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SEPARATION OF CIS DIOLS FROM ISOMERIC CIS-TRANS MIXTURES BY SELECTIVE COUPLING TO A REGENERABLE SOLID SUPPORT.

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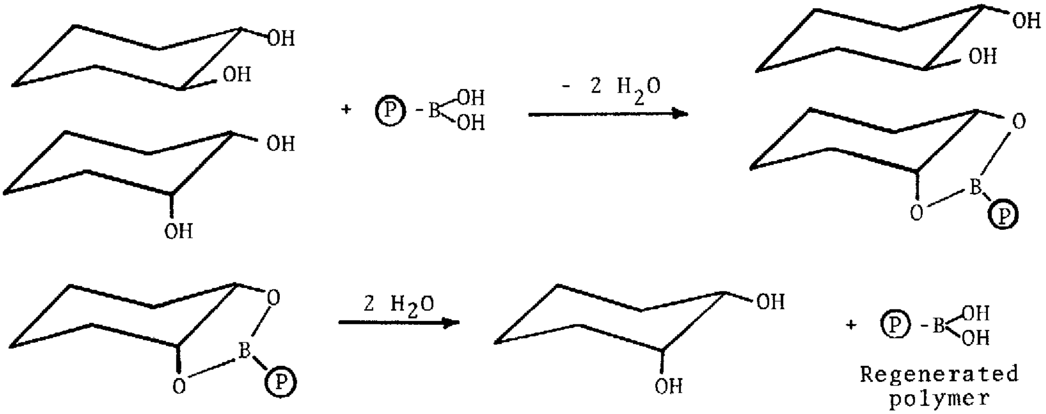
The development of affinity absorbent gels which can bind specifically various types of diols has received much attention recently due to the numerous possible applications in the separation of nucleosides or saccharides[1-4], and in the analysis of body fluids[5]. Absorbents capable of binding selectively one diol grouping in a mixture of diols or in a polyol can also be very useful in general organic synthesis for the selective protection of one diol grouping in a multistep synthesis, or for the removal of one product from a reaction mixture containing one or more diols. Several bead polymers which have been described recently were used as temporary diol protecting groups in the synthesis of selectively substituted glycosides[6,7]. Other resins capable of blocking one hydroxyl group have also been prepared[8-10].

We report here on the application of a fully regenerable polystyrylboronic acid resin to the efficient separation of the components of cis-trans diol mixtures. Similar separations have been carried out on cyclohexanediols using n-butylboroxine[11] or triethylborate[12]. However, these separations which required the fractional distillation of boron containing intermediates were relatively time-consuming and, in some instances, were not possible due to the similarity of the boiling points of the boronates of the isomeric diols.

Our method shown on scheme I for 1,2-cyclohexanediol involves the reaction of the diol mixture with a suspension of the boronic acid resin in benzene or pyridine with azeotropic removal of water, followed by filtration to effect the separation of the <u>trans</u> diol which remains in solution from the <u>cis</u> diol which

Our best results were obtained using solvent swellable 1% crosslinked polystyrene resins. Macroreticular resins were also used but were found to give consistently lower yields, and in addition, could not be recycled as many times as the swellable resins due to their tendency to break down on repeated handling. The polystyrylboronic acid resins were prepared[7] by bromination of polystyrene followed by lithiation with n-butyllithium in benzene, reaction with trimethyl borate, and finally hydrolysis with aqueous acid. Most of the resins used in this work contained from 1.7 to 3.2 milliequivalents of functional groups per gram.



SCHEME I. Solid phase separation of cis-trans diol mixtures.

