Receptors functionalized with chiral aza-crown ether rings.
Attempted enantioselective catalysis of a Michael addition reaction

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Abstract. A series of receptors functionalized with chiral aza-crown ether rings was synthesized. These compounds were studied as enantiopure catalysts for the addition of benzenethiols to cyclohex-2-en-1-one. Binding of 4-hydroxybenzenethiols in these molecules allows for the orientation of the thiol with respect to an asymmetric catalytic site. This orientation was, however, found to be counterproductive for enantioselective catalysis.

Introduction

One of the challenging goals of host-guest chemistry is the development of synthetic receptor molecules that are able to function as stereoselective catalysts for organic reactions. The design of such artificial catalysts is inspired by nature's enzymes. These biomacromolecules have a well-defined three-dimensional structure with a cavity or cleft. The bond-making or -breaking reaction catalyzed by enzymes is preceded by the formation of an enzyme-substrate complex. Substrates can be bound by hydrogen bonds, electrostatic interactions, and Van der Waals forces. The three-dimensional structure of an enzyme is not rigid but exhibits some flexibility, allowing for an adjustment of the shape of the active site such that, upon binding, a better fit is obtained between enzyme and substrate. After the initial binding a stereoselective conversion is achieved due to a specific ordering of catalytic groups at the active site. In addition to being stereoselective, enzymatic reactions are very fast. Compared to uncatalyzed reactions, acceleration by a factor of $10^5$ or more is very common.

In this paper we focus on mimicking one of the features of enzymatic catalysis, viz. the stereoselective modification of a substrate. This is attempted with the help of synthetic receptors derived from the concave molecule 1 (Scheme 1). If 1 reacts with two chiral or achiral primary amines, basket-shaped receptors 2a-k are obtained. These receptors possess: (i) a cavity in which a substrate can be bound, (ii) a tertiary amine group which can act as a basic catalyst, (iii) a hydroxyl substituent which may function as an activating and/or orientating group, and (iv) a chiral structure (except 2a). Here we report on our efforts to use novel receptors 2 as enantiopure catalysts for the enantioselective addition of benzenethiols to cyclohexenones.

Results and discussion

Synthesis of receptors

The synthetic methods used to prepare 1 have already been published. Previously, receptor 2a was synthesized from 1 and benzylamine by applying 0.02M solutions of 1 in DMSO. Under these conditions several by-products were obtained that could only be removed by tedious separation procedures on relatively small samples using long Sephadex columns. These
by-products are formed because additional molecules of the amine react with 1 to give secondary amines, which prevents the ring-closure reaction going to completion. We also suspected that the oxidative properties of the solvent DMSO caused the formation of by-products. We therefore developed an alternative method based on the procedure used by Dale et al. The reaction was performed in acetonitrile under dilute conditions (e.g. solutions containing 0.01–0.001 M of 1), and the amine was added to the reaction mixture over a period of days. This procedure yielded much cleaner products in high yields. Only in the case of 2e was a substantial amount of by-product containing three amine moieties obtained. For this compound, ring closure may be somewhat hampered due to the presence of a rigid phenyl group on the α-carbon atom of the amine. NaI and K₂CO₃ were used as catalysts for the reactions. Nucleophilic attack of the amine is facilitated when the chloride is substituted in situ by iodine. The potassium carbonate acts as a base for the deprotonation, once the ammonium salt of the secondary amine is formed. In addition, the alkali metal ions present in solution act as a template for the formation of the crown ether rings. This is supported by the observation that 1, which is not very soluble in acetonitrile at room temperature, is completely dissolved when sodium iodide is added. Apparently, 1 is present as a sodium iodide complex in acetonitrile solution.

