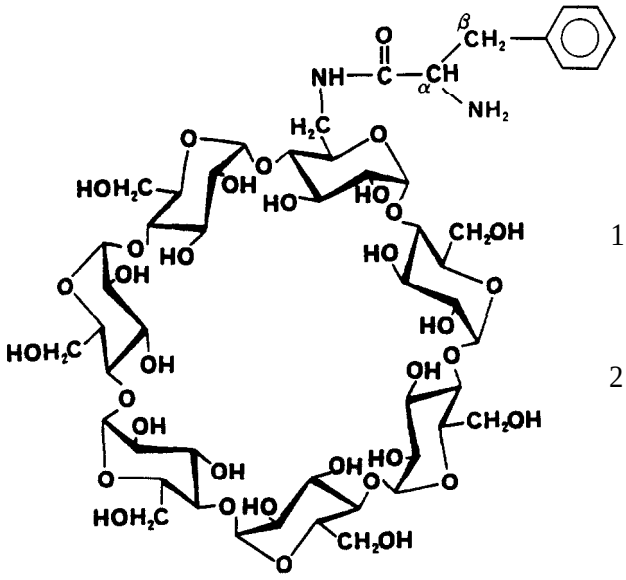
(Received 14 *May* 1990)

Abstract : Coupling of L- and D-phenylalanine to mono 6-amino-β-cyclodextrin leads to the formation of diastereoisomeric intramolecular inclusion compounds. The proton NMR spectra of the two products show clear chiral discrimination between the two molecules with regard to the interaction of the aromatic moieties with the cyclodextrin cavity.

Chiral differentiation in host-guest systems has received extensive study in recent years in view of its importance in bio-organic chemistry and its applications in enantio-selective separation&b. The cyclomalto-oligosaccharides (cyclodextrins or CD's) represent a particularly am-active class of readily available natural host molecules exhibiting chiral discrimination properties in inclusion processes[2,3], and in separation technology[4,5]. The enantio-selective properties are dependent on differences in interactions between the host cavity and the substrate isomers. It is hence expected that chemical modification of the cyclodextrin will strongly affect this selectivity owing to possible variations in both the interactions and the conformation of the host molecule[6]. The D- and L- mono-6-phenylalanylamino-6-deoxy-cyclomalto-heptaose (D- and L-Phe-NH-P-CD, Figure 1) are diastereoisomers resulting from the grafting of L- or D-phenylalanine on mono 6-amino-6-deoxy cyclomalto-heptaose (6-NH2-β-CD). They were synthesized as models of host molecules possessing both an hydrophobic cavity and a chiral aromatic moiety. The present ^{1}H NMR study of the title compounds in aqueous solutions reveals the formation of intramolecular inclusion complexes with strong differentiation between the two diastereoisomers in terms of the conformational adaptation required to optimize the interaction of the aromatic moiety with the hydrophobic cyclodextrin cavity.

D- and L-Phe-NH-P-CD were prepared by the following synthetic route. Mono-6-azido-cyclomalto-heptaose[7] (N3-β-CD, 0.86 mmol.) was reduced smoothly by treatment with triphenylphosphine (3.45 mmol) in anhydrous dimethylformamide (15 mL) for 1 h at room temperature followed by addition of conc. ammonium hydroxide (28%, 2 mL). After 12 h at room temperature, the solvent was removed in vacuo and the solid residue taken up in water. Removal of the insoluble triphenylphosphine and triphenylphosphine oxide by filtration and recrystallization in water afforded the mono-6-amino-cyclomalto-heptaose in 99% yield. The latter compound was coupled to the pertinent N-Boc protected isomer of phenylalanine by the dicyclohexylcarbodiimide/hydroxybenzotriazole procedure8 in dimethylformamide at 0' and the protecting group was cleaved in neat trifluoroacetic acid. **1** and 2 were obtained in 75% yields. Purification was achieved by recrystallization at pH 8-9 since both compounds are sparingly soluble in water as free amines.

For NMR experiments, they were converted into the corresponding hydrochlorides. It is noteworthy that the ionic state does not affect the major results presented in paper. The chemical integrity and purity of the title and intermediate compounds were checked by proton NMR and by thin-layer chromatography.