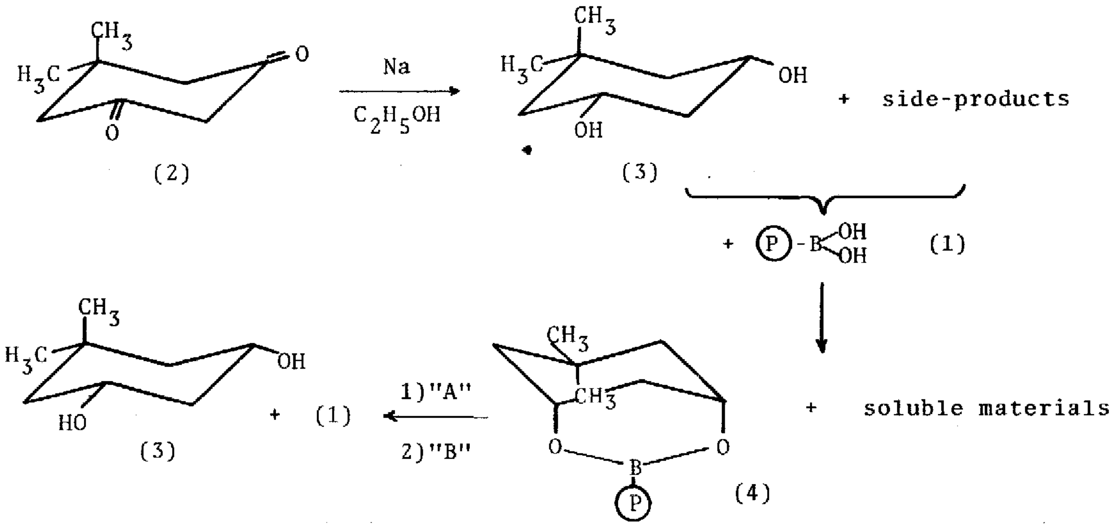
In a typical reaction sequence, 1g of a 1:1 mixture of <u>cis</u> and <u>trans</u> 1,2-cyclohexanediols was added to a suspension of 2g of polystyrylboronic acid resin in 50 ml of dry benzene. The mixture was stirred and approximately 15 ml of solvent was distilled to remove the water which was formed in the coupling step. The resin was then collected on filter and the filtrate evaporated to yield 0.4g (80%) of <u>trans</u> 1,2-cyclohexanediol (m.p.: 102-103). The resin was then washed several times with benzene, and the benzene washings evaporated to yield a fraction containing both diols. Cleavage of the <u>cis</u> diol from the polymer was accomplished by two successive treatments with 10 ml of acetone-water (10:1). After filtration of the regenerated resin and evaporation of the solvents, 0.42g (84%) of <u>cis</u> 1,2-cyclohexanediol was obtained. The diols were easily characterized by their nmr spectra which included methine signals centered at δ 3.78 for the <u>cis</u> isomer and δ 3.34 for the <u>trans</u> isomer ($CDCl_3$).

A similar reaction sequence was also used to separate and selectively deuterate the <u>cis</u> 1,2-cyclohexanediol of a 1:1 mixture of <u>cis</u> and <u>trans</u> isomers. The reaction sequence was performed exactly as described above except for the cleavage step in which deuterium oxide was used insted of water.

The variance in reactivity of the two 1,2-cyclohexanediols with the polystyrylboronic acid resin is explained by the ease of formation of the five membered ring boronate with the cis isomer, since the movement of the cis groups to achieve a coplanar arrangement resemble the partial inversion of a chair form into a boat form. In contrast, the forcing of two trans substituents into coplanar positions increases the strain in the cyclohexane ring and make formation of the cyclic boronate more difficult[13].

The separation of a mixture of cis and trans 1,3-cyclohexanediols[14] was also carried out by this method. The polymer reacted rapidly with the cis isomer in its cis-diaxial conformation to yield the cyclic boronate, while the trans isomer which remained in the soluble phase could be separated by a simple filtration. Pure cis 1,3-cyclohexanediol (m.p.: 84-85) could be cleaved from the polymer by addition of water[13].

Another useful application of the polystyrylboronic acid resin (1) involves the selective removal of one product from a complex reaction mixture (Scheme II)



"A" = Removal of the soluble phase
"B" = Cleavage with water

SCHEME II. Extraction of a cis diol from a complex reaction mixture.

Thus, the oily material obtained in the reduction[15] of 5,5-dimethyl-1,3-cyclohexanedione (2) which showed several spots on thin layer chromatography, was treated with resin (1) in benzene with azeotropic removal of water to yield the polymer bound diol (4) which could be washed free of all the soluble impurities. Cleavage with water regenerated the resin and afforded pure cis 5,5-dimethyl-1,3-cyclohexanediol (m.p.: 145-146).[16] This simple procedure can be applied to the separation of complex mixtures such as those which are obtained in the selective acylation of carbohydrate derivatives.

The regenerated resins were unaffected by the successive coupling-cleavage cycles and could be reused efficiently without appreciable loss.

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13. We have also observed some coupling of the trans diols to the polymer in the cases where a large excess of the resin, with respect to the cis diol, was used. This coupling could conceivably involve linkage of the diol to more than one boron atom on the polymer backbone since the formation of a six-membered ring boronate with trans 1,3-cyclohexanediol is highly unlikely.
14. The nmr spectra of the 1,3-cyclohexanediols in pyridine-d_5 included signals for the methine protons centered at δ 3.78 for the cis isomer and at δ 4.10 for the trans isomer.
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16. The nmr spectrum of (3) was in agreement with the proposed structure and with literature data: H. Finegold and H. Kwart, J. Org. Chem., 27, 2361 (1962).