The receptors could be separated on TLC plates but excessive tailing occurred, when 10% MeOH/CHCl₃ was used as the solvent. Similar behaviour was observed when the product was purified over silica-gel columns using this solvent system. Only ca. 40% of the product could be recovered. A fraction of the receptor molecules is probably irreversibly bound to strong Lewis-acid sites on the silica gel. When a small amount of Et₃N was added to the solvent system, tailing was prevented and practically all material could be recovered after column chromatography. Using this procedure, receptors 2a, 2h, and 2i could be purified completely. For the other receptors a problem remained as the Rᵣ values of the product and contaminations were very similar. Larger differences in Rᵣ values could be achieved by impregnating the TLC plates and the silica-gel columns with NaBr or KBr. In this way, the product is chromatographed as the alkali metal salt complex which leads to a much higher mobility. KBr plates gave the largest differences in Rᵣ values between product and contaminations for all the receptors. This is in accordance with the fact that larger binding constants are found for the complexes between the receptors and potassium than for the receptors and sodium. Excellent separations could be achieved for all receptors using 10% MeOH/CHCl₃ as the solvent system. A drawback of this procedure is that only 40–60% of the material can be recovered after chromatography.

**Binding of substrates**

It was shown previously that dihydroxy-substituted aromatic molecules are bound by molecular baskets of type 2ₙ. The guests are wedged between the cavity walls of these receptors. For 2a, binding constants between 50 and 300000 M⁻¹ were found for various benzenediols. The guest’s hydroxyl groups form (probably bi-furcated) hydrogen bonds with the crown-ether nitrogen atoms and/or carbonyl groups of the receptor. The complexes are further stabilized by π–π stacking interactions between the guest and the walls of the receptor.

To test whether the above-mentioned binding interactions can be used to orientate reactants with respect to an asymmetric catalytic site, we performed binding studies with benzene-1,2-diol (3) and 4-hydroxybenzenethiol (4). When 3 was added to 2i, no upfield shifts were observed in the ¹H-NMR spectrum for the cavity-wall protons of the receptor, indicating that 3 is not bound by 2i. Also, the host NCH₂ protons displayed negligible shifts, suggesting that no ion pair is formed with the thiol. In the case of substrate 4, the cavity wall protons of 2i were found to shift upfield, indicating that complex formation does take place, but no shifts of the NCH₂ protons were observed. Apparently, host-guest complex formation involves hydrogen-bond interaction between the hydroxyl function of 4 and a carbonyl group of the receptor as well as π–π stacking interactions. The binding constant of the complex between 4 and 2i was determined to be Kᵣ = 82 M⁻¹ at 298K, which corresponds to a ΔG of binding of -10.9 kJ/mol. For host 2h a binding constant of 127 M⁻¹ was found, indicating that incorporation of a hydroxyl function in the side-chain of the basket does not interfere with the binding process. The stronger complexation of the guest by 2h may be a result of the nitrogen atoms being involved in the binding process. This is suggested by downfield shifts found for this receptor’s NCH₂ protons upon complexation.

