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Separation of diol enantiomers—a remarkable influence of water

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Abstract—The water content of ^{i}PrOH is shown to have a profound influence on the separation of two enantiomers of 2,2′-dibromohydrobenzoin on a Daicel OJ column. ^{i}PrOH containing 0.47% water gives no separation, whereas increasing the amount of water in the eluent to 3.4% effects complete separation. The influence is not general. © 2002 Elsevier Science Ltd. All rights reserved.

The separation of chiral diols by chiral HPLC to determine enantiomeric excess is a routine and well used technique and hydrobenzoin **2** is readily separated using a Daicel OJ column.[1,2] We had recently been separating enantiomers of diol **1** using a 9:1 mixture of heptane:^{i}PrOH. Fig. 1 illustrates a typical run. However, on changing to a new batch of ^{i}PrOH, separation was completely lost (Fig. 2), something that was remedied on returning to the old batch of ^{i}PrOH. The magnitude of the difference of separation between the two batches is profound. In one case there is no detectable separation and in the other there is a baseline silence of over 3 min between the enantiomers. Switching between the two batches of ^{i}PrOH showed

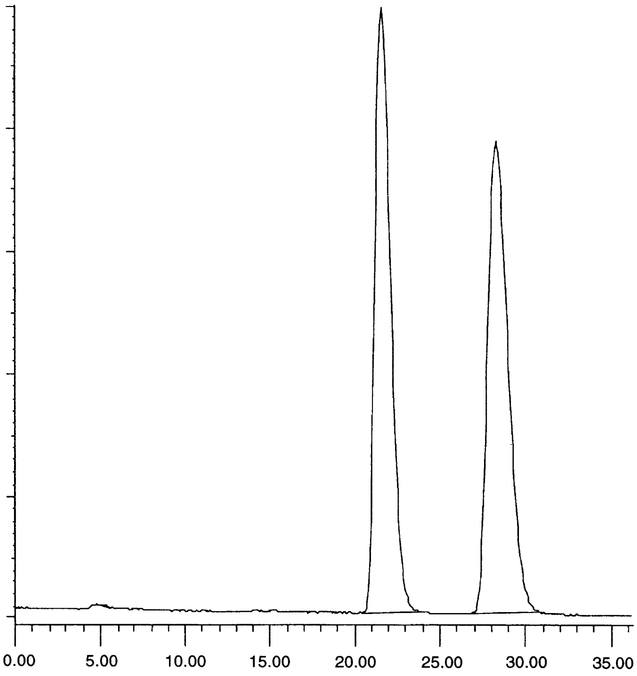

Figure 1. Separation of enantiomers of (±)-**1**. 9:1 heptane:^{i}PrOH ('old').

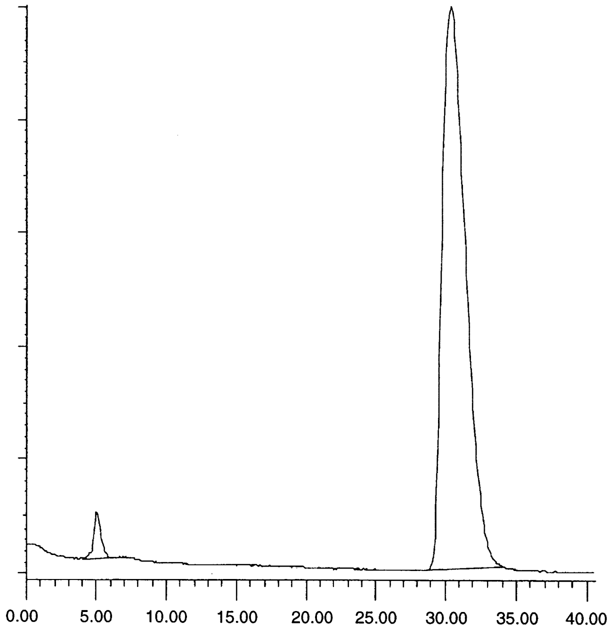

Figure 2. 9:1 Heptane:^{i}PrOH ('new').

