**1, 92%   2, 8%**

(3)

HO

HO

3, 92%   4, 8%

Consequently, hydroboration occurs predominantly in the allylic position[12] and the optical activity is predominantly retained, even at 0 °C.

Similarly, hydroboration of 1,3-cyclohexadiene by Ipc$_2$BH [from (−)-α-pinene] gave (R)-(+)-2-cyclohexen-1-ol.

The two reagents, B-2-cyclohexen-1-yldiisopinocampheylboranes [from (+)-α-pinene and (−)-α-pinene], react readily with acetaldehyde at −78 °C. Only the allylic derivative **1** reacts. The minor homoallylic derivative **2** does not, making the separation of the isomeric impurities extremely simple. The reagent from (+)-α-pinene yields a borinic ester **5**, which reacts with ethanolamine to provide (1R,1'R)-(+)-1-(2-cyclohexenyl)-1-ethanol in 94% ee and 100% erythro selectivity (eq 4).

6, diastereoselectivity 100%, 94% ee

7

(4)
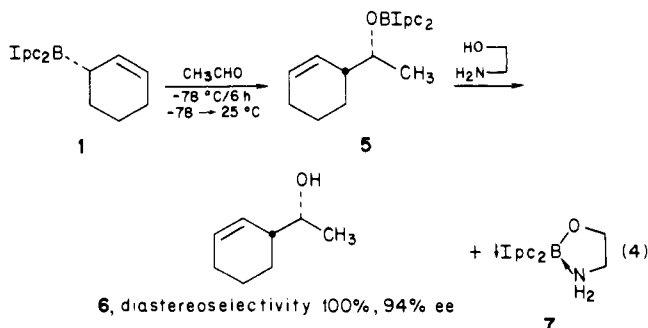
The other isomer, (1S,1'S)-(−)-1-(2-cyclohexen)-1-ethanol, is obtained from the reagent derived from (−)-α-pinene.

Catalytic hydrogenation (5% Pt on C) of (+)-1-(2-cyclohexenyl)-1-ethanol to (R)-(−)-1-cyclohexyl-1-ethanol, $[\alpha]^{23}_D$ −4.79° (neat), established the absolute configuration of the asymmetric carbon bearing the hydroxyl group.[13] The absolute configuration of the other chiral center was readily determined by tosylation, followed by reductive detosylation of (+)-1-(2-cyclohexenyl)-1-ethanol to (R)-(+)-3-ethylcyclohexene, $[\alpha]^{23}_D$ +20.73° (neat).[14]

The following experimental procedure is representative. All operations were carried out under nitrogen.[15] Diisopinocampheylborane (Ipc$_2$BH) was prepared from (−)-α-pinene following the reported procedure.[16] To the stirred suspension of Ipc$_2$BH (25 mmol) in THF at −25 °C was added dropwise 2.4 mL (25 mmol) of 1,3-cyclohexadiene. Monohydroboration of the diene was complete after stirring the reaction mixture at −25 °C for 12 h, as indicated by the disappearance of the solid Ipc$_2$BH and ^{11}B NMR (δ +80) examination of the solution. The orga-

noborane **1** was cooled to −78 °C and treated (dropwise addition) with 1.4 mL (25 mmol) of acetaldehyde. The contents were stirred at −78 °C for 6 h, the dry ice–acetone bath was removed, and the mixture was allowed to warm to room temperature. ^{11}B NMR indicated formation of borinate **5** (δ +56). Excess α-pinene and THF were removed under reduced pressure (25 °C/18 mm/1 h, 0.05 mm/6 h) and the residue was then dissolved in dry *n*-pentane (15 mL). The borinate **5** was cooled to 0 °C and treated with 1.5 mL (25 mmol) of ethanolamine. The contents were stirred at 0 °C for 0.5 h and allowed to warm to room temperature. ^{11}B NMR (δ +13) of the mixture indicated formation of the ethanolamine adduct **7**, a white crystalline solid, which separated after stirring the contents at 25 °C for 1 h. The mixture was cooled to 0 °C and filtered and the solid washed with cold pentane (2 × 10 mL). The residue, following removal of the solvent from the combined filtrate, was distilled to provide 1-(2-cyclohexenyl)-1-ethanol: bp 82 °C (18 mmHg); 2.07 g (66% yield); $[\alpha]^{23}_D$ −29.17° (*l* = 0.5, neat), 94% ee.[17]

