1-1-1997

The Resolution of Chiral Dialkylarylsufonium Ions by 1H NMR Spectroscopy

Johnathan Whetstine
Western Kentucky University

The Resolution of Chiral Dialkylarylsulfonium Ions by ^{1}H NMR Spectroscopy

A Thesis
Presented to
The Faculty of the Department of Chemistry
and the Honors Program
Western Kentucky University
Bowling Green, Kentucky

by
Johnathan R. Whetstine
April 22, 1997

The Resolution of Chiral Dialkylarylsulfonium Ions by ^{1}H NMR Spectroscopy

Recommended 4-30-97

Thomas K. Green
Director of Thesis

John W Reasoner

Matt Kulat

Jerry M Fonbad 4/30/97

Approved 4/30/97

Jerry M Fonbad, Honors Director

ACKNOWLEDGMENTS

There are a few groups or individuals that I would like to thank for all their support during my work on this project.

First, I would like to thank the Honors Program at Western Kentucky University for the research grant that allowed me to travel and present this work at the National American Chemical Society meeting in Orlando, Florida.

Secondly, I would like to thank Dr. Tom Green for all his support and guidance throughout this project and my undergraduate career. He has enabled me to advance and enter the research community with an open mind and a strong sense of self. For these reasons, I am very grateful to Dr. Green.

Finally, I would like to thank Jeanne, Stephen, and Elizabeth for all their support and help throughout my educational career. I would also like to say that they are my strength and motivation. To them, I truly owe my gratitude.

TABLE OF CONTENTS

ABSTRACT

The goal of this research was to design a rapid Nuclear Magnetic Resonance method to measure enantiomeric excess of chiral sulfonium ions by using chiral lanthanide shift reagents. The sulfonium ions studied were dialkylarylsulfonium ions. The shift reagent that was employed was Europium (III) surrounded by chiral ligands of 3-trifluoroacetyl-*d*-camphor (tfc), which is derived from (+)-camphor. Ethylmethylphenylsulfonium ion was synthesized for study as a racemic and enantiomerically enriched mixture. The sulfonium ion was then ion-paired with the shift reagent for resolution of R and S enantiomers. The best resolution was obtained with the $Eu(fod)_4^-$ shift reagent, with nearly baseline resolution of the aromatic ortho hydrogens of the phenyl ring. An analysis of the R-enriched mixture allowed assignments of the peaks as either R or S isomer. Heating of this R-enriched ion in the presence of the shift to 60°C allowed the observation of pyramidal inversion of the sulfonium ion. Other sulfonium ions were studied, including benzylmethylphenylsulfonium ion. The diastereotopic hydrogens of this ion were baseline resolved into R and S isomers.

INTRODUCTION

Enantiomers have been a focus for resolution and analysis for a very long period of time. The pharmaceutical and chemical industries have been interested in the enantiomeric excess so many techniques have been developed to analyze these compounds. Some common techniques are optical rotation, X-ray crystallography, Circular Dichroism, and Nuclear Magnetic Resonance spectroscopy (NMR).

The focus of this research is the stereochemistry of chiral sulfonium ions. Stereochemistry is an extremely important branch of organic chemistry, dealing with the three dimensional relationship of molecules.[1] The pharmaceutical and chemical industries have a particular interest in the stereochemistry of organic molecules. The stereochemistry of molecules--drugs or chemicals--determine whether they will be beneficial, harmful, or neutral in the biological system being studied. The enantiomeric purity is important to ensure that the appropriate amount of the right type of enantiomer is being given to the patient. Therefore it is no longer sufficient to describe purity without a knowledge of enantiomeric purity.

Stereochemistry of organic molecules is an immense subject of study, but there are a few key ideas that need to be discussed and understood. The area that this research mainly deals with is stereoisomers, molecules that only differ in configuration and/or conformation. A special kind of stereoisomer is an enantiomer. Enantiomers are molecules that are mirror images but nonsuperimposable and have the same physical and spectroscopic properties, with the exception of polarimetric properties. An understanding of enantiomers can easily be described by using a hand. The left hand looks like the right hand in a mirror but cannot be superimposed on the left.

Therefore the hand is chiral object. A chiral molecule is one that lacks a plane of symmetry, and its mirror image is different than the original. One possible cause of chirality is the existence of a stereocenter. In the case of carbon, the carbon would have four different groups bonded to it.[1] There is another type of stereoisomer besides enantiomers. These molecules are called diastereomers. Diastereomers are not mirror images and have different physical and spectroscopic properties.[2] The difference in spectroscopic properties for the diastereomers allows the resolution and analysis of these compounds by a variety of conventional techniques.

