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Barry W. Fisher

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BARRY WAYNE FISHER

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Toward the Synthesis of an
Optically Active Aminophosphonic Acid

Introduction

Direct liquid chromatographic resolution of enantiomers offers a very rapid and simple solution to the problem of resolution. For this reason, chiral liquid chromatography columns have built by a number of workers with varied success.\(^1\)\(^-\)\(^3\) Since the "ideal" column (one which will resolve any pair of enantiomers regardless of functional groups) is not possible, the best approach toward liquid chromatographic resolution should involve a series of chiral stationary phases each useful for the resolution of a wide range of enantiomeric pairs.

Pirkle and House\(^4\) have reported the preparation of such a chiral stationary phase and found it useful for the resolution of over 200 different enantiomeric pairs of amines, amino acids, hydroxy acids, lactones, mercaptans, and sulfoxides. Current work within the Pirkle research group is being directed toward the perfection of other chiral stationary phases with greater separation efficiency and wider ranges.

The principle of resolution by chiral stationary phase involves differing affinities of the enantiomers, and this
must involve at least three points of interaction with at least one of the enantiomers.\textsuperscript{5,6} One of these three interactions must be stereochemically dependent and it may be either attractive or repulsive to be effective.

Figure \#1 shows the chiral stationary phase reported by Pirkle and House, and Figure \#2 shows diagramatically how the column works resolving the enantiomeric forms of solute X. The hydroxyl hydrogen lends itself to hydrogen bonding with substituent $B_1$ as the first point of interaction. The carbonyl hydrogen lends itself to carbonyl hydrogen bonding with substituent $B_2$. The third interaction is (as required by the model for chiral stationary phases) stereochemically dependent, and it is the interaction of the aryl functionality with substituents Y and Z. In the specific case of the chiral stationary phase depicted in Figure \#1, the anthryl group serves as a pi-base for the purpose of interaction with a pi-acid group (either Z or Y) attached to X.

The solutes, X, were intentionally designed so as to have this type of interaction available. The different affinities for the chiral stationary phase shown by the enantiomers of X result in different retention times, and thus the resolution is accomplished.

Many of the solutes resolved by Pirkle and House required derivitization in order to incorporate the pi-acid into their structures. This was done by the formation of the 3,5-dinitrobenzoyl derivative of the amines, amino acids, amino alcohols, hydroxy acids, and mercaptans. The ability of these
solutes to incorporate the pi-acid functionality greatly increases the scope of the chiral stationary phase shown in Figure #1.

**Objective**

The objective of the assigned project was the synthesis of a series of aminophosphonic acids. Within this series, the aminophosphonic acid which is best resolved (the aminophosphonic acids are intended to be optically active) on the chiral stationary phase in Figure #1 could then be used as a chiral stationary phase itself. This could, in future work, be used to ascertain the suitability of other fluoroalcohols as chiral stationary phases eventually leading to a series of efficient chiral columns.

The synthetic route chosen for the attempt was reported originally by Gilmore and McBride and consists of the addition of diethylphosphite to Schiff's bases formed by addition of optically pure phenylethylamine to the necessary aldehyde. The resulting aminophosphonic ester was then hydrolyzed and subjected to catalytic hydrogenolysis yielding the desired optically active aminophosphonic acid. This scheme is shown in Figure #3.

Gilmore and McBride found that if the S configuration (levorotary) is used in the imine formation that the dextrorotary enantiomer of the resulting acid is formed. Use of the R configuration (dextrorotary) of the amine gave the levorotary enantiomer of the phosphonic acid. Enzymatic testing did not
yield the absolute configuration of the resulting aminophosphonic acids to Gilmore and McBride; but Glowiak, et al. found through x-ray crystallography that the levorotary enantiomer of the aminophosphonic acid has the S configuration. Thus, the S(-) amine induces the R configuration at the new asymmetric center preferentially.

Another method of synthesis of optically active aminophosphonic acids appeared in the literature while attempts were being made with the above method. This method, reported by Huber and McBride, involves acid catalyzed reaction of substituted ureas with trivalent phosphorus esters and aldehydes. This yields ureidophosphonates which may then be subjected to hydrolysis and neutralization to yield free aminophosphonic acids. The ureas may be made optically active by deriving them from R or S phenylethylamine; and thus yielding optically active aminophosphonic acids. This reaction sequence is shown in Figure #4. As will be discussed in the Experimental section, many difficulties were encountered with the Gilmore and McBride route; but the author felt that it was necessary to continue with it rather than try the Huber and McBride method since the first method mentioned had been confirmed by Glowiak, et al. This was a mistake as will be seen.

Huber and McBride point out that contrary to the phosphite addition method, the R enantiomer of the amine preferentially induces the dextrorotary enantiomer of the resulting aminophosphonic acid. The S enantiomer of the amine, on the other hand, induces the levorotary enantiomer of the aminophosphonic
acid. This indicates that the two reactions (phosphate addition and ureidophosphonate hydrolysis) are proceeding by different mechanisms.

**Experimental**

Compounds used for the synthesis described were either readily available commercially or from previous studies, and were used without further purification except as noted. Whenever possible, Aldrich chemicals were used in order to be able to examine observed NMR spectra with the ones reported by Aldrich.

A number of bizarre attempts at imine synthesis were attempted before success was found. One method involved dissolving equimolar amounts of the amine (S-(-)-phenylethylamine) and the aldehyde (benzaldehyde or naphthaldehyde) in benzene, mixing the solutions, and removing the water as an azeotrope through refluxing into a Dean-Stark apparatus. Another attempt involved allowing the reflux condensate to filter through molecular sieves. A third method was to perform the reflux (after addition of the reactants) with the molecular sieves added directly to the reflux flask. Strangely, in each case, a dry flask resulted upon rotary evaporation of the solvent; and neither products nor starting compounds could be found.