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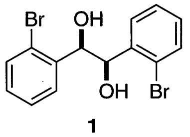
that the effect was entirely reproducible. Separations were performed on an OJ column with an eluent flow rate of 0.8 mL min^{-1} and with detection at 225 nm.[3]



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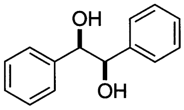

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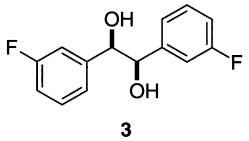

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After investigating several potential reasons for this change, the difference between the two batches was found to be water content. The water content of the new batch of ^{i}PrOH was found to be 0.47% v/v, whereas the old batch had acquired seven times this amount at 3.4% v/v. The water content was readily determined by ^{1}H NMR analysis.

Addition of water to this 'dry' ^{i}PrOH then gave the separation shown in Fig. 3. The effect of water is to reduce the retention time of both enantiomers but one much more than the other. Once again, the effect was entirely reproducible and we switched back and forth between the two systems several times. Addition of more water did not seem to improve the separation and, in fact, full separation was achieved using ^{i}PrOH with just 2% water.

Although modifiers like diethylamine or trifluoroacetic acid are well known and mentioned by Daicel for the OJ column, we had not come across water as a modifier. Indeed, Daicel do not recommend solvents other than hexane, ethanol or isopropanol with the OJ column and specifically warn against the use of water, and other polar solvents.[4]

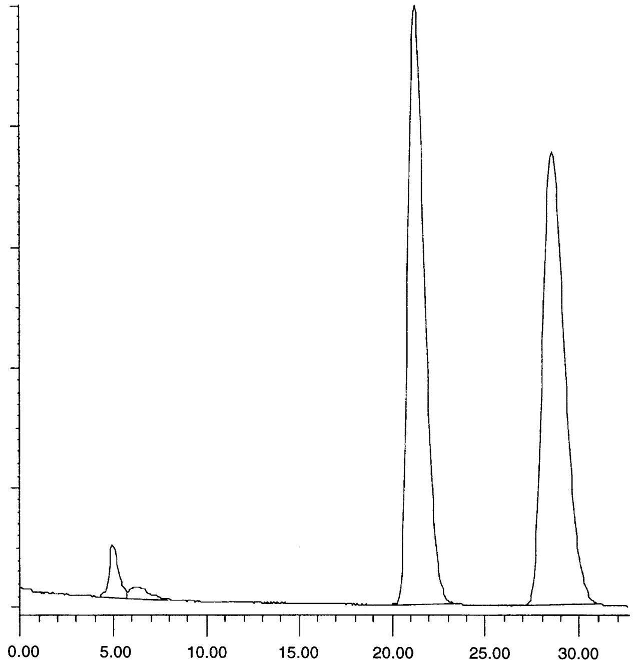

Figure 3. 9:1 Heptane:^{i}PrOH ('new'+H_2O).

Nevertheless, the influence of water on two similar diols was also investigated. Ordinary hydrobenzoin **2** and its 3,3′-difluorinated derivative **3** were also subjected to HPLC using ^{i}PrOH with differing water content. At one end of the scale, a solvent system using fresh ^{i}PrOH was used, and at the other extreme the solvent was saturated with water. Solvent systems with intermediate water content were also examined.

However, water had a negligible effect on the enantioseparation of both diols. Figs. 4 and 5 show the chromatograms for **2** and **3**, respectively, using both ^{i}PrOH with a water content of 0.5% ('dry') and 3.5% ('wet').[5]