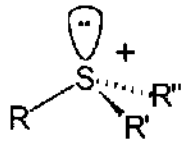
If the chiral enantiomers are coupled with chiral lanthanide shift reagents (LSR), the molecules become diastereomeric and can be analyzed by using NMR. The lanthanide shift reagent couples more strongly with one enantiomer and allows there to be a difference in the induced chemical shift.[2] NMR techniques have been used to analyze many chiral molecules such as alcohols, amines, aldehydes, ketones, and carboxylic acids.[3]

The goal of this project was to develop an NMR technique using chiral lanthanide shift reagents for the determination of enantiomeric excess and the rate of pyramidal inversion of the dialkylarylsulfonium ions.

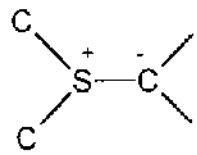
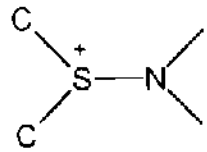
LITERATURE REVIEW

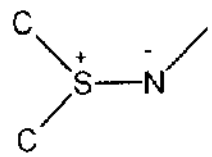
I. Structure of Sulfonium Ions.

Type 1 sulfonium ions possess a sulfur atom with three singly bonded carbons attached directly to it. The sulfur also has a lone pair of electrons that will have special effects on its structure. The structure looks like this



There are other types of sulfoniums that have important functions in the chemical world but will not be discussed in the context of this research. A table for these types of sulfoniums can be seen below.

TYPES	STRUCTURE
2. part ylide with negatively charged carbon	
3. one atom to sulfur is nitrogen	

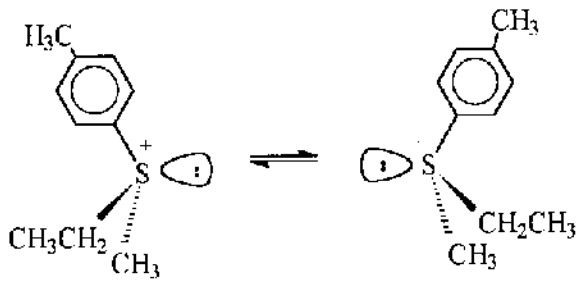
4. part ylide with negatively charged nitrogen	
5. selenium salts (rare)	

Most of the work to determine the structure of the sulfonium salts was done by x-ray diffraction . This technique became especially active about 10-15 years ago. The first studies used photographic film and more recently photometers. In 1959, the earliest work done using X-ray methods was done by Zaccaro and McCullough on trimethylsulfonium perchlorate.[4] By using this technique, type 1 sulfoniums were determined to possess a pyramidal geometry with the sulfur about 0.8 Å above the three carbons, which serve as the base of the pyramid. The carbon-sulfur-carbon bond angle is slightly less than the tetrahedral bond angle of 109°, resulting from the repulsion between the lone pair of electrons and the atoms bonded to the sulfur. An example of pyramidal geometry is observed in dimethylphenylsulfonium perchlorate. The average sulfonium ion carbon-sulfur bond length is 1.806 Å with a range of 1.753-1.882 Å ; the carbon-sulfur-carbon angle has an average of 102.5° with a range of 97.5-108.6°.[4] This data is well supported by a more recent article that calculates the lengths and angles by using certain calculation methods on the Gaussian 90 programs and the use of the Restricted Hartee-Fock calculations.[5] At this point, there is not enough data to separate aromatic carbon-sulfur+ dimensions from carbon (sp^3)-sulfur relationship.

The molecular geometry of the sulfonium ion can be perturbed in two principle ways.

First, if the sulfur atom is in a cyclic compound, this may cause the carbon-sulfur-carbon angle and the carbon-sulfur length to be smaller than expected. Second, the structure can possibly be affected by the solvent.

Type 1 sulfonium ions can exist as chiral enantiomers when the three groups bonded to the sulfur are different, resulting in the sulfur being a stereocenter. Below are two enantiomers that are examined in this research. The R and S enantiomers can interconvert by a process called pyramidal inversion.[6] Pyramidal inversion was first reported by Darwish. He demonstrated that the sulfonium ion undergoes the inversion through a transition state with the sulfur having a planar configuration with the groups bonded to it, allowing for the lone pair to "flip" from one side to the other. The molecule continues to undergo pyramidal inversion until equilibrium has been established and a racemic mixture forms (50% R : 50% S), as demonstrated in the diagram below.