No difficulty was observed in extending the synthesis to other representative aldehydes, such as propionaldehyde, 2-methylpropionaldehyde, 2,2-dimethylpropionaldehyde, acrolein, and benzaldehyde. In all cases comparable optical purities and erythro diastereoselectivities were realized.

It is evident that this development establishes the feasibility of synthesizing chiral allyldiisopinocampheylboranes, R*BIpc$_2$, and thus makes available a "one-pot" procedure for carbon–carbon bond formation, with 100% diastereoselection and excellent enantiomeric excess. The selectivity is for the erythro isomer, which nicely complements the existing methods for preparing the threo isomers.[7,8] Further, the homoallylic alcohols formed can be ring opened to the corresponding acylic erythro products, thus greatly expanding the range of applicability of the allylboration reaction.

(17) The percent ee was determined by ^{19}F NMR of the MTPA ester of the alcohol by using a Varian XL-200 spectrometer.

Potential of Mean Force for the Stacking of Phenyl Rings in Aqueous Solution

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Recently, diverse theoretical studies of hydrophobic interactions involving liquid state computer simulation and in some cases potential of mean force determinations[1–8] have given computational support to the idea[9] that the hydrophobic effect can act over longer

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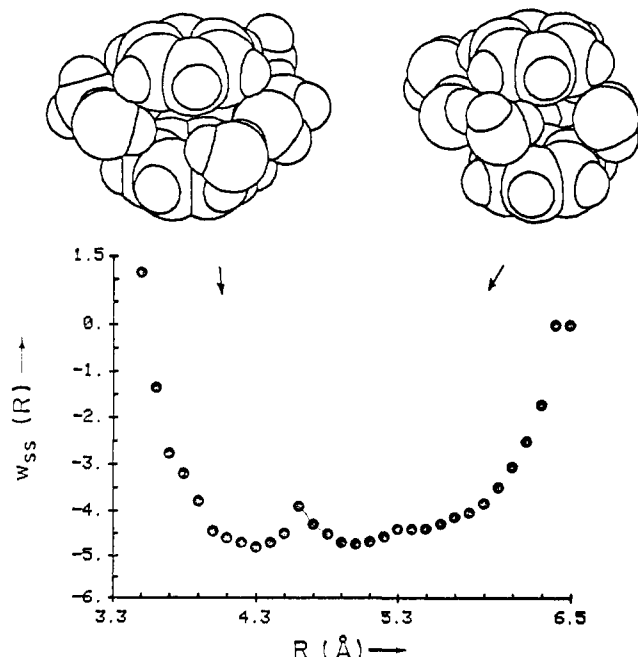
Figure 1. Calculated potential of mean force for two benzene molecules in water, along the C_6 stacking coordinate (kcal/mol). Insets show the structures of contact and solvent-separated forms of the $[(C_6H_6)_2]_{aq}$ complex.

distances than originally expected via solvent–separated associations. Studies to date have been carried out on aqueous solutions of spherical apolar solutes and of methane molecules, prototypical of hydrophobic interactions involving alkyl groups.

A second important class of hydrophobic systems is that of molecules containing unsaturated π electrons and aromatic rings. The stacking interaction of the π clouds of nucleotide bases is generally considered to be the primary stabilizing structural feature of the DNA double helix in water,[10] and it is well established that nucleotide bases stack rather than form complementary hydrogen bonded pairs in aqueous solution.[11] Recent experimental[12] and theoretical[13] studies have dealt with thermodynamics and Henry's law behavior of benzene dimers in water. Recently we described the hydration of benzene in aqueous solution based on results of liquid state computer simulation using the Monte Carlo method.[14] We have now extended our computer simulations to study the interaction of phenyl rings in water, selected as a first prototype problem for a consideration of base stacking in water. In this paper, we report the determination of the potential of mean force for stacking interactions in the system $[(C_6H_6)_2]_{aq}$ and explore the possibility of solvent-separated hydrophobic interactions in this system. We note in passing that the lowest energy interaction for two isolated benzene molecules is not a stacked form but a T-shaped complex.[15] We restrict our consideration here to the stacking coordinate, due to the implications in nucleotide base interactions.