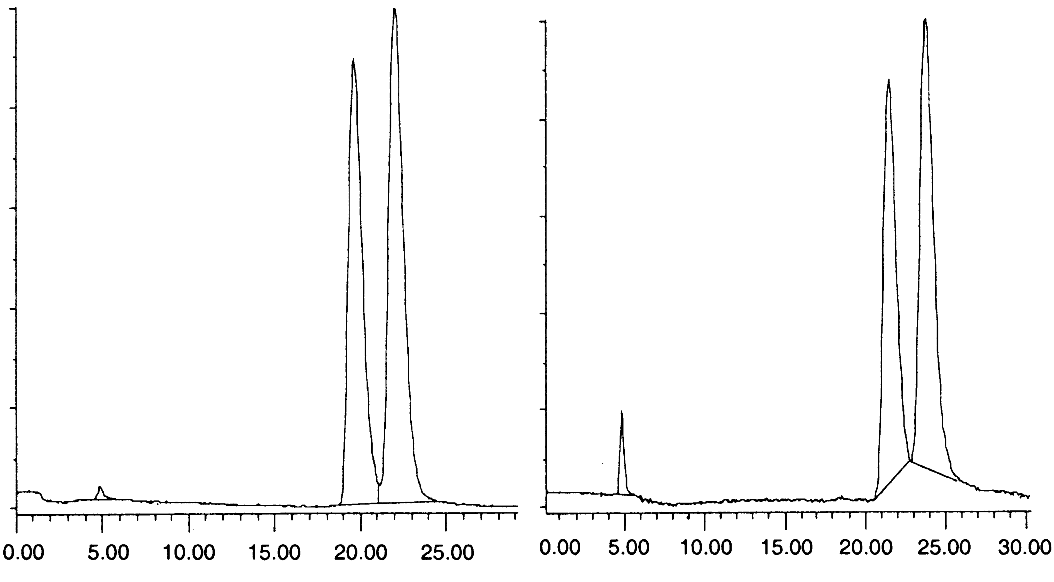

Figure 4. Separation of (±)-**2** using 'dry' (left) and 'wet' (right) ^{i}PrOH.

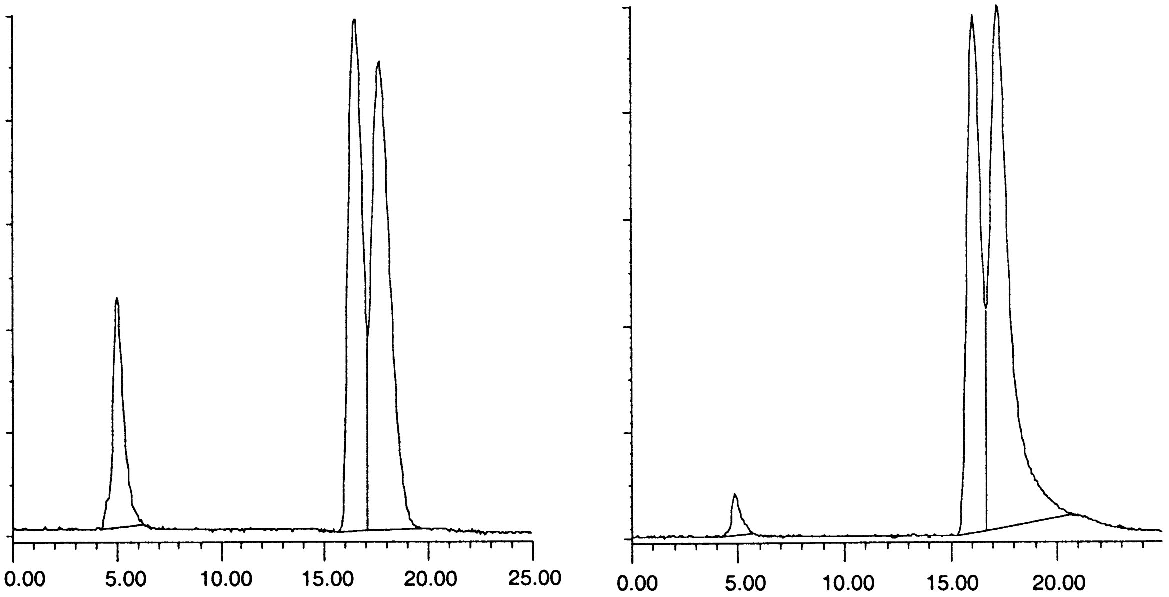

Figure 5. Separation of (±)-**3** using 'dry' (left) and 'wet' (right) ^{i}PrOH.

Conclusion

The enantiomers of 2,2′-dibromohydrobenzoin are completely resolved on an OJ column with a 1865:200:7 heptane:^{i}PrOH:H_2O solvent system and not resolved at all with a 1810:200:1 solvent system. Isopropanol and ethanol are very commonly used eluents for HPLC and although the water content is likely to vary greatly with these solvents it is scarcely considered as a factor. These results show that although water may well not be important, its influence may also be profound. We speculate that the *ortho* positioning of the substituent may well be more important than the nature of the substituent itself.

References

1. Okamoto, Y.; Aburutani, R.; Hatada, K. *J. Chromatogr.* **1987**, *389*, 95–102.
2. Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411–1412.
3. The chromophore is very weak at 254 nm.
4. http://www.daicel.co.jp/chiral/e/product/instruction/oj.htmL
5. Water content of 3.5% is near the saturation point of the solvent system. Although 500 μL of water may be mixed with ^{i}PrOH to a total volume of 10 mL (5% v/v), an emulsion is formed when heptane is then added to form a 9:1 mix of heptane:wet ^{i}PrOH.