R S

II. Techniques for determining enantiomeric excess (ee) of sulfonium salts.

Enantiomeric excess of a mixture of R and S enantiomers is defined as the percent excess of the one enantiomer over the racemate (50/50 mixture).

$$ee = [\,|R - S|\,/\,(R + S)] \times 100 = |\%R - \%S|$$

In the past, ee of chiral sulfonium ions had been determined by the classic method of polarimetry.[6] The mixture is dissolved a solvent and then analyzed in a polarimeter. The specific rotation of the mixture is measured and compared to a rotation of a solution of the pure enantiomer, obtained by recrystallization of diastereomeric salts.

There are two distinct disadvantages of this technique. First, the specific rotation of a pure enantiomer must known. This requires careful, and sometimes tedious, resolution of a single enantiomer by recrystallization techniques. A second disadvantage is that relatively large amounts of the sulfonium ion are required. In a typical experiment, gram quantities of the mixture are required for significant rotation of the polarized light. NMR techniques circumvent both of these disadvantages.

III. NMR Lanthanide Shift Reagents for determining enantiomeric excess.

Lanthanide III shift reagents are known for causing changes in chemical shifts for compounds. The three primary lanthanide metals used are Pr (III), Eu (III), and Yb (III). Eu (III) and Yb (III) cause shifts to higher frequencies, while the Pr(III) cause shifts to lower frequencies. There are a several types of chiral ligands that can be associated with the complex. These ligands are pvc, dcm, hfc, and tfc. These ligands are diketonates that coordinate to the lanthanide (III). When the enantiomers interact with the chiral shift reagent, they form diastereomeric complexes or ion pairs, which can be resolved by NMR techniques. This allows for the resolution of the enantiomers into the R and S forms. The type that was employed in this research was the tfc ligand also known as 3-trifluoroacetyl-*d*-camphor, which was derived from (+)-camphor. The metal that was focused on was Eu (III).

The size of the shift will be determined by three factors; (1) the distance of the nucleus

from the lanthanide (r), (2) the angle (θ) between the line joining the nucleus to the lanthanide and (3) the direction of the magnetic dipole passing through the lanthanide and the atom coordinated with it.[2] The magnitude of the lanthanide induced shift can be approximated using the McConnell-Robertson equation.

$$\text{Chemical shift change} = (3\cos\theta - 1)/r^3$$

By using these chiral Lanthanide III shift reagents and resolving the enantiomers of the compound being studied, the enantiomeric excess can be estimated by integrating the area under the peaks or curves. This NMR technique does not require the optically pure enantiomer to be compared to the mixture in order to determine the enantiomeric excess, and this is why the NMR method is a distinct advantage. Another reason this method is an advantage is the need for only milligram quantities for the analysis.

Presently, this is the first time that lanthanide (III) shift reagents has been used for the evaluation of enantiomeric excess of sulfonium ions.

IV. Functions and Uses of Sulfonium Ions.

Sulfonium ions have certain important functions in biological systems and uses in the chemistry laboratory. Some sulfonium ions act like methylating agents or transferring reagents in cells. An example of this activity is found in the sulfonium metabolite S-adenosyl-L-methionine, which is involved in the biological formation of epinephrine by methylation of norepinephrine.[7] This discovery led to many others that showed that the alkyl group, usually the methyl group, was transferred from the sulfonium moiety.[5] Methylases have important functions because they are

found in stabilizing some DNA and RNA strands that are essential for the cells existence.[8]

Another main function that sulfonium ions have is producing sulfur ylides. Ylides are compounds that have a carbon with a negative charge and the heteroatom bonded to the carbon has a positive charge. The sulfonium is used to produce the ylide by reacting the sulfonium with a base like NaOH. One of the hydrogens on a carbon next to the sulfur acts as an acid and protonates the base. An example of this type is seen when trimethylsulfonium ion is reacted with a base yielding the ylide.

