SHORT PAPER

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Preparation and chiral discrimination of R-(-)-2-phenylglycinol modified β-cyclodextrin†

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R-(-)-2-phenylglycinol monomodified β-cyclodextrin (β-CD) was synthesised under microwave irradiation. It displayed high chiral discrimination when it was complexed with amino acids.

Keywords: R-(-)-2-phenylglycinal modified β-cyclodextrin

Cyclodextrins (α, β and γ) containing six, seven or eight α-1,4-linked β-(+)-glucopyranose units respectively, are cyclic oligosaccharides. Their significant character is to form inclusion complex with a wide variety of substrates.[1,2] When they act as host molecules, interaction with a racemic guest may lead to the formation of diastereoisomeric complexes with differing thermodynamic stability. This chiral discrimination by cyclodextrins and their derivatives has been studied extensively. Many new derivatives have been prepared[3–6] to fit the bill for this purpose.

There is an increasing interest to couple chiral pendant groups with cyclodextrins. In the presence of DCC/HOBT, BOP/HOBT or TBTU/HOBT, protected amino acids have been coupled with cyclodextrins to give a new cyclodextrins, which have potential applications in the area of chiral separation and asymmetric synthesis.[7–10] Many organic reactions may be conducted safely in microwave ovens with remarkable rate enhancements and dramatic reductions in reaction times compared with conventional heating.[11,12] To our knowledge, there is no report of the microwave-assisted substitution reaction of β-cyclodextrin by chiral aminoalcohol. In the present paper, we describe a facile preparation of R-(-)-2-phenylglycinol modified β-cyclodextrin (as shown in Scheme 1) and its chiral discrimination.

The compound **3** was dissolved in the solvent water-methanol (9:1). When two drops of 1.0 mM 1- adamantanol was added to the solution, its UV absorbance declined (shown in Fig. 1). Since it is an excellent guest for inclusion complexation by β-CD, 1- adamantanol completes effectively with the phenyl group for the available CD binding sites. This indicates that the phenyl group is shielded within the cavity of β-CD residue.

The stability constants for complexation of the enantiomers of some amino acids by compound **3** which determined using the method of UV difference spectra,[13] are presented in Table 1.

Table 1

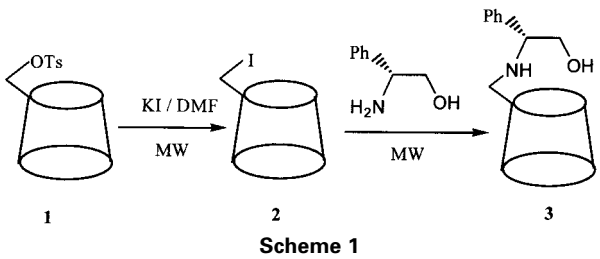
Guest	-Δ*G*/kJ/mol	Log *K*	K_D/K_L
L-Ala	11.65	2.077	3.6
D- Ala	14.75	2.629	
L-Val	12.03	2.145	4.5
D-Val	15.69	2.798	
L-Leu	12.26	2.186	5.1
D-Leu	16.23	2.895	

Conditions: T=293K, solvent H_2O, 0.05mol/dm^3 phosphate buffer solution pH=7.2.

The extent of chiral discrimination by natural cyclodextrins is quite modest,[3] but in this case, the association constants between compound **3** and enantiomers of the three amino acids differed by a factor (K_D/K_L) of 3.6, 4.5, 5.1 respectively. There is the possibility of greater interaction between chiral portion of cyclodextrin and those of substrates, which lead to the good chiral discrimination.

Experimental

The UV and FT-IR spectra were recorded with Shimadzu UV-240 spectrophotomer and Bio-Rad Win-IR spectrometer respectively, NMR spectra were measured on Bruker 400 NMR spectrometer, using D_2O as the solvent. C, H, N analyses were performed with a



Scheme 1

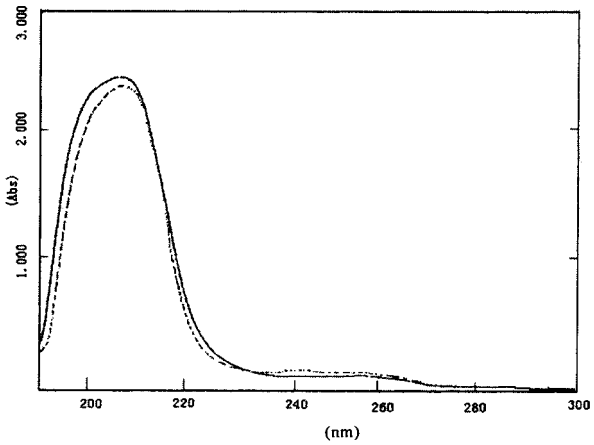


Fig. 1 UV spectra of compound 3 alone (—) and in the presence of 1-adamantanol (- - -) in a solution of water-methanol (90:10, V/V), [CD]=5×10^{-4}mol/cm^3.

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CE-1106 microanalyzer. Microwave irradiation was carried out with a modified Galanz WP800BS microwave oven. R-(-)-2-Phenglglycinol, Aldrich , 98%, $[\alpha]^{24}$ -31.7 (c=0.76,1NHCl)

Preparation of compound **3**: The mono-6-deoxy–6-(*p*-tolysulfonyl)-β-CD (1) was synthesised according to the improved procedure.[14–15] Compound **1** and 10 equiv. Excess of potassium iodide were dissolved in DMF, irradiated in microwave oven at 475 W for 6 min, and then the solvent was evaporated in vacuum. Acetone was then added. The white solid was filtered out and dissolved in water. A further amount of acetone was added again. This procedure was repeated for three times. Recrystallisation from the mixture of *n*-butanol–alcohol–water (5:4:3), gives the white solid **2**, yield 85%.

Mono-6-iodo-6-deoxy-β-CD (2) 500 mg and 5 equiv. excess of R-(-)-2-phenylglycinol were dissolved in 15 ml of N-methyl-2-ketopyrrolidine(NMP), irradiated in microwave oven at 475 W for 10 min, then cooled to ambient temperature, and precipitated by acetone. The white solid was recrystallised several times from water to afford the desired product **3**, yield 54%. TLC (*n*-propylalcohol-ammonia-water = 5: 1: 3), Rf = 0.48. ^{1}H-NMR: 7.35–7.15 (m, 5H), 5.60–6.0 (m, 14h), 4.90–4.70(m, 7H), 4.60–4.40(m, 6H), 4.18 (t, 1H), 3.19–3.20 (broad, overlaps with H_2O), 2.70(m, 1H). C^{13}–NMR: 141.81, 128.07, 127.07, 126.82, 102.07, 101.7, 84.43, 81.9, 81.55, 73.2–70.79, 66.89, 64.7, 59.89, 58.36, 48.2 (cm^{-1}). IR: 3391, 2924, 2160, 1647, 1415, 1367, 1155, 1080, 1030, 945, 757, 705, 581. Anal. Calcd for $C_{50}H_{29}O_{35}N{\cdot}4H_2O$, C 45.28, H 6.56, N 1.01, found: C 45.29, H 6.51, N 1.33.

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