**Addition of aromatic thiols to cycloalkenones catalyzed by receptors 2**

To investigate whether or not the binding properties of 2 can be used to achieve selectivity in a reaction, we studied the...
addition of 4 to cyclohex-2-en-1-one (Scheme 2) in the presence of receptors 2b-k. For comparison, the addition of the non-bonding substrate 3 to cyclohex-2-en-1-one was also studied. The reactions of thiols with cyclic α,β-unsaturated ketones catalyzed by cinchona and ephedra alkaloids have been thoroughly investigated by the groups of Wynberg and Kellogg\(^{11,12}\). They demonstrated that the reaction is first order in catalyst, first order in benzenethiol, and also first order in cyclohex-2-en-1-one. Furthermore, it was found that amines possessing a β-hydroxyl function act as bifunctional catalysts. During the reaction, the thiol function becomes activated, because it forms an ion pair with the tertiary nitrogen function of the chiral catalyst. The double bond of cyclohex-2-en-1-one is made reactive via the formation of a hydrogen bond between the carbonyl group of this reagent and the hydroxyl group of the catalyst. In this way, both reactants are oriented by the catalyst in the correct position for a stereoselective reaction. This resulted in ee (enantiomeric excess) values for this reaction of up to 75%. We envisaged that the same bifunctional interactions as found for the alkaloids, could be present in the reaction catalyzed by receptors 2. In addition, a third interaction, schematically illustrated in Figure 1, may be operative. The position of the phenyl ring of the 4-hydroxybenzenethiol could be fixed by complexation in the cavity of the receptor, and the orientation of the thiol function could be controlled by formation of an ion pair with the nitrogen atom of the crown-ether ring. In the model of Figure 1, the position of the double bond of the alkene is determined by the hydrogen bond between the carbonyl group in this molecule and the hydroxyl function of the receptor. If the three-point attachment model is valid, an enantioselective reaction would be achieved, if the thiol function attacks preferentially at either the Re or the Si face of the cyclohex-2-en-1-one. This leaves open the following possibilities: (i) attack of the thiol on cyclohex-2-en-1-one with the double bond of the latter molecule facing the crown-ether ring (see Figure 1), (ii) idem with the double bond turned away from the crown-ether ring, (iii) and (iv), as in (i) and (ii) but with the attack of the thiol function at the “front” (F) instead of the “back” (B) side of the catalyst. If one of these four possibilities is energetically favoured (or two if the same enantiomer is produced), enantioselective catalysis can be expected. The above-mentioned requirements can be fulfilled, if there are local minima for rotations around bonds 1 and/or 2 (in Figure 1). Dijkstra has shown that, for β-amino alcohols, such discrete minima in energy do indeed exist\(^{14}\). Extensive variation of the substituent in the side-chain of the receptor may enhance the chance that the requirements are met.

We first tested our receptors as catalysts for the addition of benzenethiol to cyclohex-2-en-1-one. Toluene was initially chosen as the reaction medium because the highest ee values have been reported in the literature with this solvent\(^{12}\). All catalysts were carefully dried before use, because moisture can have a negative effect on the asymmetric induction, as pointed out by Dijkstra\(^{14}\). For all receptors we found that the reaction is essentially complete after 15 hours. This result is in agreement with similar findings of Hiemstra et al.\(^{12}\) for the alkaloid catalysts. For most receptors the optical purity values of the reaction products were negligible. Some asymmetric induction occurred in the presence of hosts 2c and 2d, for which the reaction products were found to have optical purities of 5% and 9% respectively. Because the solvent toluene may prevent binding of the thiol in the cavity of our receptors, we also performed some reactions in dichloromethane. However, the optical purity values were also very small in this solvent.

In a second series of experiments we tested 4-hydroxybenzenethiol, which was shown to be bound in the cavity of our receptors, as the reactant. Because this thiol had not been studied before, we first determined the rate of its addition to cyclohex-2-en-1-one in the absence of a catalyst. After 4 hours, no product could be detected by \(^1\)H-NMR. Product formation in the catalyzed reaction turned out to be almost quantitative for all receptors within several hours. The optical rotations of the formed products were very low. As the absolute rotation of enantiomerically pure 3-(4-hydroxyphenyl) cyclohexanone is not known, no optical-purity values could be calculated. However, comparison of the optical rotations with those of a series of aryl-substituted 3-phenylthiocylohexanones\(^{12}\) reported in the literature suggested that the optical purities are probably negligible.

The experiments described above show that the receptors are capable of catalyzing the addition reaction of benzenethiols to cyclohexenones. However, the obtained enantioselectivities are very low. The low optical purity found for the addition of benzenethiol to cyclohex-2-en-1-one catalyzed by receptor 2h is particularly surprising, since Dijkstra\(^{14}\) showed that, with N-methyl-ephedrine, an ee value of 36% can be obtained. Apparently, incorporating an ephedrine moiety into our receptor molecule leads to a dramatic loss of optical purity. This suggests that the fixation of the thiol in the cavity of the receptor is counterproductive. The lower optical rotations found for the products of the addition of 4-hydroxybenzenethiol to cyclohex-2-en-1-one as compared to those found for benzenethiol, are in line with such an explanation. A second reason might be that the conformation of ephedrine in the receptor is substantially different from that of N-methyl-
that EtOAc/n-hexane (1/2, v/v) was used as eluent to separate the diastereomers of ethyl(S)-3-(methylbenzylamino)butanoate by column chromatography. The sample was purified using silica gel (33-40 mesh). Spectral data were in agreement with recorded values for racemic 3-aminobutyl-1-ol.