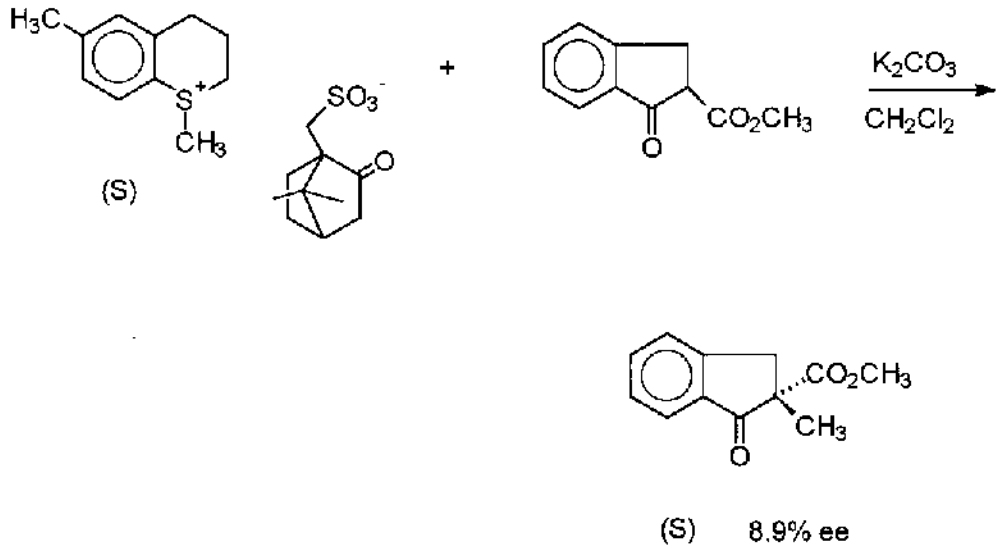
$$(CH_3)_3S^+ \quad + \quad OH^- \longrightarrow \quad (CH_3)_2\overset{+}{S}\overset{-}{C}H_2 \quad + H_2O$$

Another important use for sulfonium ions is in the production of polymers. A polymer is a long chain of organic molecules used in things like clothing, beads, and coffee cups. Sulfonium ions have been found to initiate cationic polymerization in some cases. Two types of polymers being focused on are styrene and phenyl glycidal ether, PGE. For example, substituted benzylmethylphenylsulfonium ions have allowed the polymerization of styrene and PGE to be controlled at certain temperatures.[9]

The effects of the groups in the para position of the benzyl are also being evaluated so polymerization procedures can be enhanced.[10] With these new procedures, more effective polymerization can be developed for the synthesis of the styrene and PGE monomers. Along with the improvement of these procedures, other novel polymers can be developed for future use.

The last example of the use of sulfonium ions is in asymmetrical alkylation. Asymmetrical alkylation is the use of a optically active sulfonium to alkylate a compound, especially cyclic β-

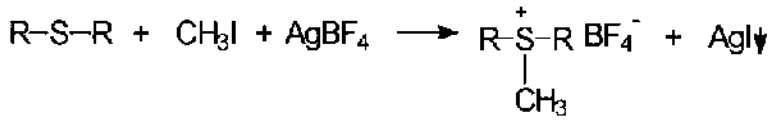
keto esters.[12] An example is seen above with the natural occurring S-adenosyl-L-methionine, which is able to methylate asymmetrically, showing that sulfonium salts have this ability. In the study done by Umemura and et al., the sulfoniums were found to asymmetrically alkylate. An example of the asymmetrical alkylation is seen in the following scheme illustrated in Umemura's paper:



The overall importance of asymmetrical alkylation is that optically pure compounds can be made for specific uses in the pharmaceutical and chemical industry.

V. Synthesis of Type I Sulfonium Ions.

The synthesis of type I sulfonium ions discussed in this paper are similar and based on R.M.Acheson's work.[12] Acheson showed that the addition of methyl iodide and a thiophene, a sulfide type structure that is cyclic and aromatic, in the presence of silver salt, produces the thiophenium or sulfonium in this case.



The silver salt used by us is silver tetrafluoroborate ($AgBF_4$) because it is not explosive like silver perchlorate used by Acheson et al.[12] The Ag ion helps push the reaction forward because the iodide from the methyl iodide causes the precipitate silver iodide to form. The basic model for how this system works is the SN2 mechanism. The nucleophile (R-S-R') attacks and inverts the molecule, releasing the leaving group, iodide. In this case, the iodide or halide acts as a good leaving group as the nucleophile, the sulfide, attacks methyl iodide. When this happens the silver and iodide react, forming the precipitate, AgI; positively charged sulfonium ion pairs the nonnucleophilic anion, BF_4^-.

