Behaviour of Stereoisomeric *O*-Methyltyrosyl-*p*-nitrophenylalanines within the β-Cyclodextrin Cavity

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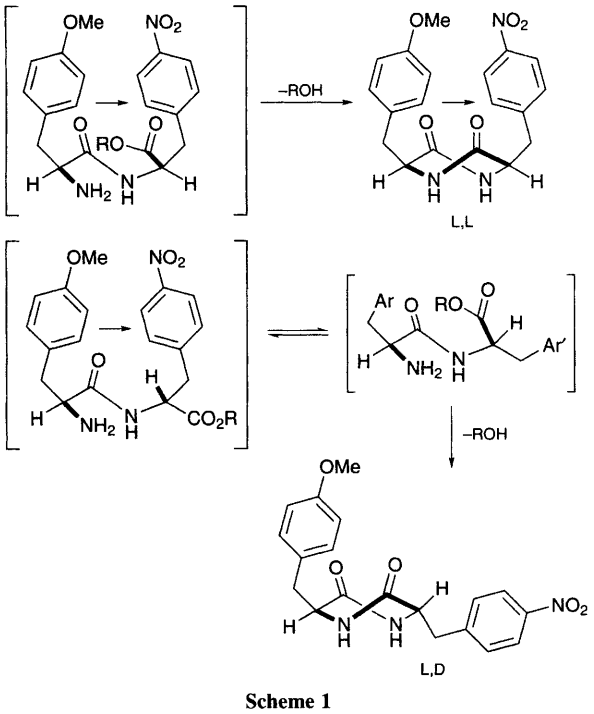
Cyclisation of the L,D- and L,L-*O*-methyltyrosyl-*p*-nitrophenylalanine methyl esters is studied; in the presence of β-cyclodextrin, reaction took place only with the L,L-isomer.

Cyclic dipeptides (piperazine-2,5-diones, DKP) continue to attract the attention of chemists because many of these substances display remarkable biological activities, *e.g.* as antineoplastics,[1] anti-virals,[2] plant growth regulators[3] and hormone secretion suppressors.[4] Recently, it has been shown that those cyclic dipeptides containing a histidine residue can catalyse selective hydrolysis and methanolysis of certain esters[5] and asymmetric α-cyanohydrination of aldehydes.[6]

The conformational properties of cyclic dipeptides are quite intriguing. In particular, a compound having a substituent at C-3 which is terminated by an aromatic ring usually prefers to present the substituent in an axial orientation. The cause of this preference is still unknown but the notion of π,π-interactions between the aromatic nucleus in the side chain with the piperazinedione ring has been invalidated. We were interested in the effect of π,π-interactions between two aryl groups of (X)Phe-(Y)Phe dipeptides on the relative rates of the substituted 3,5-dibenzylpiperazine-2,6-dione formation. We envisaged that if intramolecular π,π-interactions of the dipeptide derivatives are important the L,L-form and the D,D-forms should cyclise more readily than the L,D or D,L-forms (Scheme 1) because preorganization places the reacting amino and carboxy termini in spatial proximity in one case and drives them apart in the other; cyclisation of the L,D or D,L-isomer requires additional energy to dissociate the interactions.

We employed H_2N-(MeOPhe)-(O_2NPhe)-CO_2Me for our study. The *N*-Boc dipeptide methyl esters were prepared from *N*-Boc-*O*-methyltyrosine and *p*-nitrophenylalanine methyl ester by DCC-mediated coupling, and the cleavage of the Boc group was achieved by treatment with trifluoroacetic acid. The thermal cyclisation was conducted in solvents such as methanol, DMF and Me_2SO, and its progress was monitored by HPLC. As it was found that the completion of cyclisation of the L,L-isomer and the L,D-isomer required 32 and 31 h in refluxing methanol, respectively, and 8.5 and 9 h in DMF, no conclusion could be drawn. Evidently, the relatively weak π,π-interactions were overwhelmed by solvation effects; therefore we added β-cyclodextrin to a [$^2H_6$]Me_2SO solution of the dipeptide methyl ester and followed the cyclisation by NMR at 50 °C. β-Cyclodextrin (β-CD) has an endolipophilic cavity of about 6.5 Å in diameter which ideally accommodates two benzene rings held in parallel, and therefore the hydrophobic environment is conducive to rapid formation of the inclusion compound without exerting any electronic perturbation on the guest molecule. Cyclisation occurred only while the aromatic rings maintained a π-complexed motif. Under such conditions the L,L-isomer underwent 50% cyclisation after 31 h (k_{obs} 5.3 × 10^{-4} min^{-1}), but the L,D-isomer remained completely unchanged. Once slid into the cavity of β-CD the *N*- and *C*-termini of the latter compound were kept apart. We believe the prerequisite conformation of the dipeptide for insertion into β-CD is that the two aromatic rings are cofacial, and steric constraints did not allow entry of only one ring followed by a swing action to insert the other. Otherwise we should have observed at least a small amount of the cyclised product from the L,D-isomer deriving from an inclusion complex having one aromatic ring inside and one outside.