Compound 1 was synthesized according to a method published previously.

General procedure for the synthesis of the receptors

Nal was added to a suspension of 10 mmol of 1 in acetonitrile. The mixture was stirred for several minutes until a clear solution resulted. K$_2$CO$_3$ and 1.5x mmol of the amine were added and the suspension was placed under nitrogen. Subsequently, it was refluxed for several days while being monitored by TLC. The rest of the amine (x mmol) was added, when 1 had disappeared. After additional refluxing for several days, the reaction mixture was filtered. The filtrate was washed with 100 ml of chloroform and the combined extracts were concentrated in vacuo. Chloroform (100 ml) was added and the solution was filtered again. The receptors were purified with silica gel using MeOH/ Et$_3$N/CHCl$_3$/H$_2$O as the eluent.

The kinetic data were recorded on a Bruker AM-400 or Bruker 241 Polarimeter. Elemental analyses were performed in the analytical department of the University of Nijmegen. Melting points were recorded on a Melt-Point apparatus.
Compound 2e Reactants: 4.0 g (4.05 mmol) of 1, 15 g of Na, 36 g of K₂CO₃, and 0.83 g (11.1 mmol) of (R)-(+)-1-aminopropan-2-ol. The reaction mixture was first refluxed with 6.2 mmol amine for 4 days. Then a second portion of 4.9 mmol amine was added and the reaction mixture was refluxed again for 3 days; yield 1.30 g (53%) of 2k as a white solid; m.p. 234–236°C; [α]D 16.1° (c 0.5, CHCl₃). IR (KBr): 3420 (OH), 3060, 3020 (ArH), 2920, 2860 (CH, and CH₃), 1701 (C=O, C=O). Spectral data were in agreement with those reported in the literature19. For analysis, a sample was crystallized by purification over a silica-gel column using CHCl₃ with 10 ml of aqueous 2N HCl, twice with 10 ml of aqueous 2N KOH, and twice with a small amount of CH₂Cl₂ was added dropwise to vigorously stirred n-hexane (20 ml). After filtration of the catalyst over Hyflo (without applying vacuum), the n-hexane was evaporated in vacuo. Then 20 ml of toluene was added and the organic layer was washed twice with 10 ml of aqueous 2N HCl, twice with 10 ml of aqueous 2N KOH, and twice with 10 ml of brine. The organic layer was dried over MgSO₄, the solvent was evaporated and the product was purified over a silica-gel column using CHCl₃, with a very small volume % of methanol as the eluent. For analysis, the sample was crystalized by allowing n-hexane to diffuse into a mixture of MeOH and CHCl₃, (3-4-Hydroxyphenyl)thiocyclohexanone: m.p. 124°C. IR (KBr): 3210 (OH), 3020 (ArH), 2960, 2940 (CH₂), 1680 (CO), 1605, 1590 (Ar), 1495, 1440, 1410, 1360, 1340, 1260, 820 (Ar), 840 (Ar) cm⁻¹. 1HNMR (90 MHz, CDCl₃): δ 7.25 (m, 2H), 6.75 (m, 2H), 3.73 (m, 1H), 2.79 (m, 2H). El m/z: 993 (M + H)⁺. Anal. calcd. for C₆H₃N₂O₂: C 64.14, H 6.95, N 8.31; found: C 64.36, H 6.77, N 8.20%. General procedure for the catalytic reactions