10.61g (0.1 moles) of benzaldehyde (Aldrich) was dissolved in 40ml of anhydrous benzene (the water removed by distillation of the azeotrope into a Dean-Stark apparatus). To this was added a solution of 12.18g (0.1 moles) of S-(-)-phenylethylamine dissolved in 40ml of anhydrous benzene. The combined
solutions were swirled over a steam bath after addition of 10g of anhydrous K₂CO₃. After 10 minutes, the K₂CO₃ was removed by filtration; and the solvent was removed by rotary evaporation. This left a viscous yellow oil which was subjected to very low pressure to remove trace solvent. Loss of the aldehyde proton in the NMR (H¹) spectrum indicated a successful reaction. This imine was used without further purification in all cases.

It should be pointed out that later an even simpler method for the imine synthesis was found: the two liquid reactants were simply mixed together neat and swirled over a steam bath. After the water formed, it fell to the bottom of the flask and it was removed by Pasteur transfer pipet. Confirmation again involved observation of the loss of the aldehyde proton (approximately 10.6ppm) on the NMR spectrum.

Synthesis of the phosphite ester was effected by adding the diethyl phosphite to the imine previously formed and heating the mixture as reported by Gilmore and McBride. Rotory evaporation of the solvent (benzene, anhydrous) again left a viscous yellow oil. The product was confirmed by NMR spectra.

Chromatographic evidence confirmed the 2:1 ratio of diastereomers as reported by Glowiak, et al. In order to increase the diastereomeric ratio, the phosphite addition was attempted in two other ways: 1) Extreme pressure at room temperature was used in order to force the molecules into the conformation induced by the reaction mechanism more efficiently than simple heating. 2) Addition of the diethyl phosphite at room temperature and pressure with stirring for several days. Unfortunately, neither method yielded product. Note:
that this is contrary to the results of Glowiak, et al\(^8\) who reported that the reaction performed at room temperature afforded a diastereomeric ratio of 6:1.

Recrystallization of the crystals which resulted from the phosphite addition when the mixture was allowed to cool to room temperature was done with ethanol with a trace of water added when the ethanol solution was saturated. Several recrystallizations yielded white crystals (mp. 79-80 C). Interestingly, chromatography indicated that the crystals were of a single diastereomer. Thus, the resolution of the resulting aminophosphonic acids is effected.

Direct cleavage of the ethyl benzene from the amino phosphonic ester portion of the product was attempted using catalytic hydrogenolysis at low pressure on a Paar hydrogenator using 5% Pd/C. Several solvents were tried each without success: glacial acetic acid, 95% ethanol, methanol, methanol/water (3:1). These failures confirmed the results of Tyka\(^10\) (found later) that the esters of aminophosphonic acids resist hydrogenolysis.

In all cases, hydrolysis of the esters was trivial; and it was done by refluxing the solution containing the phosphonic esters with 6N HCl overnight. Removal of the water by rotary evaporation left white crystals of the hydrochloride salt of the aminophosphonic acid.

As with the esters, direct hydrogenolysis of the aminophosphonic acid hydrochlorides encountered difficulties. These reactions were tried using the same conditions and solvents as for the attempted hydrogenolysis of the aminophosphonic
esters. Eventually, a solvent system was found which yielded the proper cleavage: Methanol/Water (1:1) with a small amount of NaHCO₃ added to the mixture.

Before the proper solvent mixture above was found, the hydrochloride salts were treated with propylene epoxide while dissolved in a minimum amount of water to a pH of 6. This freed the acid form of the molecule when a trace of ethanol was added. The pH was followed with pH paper as the titration proceeded, and the crystals fell out of the solution upon cooling.

Hydrogenolysis to remove the ethyl benzene group from the aminophosphonic acid again presented difficulties. Several solvents were tried including those listed above for the hydrogenolysis of the aminophosphonic esters and the aminophosphonic acid hydrochloride salts. Again, the solvent system which was successful was methanol/water (1:1) with a small amount of NaCO₃. NMR spectra show that this yields the desired aminophosphonic acid as the Na salt. Unfortunately, I was unable to isolate the free acid (-OH as opposed to -O⁻Na⁺) in significant yield.

**Conclusions**

Clearly, it is difficult to draw conclusions when so many difficulties were encountered with a reported procedure. Not only was the procedure reported, but an independent group of researchers were able to successfully reproduce the work of Gilmore and McBride (Glowiak, et al.). It was for this reason that I decided to continue to work on that procedure rather than start anew on the procedure reported by Huber and Gilmore. Since I was still unable to accomplish the objective of the
project (the synthesis of the optically active aminophosphonic acid for use as a chiral stationary phase), it would have been wiser to attempt the Huber and Gilmore synthesis.

Work toward the synthesis of the optically active aminophosphonic acids should continue both for their utility in the evaluation of other flouroalcohols as potential chiral stationary phases, and for the verification of the procedure as published by Gilmore and McBride.
Captions for the Figures

Figure #1  This is the chiral stationary phase reported by Pirkle and House: 2,2,2- trifluoro-1-(9-anthryl)ethanol.

Figure #2  Representation of the model of operation of the chiral stationary phase reported by Pirkle and House. \( R_f \) = perfluoroalkyl group; \( B_1 \) = hydrogen bond receptor; \( B_2 \) = carbonyl hydrogen bond receptor; \( X = C, N, P, S \), or a group of atoms.

Figure #3  Reaction sequence reported by Gilmore and McBride.

Figure #4  Reaction sequence reported by Huber and Gilmore.
Figure #1

Figure #2
Figure #3
Figure #3 (cont'd)
Figure #4
References