In some cases the sulfide may react directly with the methyl iodide in the absence of silver ion. This happens when the sulfide being methylated is type 1 or does not have an aryl groups attached to the sulfur. The sulfide is nucleophilic enough to react on its own. All these type of reactions follow the SN2 type mechanism discussed earlier. For most of these experiments the solvent used is 1,2 dichloroethane, but Acheson states that the polarity or structure of some sulfoniums can require another solvent to be soluble.[12]

EXPERIMENTAL

I. Synthesis of the Racemic Sulfonium Ions; R,S ethylmethylphenylsulfonium and R,S benzylmethylphenylsulfonium tetrafluoroborate.

The synthesis of the two types of sulfoniums used in this experiment are very similar to the method of Acheson and Harrison.[13] Ethylphenylsulfide (1 mmol) and iodomethane (1.2 mmol) were added together and dissolved in 2 ml of 1,2-dichloroethane (DCE). While this solution was stirred, 1.2 mmol silver tetrafluoroborate is added, causing the reaction to go toward completion because the silver iodide precipitates. Slight excess of $AgBF_4$ was added to make sure the reaction was completed. The reaction continues to stir for 24 hours. The solution was then centrifuged and the supernatant was removed and added to a round bottom flask. The precipitate was then washed several times with acetonitrile. The flask with the supernatant and washings was then rotovaporized, carefully not exceeding 50°C, until the yellow oil was left behind. The oil was then placed in a vacuum oven to dry for another 24 hours at room temperature. This gives the ethylmethylphenylsulfonium tetrafluoroborate as an oil.

This same procedure was also used in making benzylmethylphenylsulfonium and benzylmethyl-*p*-tolylsulfonium tetrafluoroborate. The only difference in the procedure was that the benzyl chloride was used with methylphenylsulfide and methyl-*p*-tolylsulfide in the presence of silver tetrafluoroborate. The precipitate was silver chloride. After these steps, crystals were left in the flask - white for benzylmethylphenylsulfonium salt or brown crystals for benzylmethyl-*p*-tolylsulfonium salt.

II. A. Preparation of the (R)-ethylmethyl-p-tolylsulfonium Tetrafluoroborate.

The procedure used to make this sulfonium ion came from Anderson and Caret's work.[14] The sulfoxide used in this experiment was (R)-methyl-*p*-tolylsulfoxide with a 99% purity, the other 1% is not known; 5.9 mmol of the sulfoxide was added to 6.5 mmol trimethyloxonium in 2 mL of nitromethane and stirred for about 10 minutes. The solution was then concentrated by rotovaporization at room temperature. The resulting R-methoxyethyl-p-tolylsulfonium tetrafluoroborate was then dissolved in methylene chloride and then precipitated by diethyl ether. Each time the diethyl ether was discarded because it contains impurities. This process should be carried out three to four times. The resulting product was a thick yellow oil and was stored under nitrogen for the next step.

Diethyl cadmium (1.54 mmol) was added to the yellow oil very slowly with rapid stirring*. (Caution: The reaction was very violent and got very hot! It is best if the reaction vial and the diethyl cadmium are kept cold before the injection.) After 20 minutes, the excess cadmium was hydrolyzed with 5% sulfuric acid, causing another violent and extremely hot reaction to take place. The resulting solution was then extracted with 2ml of water 3 times, keeping the aqueous layer. The aqueous layer was then saturated with $NaBF_4$ and extracted with 5 portions of 5 ml of dichloromethane, keeping the organic layer. This layer was then dried over magnesium sulfate, decanted, and finally rotorvaporized. The end product was a thick yellow oil.

* **Caution**: People working with cadmium compounds should read the MSDS reports and wear gloves, a breathing mask, goggles, and a lab jacket at all times. It is very important to carry out the above reaction under fume hoods and to allow plenty of ventilation in the work area!!

B. Synthesis of Diethylcadmium. The diethyl cadmium used in this procedure was synthesized from cadmium bromide and ethylmagnesium bromide.[15] The use of $CdBr_2$ was found to give a good yield of diethylcadmium, while $CdCl_2$ gave no yield. Drying and pulverizing the $CdBr_2$ was found to help increase the yields of the desired product.

The reaction must be conducted under a dry, inert atmosphere shown below.