The catalyst (0.015 mmol) was dried in vacuo (0.5 mmHg) at 100°C for 6 h. In a Schlenk vessel. This vessel was then filled with argon and the solvent (3 ml), benzene/thiophenol (1.81 mmol) and the cyclohex-2-en-1-one (1.56 mmol) were added with a syringe. The reaction mixture was left overnight. The work-up procedure was essentially the same as that of Hiemstra et al12. The reaction mixture (in cases of poor solubility, diluted with a small amount of CH₃OH), was added dropwise to vigorously stirred n-hexane (20 ml). After filtration of the catalyst over Hyflo (without applying vacuum), the n-hexane was evaporated in vacuo. Then 20 ml of toluene was added and the organic layer was washed twice with 10 ml of aqueous 2N HCl, twice with 10 ml of aqueous 2N KOH, and twice with 10 ml of brine. The organic layer was dried over MgSO₄, the solvent was evaporated. In the case of 3-phenylthiothiocyclohexane the spectral data were in agreement with those reported in the literature15. For the reaction of 4-hydroxybenzenethiol with cyclohex-2-en-1-one, a different work-up procedure was used. The reaction mixture was taken up in 20 ml of toluene and washed with 10 ml of aqueous IN HCl (twice), 10 ml of water (twice) and finally with 10 ml of brine. After drying the organic layer over MgSO₄, the solvent was evaporated and the product was purified over a silica-gel column using CHCl₃, with a very small volume % of methanol as the eluent. For analysis, the sample was crystalized by allowing n-hexane to diffuse into a mixture of MeOH and CHCl₃, (3-4-Hydroxyphenyl)thiocyclohexanone: m.p. 124°C. IR (KBr): 3210 (OH), 3020 (ArH), 2960, 2940 (CH₂), 1680 (CO), 1605, 1590 (Ar), 1495, 1440, 1410, 1360, 1340, 1260, 820 (Ar), 840 (Ar) cm⁻¹. 1HNMR (90 MHz, CDCl₃): δ 7.25 (m, 2H), 6.75 (m, 2H), 3.73 (m, 1H), 2.79 (m, 2H). El m/z: 993 (M + H)⁺. Anal. calcd. for C₆H₃N₂O₂: C 64.14, H 6.95, N 8.31; found: C 64.36, H 6.77, N 8.20%.

Determination of the optical purity

In the case of the reaction of benzenethiol with cyclohex-2-en-1-one, the optical purity was determined by comparing the rotation of the product with the optical rotations and the ee values of 3-phenylthiocyclohexanone reported in the literature12. For the product obtained from the reaction catalyzed by 2a, the 13C method of Hiemstra et al.20 was followed. The ee determined by this method was in good agreement with the optical purity determined by polarimetry.

Kinetic measurements

Cyclohex-2-en-1-one [304 mg (3.16 mmol)], 9.0 g of CDCl₃, and 337 mg of (3.06 mmol) benzenethiol were weighed into a flask. To this mixture was added 22.1 mg of trioxane as an internal standard. The receptor (0.01
mmol) was weighed into a second flask to which exactly 2 ml of the above-mentioned mixture was added. Approximately 1 ml of the resulting solution was transferred into an NMR tube. In between the measurements, the tube was placed in a thermostatted bath at 25°C. ¹H-NMR (90 MHz) spectra were recorded with a relaxation delay of 4.0 s. The concentration of cyclohex-2-en-1-one was determined by comparing the integral of the ethylenic proton at C3 with the integral of the internal standard. For all measurements, the spectrum of a sample without catalyst was also measured at the beginning and at the end of each measurement. For these samples the conversion was found to be less than 5%.

References and notes

15 A detailed study of the conformation of receptors 2a-2k will be reported in a separate paper.
16 The ¹H-NMR spectra of 2b, 2c, 2i, and 2k indicated the presence of water molecules. The signals of these molecules coincided with the signals of the hosts. The amount of water calculated from the NMR spectra matched the amount found by elemental analysis. In the ¹H-NMR spectrum of 2j a broad peak at 2.48 ppm was visible. Its integral corresponded to one molecule of water. This is in accordance with the amount of water found in the elemental analysis. For compounds 2e, 2f, 2g, and 2h, the presence of water was not apparent from the ¹H-NMR spectra. The water signal in these cases was probably broadened, since elemental analysis indicated that water was present in these samples.
17 In all cases the formulae of the hosts were corrected for the presence of solvent molecules.