Our computer simulations on $[(C_6H_6)_2]_{aq}$ were carried out on a system of two benzene molecules and 510 water molecules in an FCC cell under periodic boundary conditions at $T = 25\ ^\circ C$ and a density calculated from the observed partial molar volumes of benzene and water.[16] The water–water and benzene–water

intermolecular interaction potentials and other characteristics of the calculations were chosen to correspond as closely as possible to those of our previous study on $[C_6H_6]_{aq}$, with water–water interactions described by the MCY–CI(2) potential of Matsuoka et al.[17] and the benzene–water and benzene–benzene interactions computed with the analytical functions developed by Karlstrom et al.[18] from quantum mechanical calculations.

The determination of the potential of mean force $w_{SS}(R)$ for two benzene molecules in water was carried out in a series of three simulations with the umbrella sampling procedures as developed by Valleau and co-workers.[19,20] Distribution functions $g_{SS}(R)$ were obtained for three overlapping windows on the intersolute stacking coordinate R, centered at 4.5, 5.0, and 5.5 Å, respectively. The individual distribution functions were then combined by a straightforward matching procedure to produce a $g_{SS}(R)$ over the full range of interest. Details of our Monte Carlo sampling procedure are given in a recent paper by Mehrotra et al.,[21] and the methodology for the potential of mean force determination is similar to that described in the recent paper from this Laboratory by Ravishanker et al.[6] on $[(CH_4)_2]_{aq}$.

The $w_{SS}(R)$ resulting from this procedure for two benzenes in water is shown in Figure 1. The $w_{SS}(R)$ resulting from the matching procedure differs from the actual $w_{SS}(R)$ by an additive constant. We determined this by requiring that the $w_{SS}(R)$ reproduce the experimental second virial coefficient of dilute aqueous solution of benzene,[12] assuming tentatively that the behavior at $R = 6.5$ Å approximates that at infinitely large R. Oscillatory behavior, noted in previous theoretical studies of apolar solutes in water, is clearly evident. Two distinct minima, one at 4.3 Å and the other at 5.1 Å, were found. The former corresponds to a contact interaction and the latter to a solvent-separated benzene dimer. The two minima have similar relative free energies, but the calculated equilibrium constant favors the solvent-separated form due to a correspondingly larger element of configurational volume available.

The distance between successive minima in $w_{SS}(R)$ for $[(C_6H_6)_2]_{aq}$ is considerably less than the corresponding value found in $[(CH_4)_2]_{aq}$, where in the solvent-separated structure a water molecule was found more or less directly between the two apolar species. A detailed analysis of the benzene–water distribution functions for $[(C_6H_6)_2]_{aq}$ indicates that the solvent-separated structure features some six water molecules which impinge on the edges of the $(C_6H_6)_2$ complex, as shown in the structural insert to Figure 1. No water molecules are found directly between the two benzenes in the 5.1 Å solvent-separated form. Further analysis of the $w_{SS}(R)$ indicates that more distant solvent-separated structures may be found but are beyond the limit of consideration in this study.

In conclusion, we have determined a potential of mean force for the stacking coordinate of two benzene molecules in water and found that long-range interactions corresponding to solvent-separated structures are important. This raises the possibility that the equilibrium structures of nucleotide bases in aqueous solution exist to some significant extent in stacked solvent-separated forms, and some role for this effect in nucleic acid structure is anticipated. We note also observations of water molecules intercalated between bases in oligonucleotide bases.[22]

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