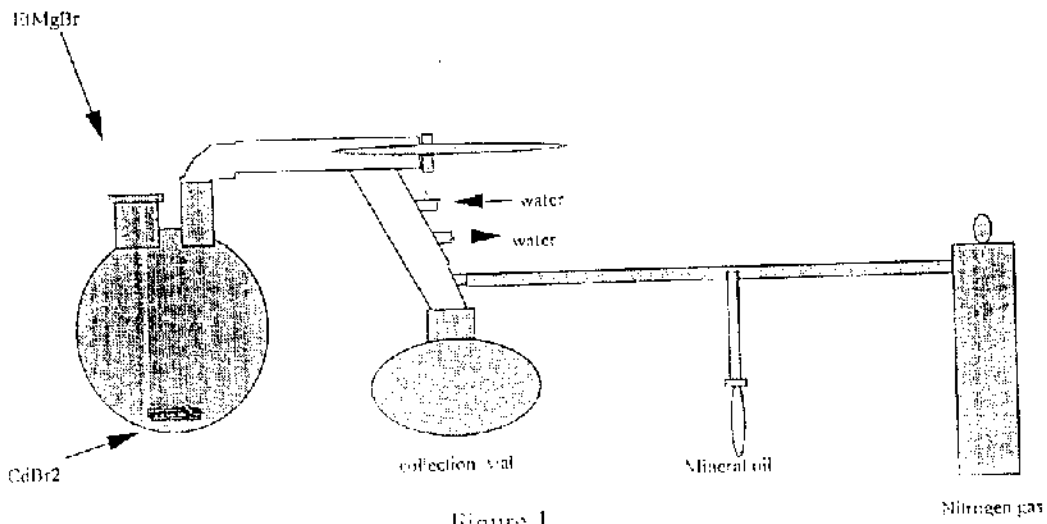


Figure 1

The system was purged first with N_2 gas for about 5-7 minutes. Approximately 14.8 ml of the 3.0 M ethylmagnesium bromide in diethylether was added to the attached vial with a spin bar at a low rate of speed. Steadily, 4 g of $CdBr_2$ was added to the ethylmagnesium bromide and then the apparatus was closed, allowing pressure to be released through the needle in the mineral oil. The reaction mixture turned a dark, black and then gray color. The reaction was carried out for at least 13-24 hours.

After letting the reaction go for the proper amount of time, the diethylether was distilled over at about 50°C and 1 atmosphere pressure. Now the vacuum and hot mineral oil bath was

prepared. While warming the reaction vial - carefully not exceeding 80°C, the collecting vial was cooled in a dry ice-acetone bath, keeping the diethylcadmium from going into the trap. After the diethylcadmium had been collected, N_2 gas was blown over the closed diethylcadmium vial. This reduced the amount of excess diethyl ether and kept the diethyl cadmium from reacting with any air that may have gotten in the vial. The cadmium product was stored in a freezer until it was needed.

III. A. Preparation of the sulfonium tetrakis lanthanide (III) ion pair.

The preparation of the sulfonium with the shift reagent came from the procedures of Wenzel and Zaia.[16] The molar ratio of 1:1 was used in the preparation of these solutions. The sulfonium tetrafluoroborate salts in 0.1 mmol amounts were added to vials under a nitrogen environment. After the sulfonium was added to the vial, 0.1 mmol of either $Eu(fod)_3$, $Eu(tfc)_3$, or $Yb(tfc)_3$ and 0.1 mmol of either Kfod or Ktfc were added. 1.0 ml of *d*-chloroform was added and stirred for 45 minutes, resulting in the formation of the ion pair - the sulfonium cation and tetrakis lanthanide anion - and the precipitate KBF_4. The solution was then centrifuged, and the supernatant was put into a NMR tube and analyzed.

B. Preparation of Kfod and Ktfc. These compounds are made by doing a normal acid-base reaction. To make 1 mmol Kfod, add 1mmol of Hfod to 1mmol KOH (0.08 g of a 50% KOH solution). The product was placed in a vacuum oven overnight at room temperature.

The same procedure was used to make 1 mmol Ktfc. The only difference was that Htfc was used with KOH.

