High Enantioselectivity in the Reactions of (*R*)-and (*S*)-1-Phenylethylamine with 6^A-Deoxy-6^A-iodo-β-cyclodextrin

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6^A-Deoxy-6^A-iodo-β-cyclodextrin reacts with (*R*)-1-phenylethylamine one hundred and sixty times faster than it reacts with the corresponding (*S*)-enantiomer of the amine.

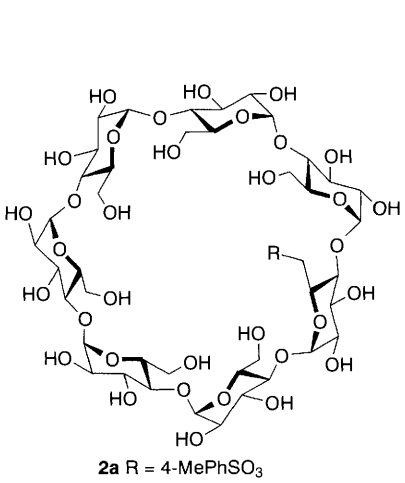
Cyclodextrins and their derivatives are chiral host molecules that are known to exhibit enantioselectivity in reactions with racemic guests. For example, stereoselectivity has been observed in the hydrolysis of esters[1–10] and in the ring opening of oxazolones,[11,12] catalysed by cyclodextrins. The greatest enantioselectivity so far reported for reaction of a cyclodextrin involved the acylation of β-cyclodextrin by the *p*-nitrophenyl ester of a ferrocene derivative, where the rates of reaction of the enantiomers of the ester differed by a factor of 62.[6] More recently, a 19-fold enantioselectivity has been reported for the reaction of β-cyclodextrin with the *m*-nitrophenyl ester of 1-phenylpropanoic acid,[7] and complementary diastereoselectivity in the synthesis and hydrolysis of a cyclodextrin ester of Ibuprofen has been observed, with an overall selectivity of 50 : 1.[10] We now report that the reaction of 1-phenylethylamine **1** with 6^A-deoxy-6^A-iodo-β-cyclodextrin **2b** is also enantioselective, with the (*R*)-amine **1a** reacting one hundred and sixty times faster than the corresponding (*S*)-enantiomer **1b**. To the best of our knowledge, this is the highest enantioselectivity reported for reaction of a cyclodextrin.

The iodide **2b** was obtained by treatment of the corresponding tosylate **2a**[13] with sodium iodide.[14] Treatment of the iodide **2b** with (*R*)-1-phenylethylamine **1a** (2 mol equiv.) in *N*,*N*-dimethylformamide at 343 K for 48 h gave the cyclodextrin derivative **3a** [δ_C (75.5 MHz, 298 K) 26.8 (Me), 40.0 (C-6^A); δ_H (500 MHz, 343 K) 1.75 (d, *J* 6 Hz, 3H, Me); HPLC (Waters Carbohydrate Analysis column with 30% aqueous acetonitrile as eluent) t_R 0.7 relative to β-cyclodextrin] in 44% yield. By comparison, under the same conditions reaction of the iodide **2b** with the amine (*S*)-enantiomer **1b** gave the diastereoisomeric cyclodextrin derivative **3b** [δ_C 26.5 (Me), 40.2 (C-6^A); δ_H 1.72 (*d*, *J* 6 Hz, 3H, Me); HPLC t_R 0.5 relative to β-cyclodextrin] in only 2% yield. More substantial yields of the cyclodextrin derivative **3b** were only obtained after longer reaction times and by using greater molar excesses of the amine **1b**.

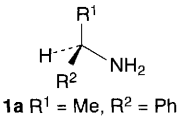
The relative yields of the cyclodextrin derivatives **3a** and **3b**, from experiments carried out under identical conditions, indicate the enantioselectivity of the reaction of the iodide **2b** with the amine **1**. To examine this stereoselectivity in more detail, the iodocyclodextrin **2b** was treated with various mixtures of the amine enantiomers **1a** and **1b**. When the reaction was carried out using the iodide **2b** and 1 mol equiv. of each enantiomer of the amine **1**, only the cyclodextrin derivative **3a**, derived from the (*R*)-enantiomer **1a**, was detected by HPLC and ^{1}H NMR spectroscopic analysis of the product mixture. When the iodide **2b**, the (*R*)-amine **1a** and the (*S*)-enantiomer **1b** were mixed in a 1 : 1 : 100 molar ratio, the cyclodextrin derivatives **3a** and **3b** were produced in the ratio 1.6 : 1. On this basis, the enantioselectivity displayed in the reaction of the iodide **2b** with the amine **1** is a factor of one hundred and sixty.

The reaction of each enantiomer of the amine **1** with the iodocyclodextrin **2b** most likely occurs in two discrete steps. The first involves formation of a host **2b**–guest **1** complex, and the second reaction of the host **2b** with the included guest **1**. In principle the enantioselectivity could derive from either or both of these processes, but the results of the experiments using mixtures of the amine enantiomers **1a** and **1b** described above indicate that the stereoselectivity most likely originates in the latter stage. As the amount of the (*S*)-amine **1b** used in the reactions was increased, the rate of formation of the cyclodextrin derivative **3a** decreased without a similar increase in the rate of production of the diastereoisomer **3b**. This decrease in the rate of formation of the cyclodextrin derivative **3a** shows that the (*S*)-amine **1b** competes with the (*R*)-enantiomer **1a** to complex with the cyclodextrin **2b**, while the fact that the rate of formation of the cyclodextrin derivative **3b** does not increase to the same extent as the rate of production of the diastereoisomer **3a** is reduced indicates that the complex of the (*S*)-amine **1b** with the cyclodextrin **2b** is less reactive.

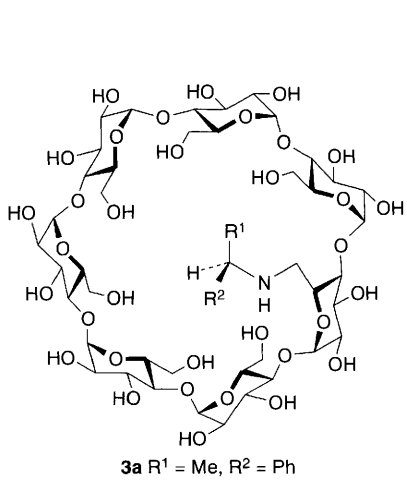
Although there is no obvious explanation for the enantioselectivity, the HPLC retention times of the cyclodextrin derivatives **3a** and **3b** relative to β-cyclodextrin indicate that the diastereoisomer **3b** is the less polar. This may reflect a lower



2a R = 4-MePhSO$_3$
b R = I



1a R^1 = Me, R^2 = Ph
b R^1 = Ph, R^2 = Me



3a R^1 = Me, R^2 = Ph
b R^1 = Ph, R^2 = Me

degree of intramolecular inclusion of the aryl moiety in that compound, which may in turn suggest that the geometry of the inclusion complex formed between the iodide **2b** and the (*S*)-amine **1b** is unlike the product **3b** and therefore unsuitable for reaction. In any event the enantioselectivity displayed by the iodide **2b** is sufficient for a kinetic resolution of the amine **1**, as demonstrated in a preliminary experiment through the enrichment of a racemic sample to give the (*S*)-enantiomer **1b** in 90% enantiomeric excess with no detectable reaction of that isomer. The amine enantiomers **1a** and **1b** were distinguished by HPLC analysis of their diastereoisomeric amide derivatives formed through reaction with (*S*)-2-phenylpropanoic acid.

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