A pertinent observation is that β-CD included only *one* *O*-methyltyrosine or *p*-nitrophenylalanine when mixed with either one of these amino acids, but the formation of a 1 : 1 : 1-triplex by inclusion of two amino acids into one β-CD molecule was detected when both amino acids were present. The inescapable conclusion is that π,π-interactions between proper partners indeed existed, and in this research we have found a way to differentiate diastereoisomers by conformational restriction through formation of inclusion complexes.



Scheme 1

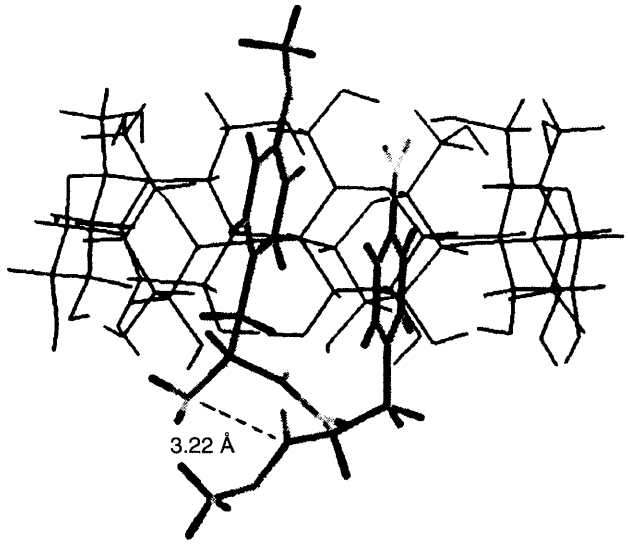


Fig. 1 L,L-Dipeptide ester in β-cyclodextrin

We have also done some molecular modeling studies using the INSIGHT II program on a Silicon Graphics IRIS work station. After energy minimization the conformation of the L,L-cyclodipeptide (E_{total} 82.52 kcal mol^{-1}) (1 cal = 4.184 J) was found to have the two aromatic rings occupying approximately parallel planes separated by 4.08 Å between two centres, whereas three different conformations for the L,D-isomer are of similar energies (E_{total} 89.63, 89.98 and 90.58 kcal mol^{-1}, respectively, for the antiperiplanar, synperiplanar-MeOPhe inside and synperiplanar-MeOPhe outside conformations). Thus both aromatic residues may insert into β-CD, or either one of the *p*-substituted phenylalanine residues may be trapped while leaving the other outside. The estimated N···C=O distance is 3.22 and 3.95 Å, respectively, for the wholly trapped L,L- and L,D-dipeptide precursors (Figs. 1 and 2); furthermore, the models show the former compound is subject to less strain during twisting to bring the nitrogen atom and the carbonyl group closer, and when a dipeptide substrate is inserted into the β-CD cavity with only the *O*-methyltyrosyl residue the *p*-nitrophenylalanyl portion can no longer be placed inside by mechanical manipulation.

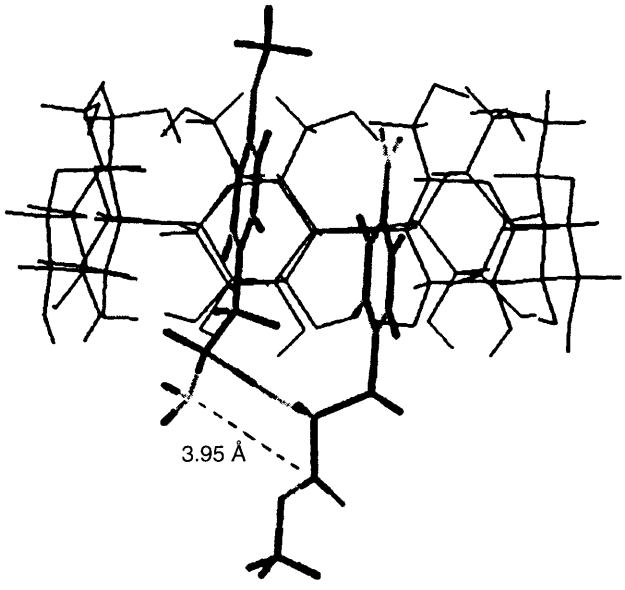


Fig. 2 L,D-Dipeptide ester in β-cyclodextrin

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