RESULTS AND DISCUSSION

I. Analysis of Racemic Mixtures.

A. Ethylmethylphenylsulfonium Ion Analysis.

The model system that was used for this study was racemic ethylmethylphenylsulfonium tetrafluoroborate. The reference spectra for this sulfonium salt can be seen in Figure 2. This figure shows the ^{1}H NMR spectrum of the ethylmethylphenylsulfonium tetrafluoroborate in d_6-acetone. This spectrum represents the reference spectrum. The key regions to focus on are the aromatic hydrogens at ~8 ppm. and the diastereotopic hydrogens at ~3.5 ppm. Enantiomeric components have not been resolved in this spectrum. After setting up the reference spectrum, the sulfonium salt was analyzed with the following: $Eu(fod)_4^-$, $Eu(tfc)_3fod^-$, and $Eu(tfc)_4^-$. The concentration used for each of the analysis was 0.1 M.

The spectrum of the ethylmethylphenylsulfonium and $Eu(fod)_4^-$ shift reagent (Figure 3) shows that the diastereotopic hydrogens are resolved into the two hydrogens at about 15 and 18 ppm. The aromatics are resolved into the different types of hydrogens: ortho hydrogens, our primary focus at 12 ppm, metas and para. Along with the resolution of individual hydrogens associated with the diastereotopic hydrogens and the aromatic hydrogens, the methyl directly attached to the sulfur is also shifted from about 3.2 ppm to 24 ppm. This large shift is probably a result of this methyl group being directly bonded to the positively-charged sulfur atom. The anionic shift reagent should interact more strongly at the sulfur center.

Figure 4 shows the same sulfonium ion with the chiral shift reagent, $Eu(tfc)_3fod^-$, where tfc is derived from the (+)-camphor. The diastereotopic hydrogens are resolved into enantiomers at

about 20 ppm (four small peaks). This spectrum reveals enhanced resolution of the ortho hydrogens at 13 ppm, which is shown as a doublet. The doublet has a spacing of 17.2 Hz, which is greater than the ortho-meta coupling constant of 7.2 Hz, which demonstrates that the R and S enantiomers are being resolved in this spectrum. This resolution led to the use of the chiral shift reagent, $Eu(tfc)_4^-$. This chiral shift reagent caused the ortho hydrogens to be dramatically resolved, with a separation of 72 Hz. These results can be seen in Figure 5. The diastereotopic hydrogens were shifted into the methyl peak at 28.5 ppm, indicated by the integration value of 5.

$Eu(tfc)_4^-$ seemed to cause the best resolution of the R and S ortho hydrogens for ethylmethylphenylsulfonium ion. This was in contrast to the butylmethylphenylsulfonium ion (Appendix I). The optimal shift reagent in this case was $Eu(tfc)_3fod^-$, indicating that the best resolution of a system will vary between the two types of chiral shift reagents.

B. Benzylmethylphenylsulfonium and benzylmethyl-*p*-tolylsulfonium tetrafluoroborate.

The next sulfonium salts that were analyzed with the lanthanide shift reagents were benzylmethylphenylsulfonium and benzylmethyl-*p*-tolylsulfonium tetrafluoroborate. Benzylmethylphenylsulfonium ion was analyzed with the achiral shift reagent, $Eu(fod)_4^-$, and the spectrum can be seen in Figure 6. This spectrum reveals the diastereotopic hydrogens resolved into the two types at about 18-19 ppm. The aromatic hydrogens of the phenyl group were separated into the three types; ortho, meta, and para. The ortho, meta and para hydrogens of the benzyl group are also resolved. Since the results were similar to the ethylmethylphenylsulfonium ion, the chiral shift reagent, $Eu(tfc)_3fod^-$ was used to analyze both these sulfonium ions. The best results for this study were showed to take place when the concentration was between 0.05 M -

0.1 M. Figures 7 and 8 show the shift and resolution of the aromatic hydrogens of these sulfonium ions.

Figure 7 shows that the aromatic ortho hydrogens of the benzyl group of benzylmethylphenylsulfonium ion were baseline resolved into R and S with the chiral shift reagent, $Eu(tfc)_3fod^-$, between 11.5 and 12.5 ppm. The ortho hydrogens of the phenyl group were not resolved into R and S. The metas and para hydrogens associated with the benzyl group were also resolved into the R and S at 8.5 ppm, even though the metas and para of the phenyl group were not resolved into R and S. The resolution of the meta and para hydrogens for the benzyl group were determined by integration, indicating overlap of the meta and para peaks.

Figure 8 shows the benzylmethyl-*p*-tolylsulfonium ion was shifted very similarly to the benzylmethylphenylsulfonium ion, except the farthest shifted aromatics were missing the para position. This was expected because the phenyl group associated directly with the sulfur is shifted the farthest. The benzyl orthos were shifted and resolved between 12 and 13 ppm. The meta and para hydrogens associated with the benzyl were also resolved into the R and S. The *p*-tolyl group was not resolved into enantiomers but was shifted farther than the benzyl group because the *p*-tolyl is closely associated to the sulfur atom.