1: L-Phe-NH-P-CD

S configuration at C_α

2 : D-Phe-NH-P-CD

R configuration at C_α

Figure 1 : Molecular structures of the title compounds **1** and **2.**

The 600 MHz ^1H NMR spectra of **1** and 2 in deuterium oxide are displayed in Figure 2. All experiments were performed using 10 mM solutions of the corresponding hydrochlorides (pH = 4.0) in deuterium oxide at 298 K. The most striking effect of the reduction of symmetry to Cl is provided by the anomeric protons in the 4.95 - 5.20 ppm range. The seven expected individual signals are indeed observed for 2. The corresponding spectral region of 1 shows slightly weaker inequivalence of the anomeric protons. Mono-substitution indeed leads to a Cl symmetry in which every proton becomes theoretically inequivalent. This inequivalence has been observed for other derivatives[7,9] but such a striking modification of the NMR spectra is not commonly encountered. A more classical situation was found for the intermediate compounds used in this synthesis[6]. The high field region containing all non-anomeric protons of the cyclomalto-heptaose and the aliphatic protons of the amino-acid moiety is strongly different for the two diastereoisomers. A general feature is however the considerable spectral dispersion as compared to unmodified cyclodexttin for which the corresponding protons appear in the 3.6 - 4.0 ppm range. Besides the expected effect of substitution by the amino group, a large number of signals are shifted upfield and the observed spectral complexity implies that all protons are affected by the reduction of molecular symmetry.

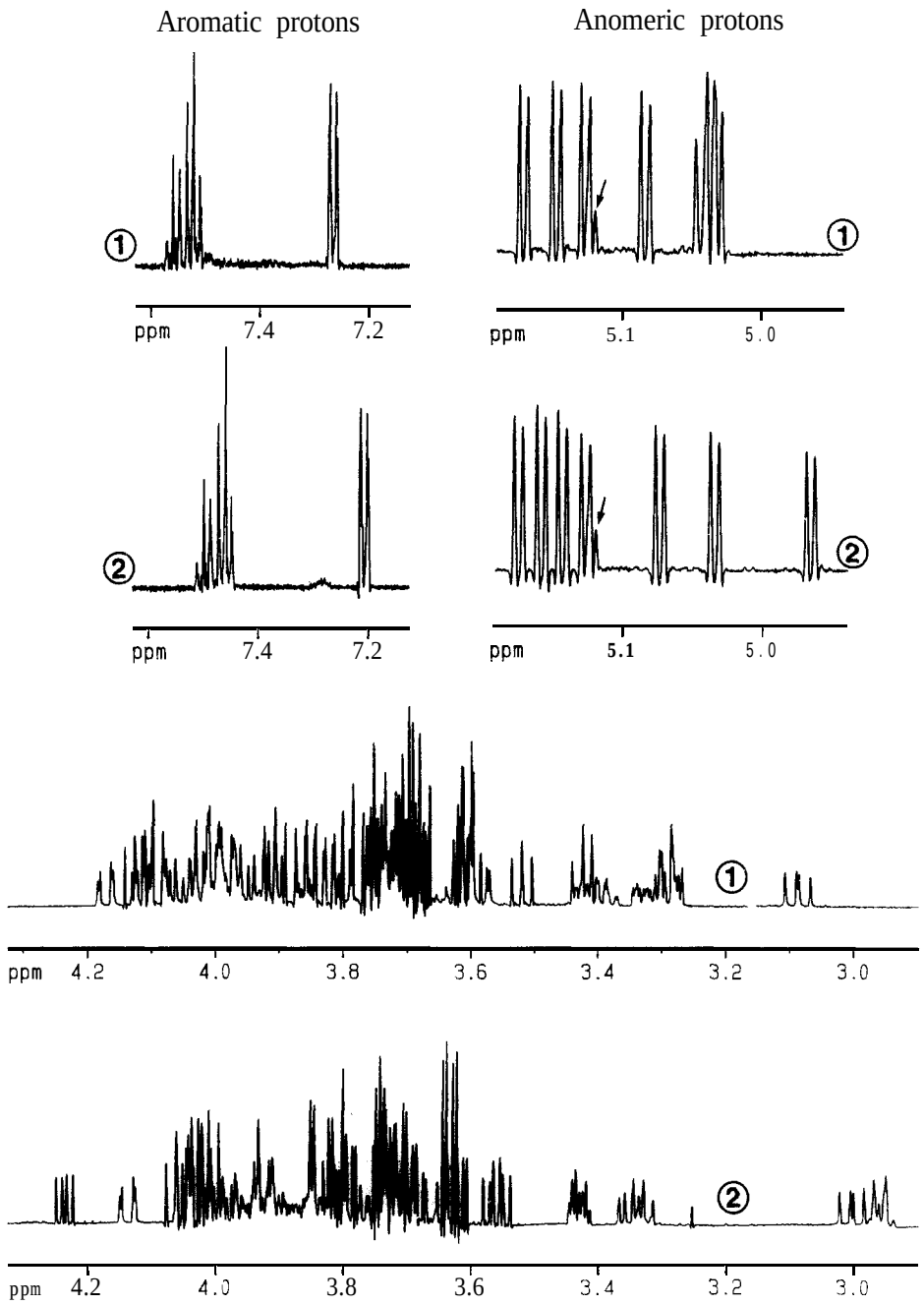


Figure 2 : 600 MHz ^1H NMR spectra of 10 mM solutions of **1** and 2 in deuterium oxide at 298 K. Signals indicated by arrows arise from a small (ca. 4 %) amount of residual unmodified cyclodextrin.

The large shielding effects can be rationalized by considering inclusion of the aromatic ring into the internal cavity. This phenomenon is indeed expected to induce shielding ring currents and to enhance the inequivalence due to substitution. This assumption is further supported by the chemical shifts of protons from the phenyl ring of the amino-acid. The corresponding signals are indeed deshielded relative to free phenylalanine as encountered for the inclusion of the free amino-acid in β-cyclodextrin[10]. This deshielding effect is due to a strong modification of the polarity experienced by the phenyl ***ring*** upon inclusion in the relatively hydrophobic cavity of the cyclodexttin.

At this point, one must make a clear distinction between inter- and intramolecular complexes. NMR provides evidences for the reality of the latter situation leading to a model where the modified cyclomalto-heptaose includes its own aromatic ring in the hydrophobic cavity. This is indeed supported by the fact that the NMR spectra of both compounds in deuterium oxide are not affected by concentration in the l-20 mM range. In the case of intermolecular inclusion complexes, a large concentration dependence is expected owing to the generally weak association constants involved in these processes[11]. In the present case, additional interactions have to be considered (i.e. intramolecular hydrogen bonds) to account for the unexpected stability of these inclusion complexes. New ultra-high resolution bidimensional NMR experiments dedicated to an accurate sequential determination of chemical shifts and coupling constants for all protons are currently being undertaken and will be described elsewhere. Preliminary data has already shown that several torsional angles derived from the coupling constants are unusual and fully support the presence of intramolecular complexes. These molecules are hence of considerable interest as they provide pure inclusion complexes in solution. A complete NMR analysis and the subsequent modelling of ring current effects and coupling constants is expected to provide, in conjunction with molecular graphics analysis, the first example of three-dimensional structure determination in these series and a better understanding of molecular adaptation phenomena involved in inclusion processes.

References :

1. (a) Armstrong, D.W. ***J. Liq. Chromarogr.* 1983,*7*, 353-376** (b) Toda, F. ***Topics in Current Chemistry* 1987, *140*, 43-69**, Springer Verlag, Berlin.
2. Casy, A.F.; Mercer, A.D. ***Magn. Res. Chem.* 1988, *26*, 765-774**
3. Tanaka, Y.; Sakuraba, H.; Nakanishi, H. ***J. Org. Chem.* 1990, *55*, 564-567**
4. Warsh, D.; Vbgtle, F. ***Topics in Current Chemistry* 1987, *140*, 21-41**, Springer Verlag, Berlin.
5. Boland, W.; König, W.A.; Krebber, R.; Müller, D.G. ***Helv. Chim. Acta 1979, 72, 1288-1292***
6. Murakama, T.; Harata, K.; Morimoto, S. ***Chem. Lett.* 1988, 553-556**
7. Parrot-Lopez, H.; Djedaïni, F.; Perly, B.; Coleman, A.W.; Galons, H.; Miocque, M. ***Tetrahedron Lett.* 1990, *31*, 1999-2002**
8. König, W.; Geiger, R. ***Chem. Ber. 1970,103, 788-798***
9. Spencer, C.M.; Stoddart, J.F.; Zarzycki, R. ***J. Chem. Soc. Perkin. Trans. II 1987, 1323-1336***
10. Inoue, Y.; Kuan, F.H.; Chûjô, R. ***Bull. Chem. Soc. Jpn.* 1987, *60*, 2539-2545**
11. Djedaïni, F.; Lin, S.Z.; Perly, B.; Wouessidjewe, D. ***J. Pharm. Sci.* 1990,** in press.