These same two sulfonium ions were next analyzed with the $Eu(tfc)_4^-$ as shown in Figure 9 for the benzylmethylphenylsulfonium ion. This shift reagent gave remarkable shifts and resolution of the diastereotopic and ortho hydrogens. The diastereotopic hydrogens associated with the benzylmethylphenylsulfonium are shifted to distinct locations; 25.5-26.7 ppm and 35.5-37.5 ppm, as shown in Figure 9. The R and S enantiomers of the diastereotopics are separated by 1.2 ppm and 2.0 ppm. Even though there is such resolution, the absolute

assignment of R and S has not been made for this system yet. The ortho hydrogens of the benzyl and phenyl were also resolved into R and S enantiomers at 14.5 ppm and 15.5 ppm, respectively. The other aromatic hydrogens on the benzyl and phenyl are not resolved into enantiomers. The methyl group that was associated with the sulfur was also resolved into enantiomers at about 29 ppm.

The benzylmethyl-*p*-tolylsulfonium ion was also ion-paired with $Eu(tfc)_4^-$ and exhibited similar resolution. The diastereotopic hydrogens of this system are resolved at 27-28 ppm and 36.5- 38.5 ppm. The distance between the base line resolved enantiomers was 1 ppm and 2 ppm. Along with this resolution, the ortho hydrogens of the benzyl were resolved into R and S at 16 ppm. The ortho and meta hydrogens of the phenyl group and the methyl hydrogens were not resolved into enantiomers. The para position for the *p*-tolyl was missing because of the methyl group at that position.

II. Analysis of R-Enriched Enantiomer.

A. (R)-ethylmethyl-p-tolylsulfonium Tetrafluoroborate.

The R-enriched enantiomer of ethylmethyl-*p*-tolylsulfonium tetrafluoroborate was analyzed so the absolute assignment of R and S could be made. The sulfonium was first analyzed with the chiral shift reagent, $Eu(tfc)_3fod^-$, shown in Figure 10. This chiral shift reagent resolved the diastereotopic hydrogens like it did with ethylmethylphenylsulfonium ion. The farthest shifted peak for the diastereotopic hydrogens corresponded to the R enantiomer because this enantiomer was in slight excess. The signal is observed at 16.5 ppm and 18 ppm. The ortho hydrogens were not resolved so the chiral shift reagent, $Eu(tfc)_4^-$, was used.

After adding the $Eu(tfc)_4^-$ to the sulfonium, the ortho hydrogens were resolved, as shown

in Figure 11, and the enantiomeric excess was analyzed. The integration values of the methyl hydrogens of the ethyl group showed that there was approximately 61% R and 39% S as shown in Figure 12. The percentages were determined by curve fitting using the ACORN Nuts NMR processing software. A similar analysis of the ortho hydrogens yielded the same percentages. The R enantiomer was not shifted as far as the S enantiomer. Other than the enantiomeric excess, the spectrum of this mixture was similar to that of the racemic mixture of ethylmethylphenylsulfonium ion.

The next step was to try and approximate the rate of pyramidal inversion using the NMR technique.

III. Observation of Pyramidal Inversion of (R)-ethylmethyl-*p*-tolylsulfonium Ion.

The best temperature for observing the rate of pyramidal inversion is 60°C. At this temperature, the rate of pyramidal was observable over a 2 hour time frame. This observation can be seen in Figure 13, which shows the spectra of the ortho hydrogens of the R enantiomer at 0.025 M as a function of time at 60°C. The area of the S peak is observed to increase with time, demonstrating that racemization by pyramidal inversion is taking place. After two hours, the peaks areas are nearly equal.

CONCLUSION

The conclusions that can be drawn from this research are as follows:

1. A variety of sulfonium ions has been studied by NMR and the best resolution for the R and S enantiomers has been observed with the ortho hydrogens. The absolute assignment of the R and S enantiomers for the ortho and diastereotopic hydrogens of the ethylmethyl-*p*-tolylsulfonium ion have been made.

2. The ortho and diastereotopic hydrogens of benzylmethylphenylsulfonium ion were resolved into the R and S enantiomers, and the diastereotopic hydrogens are baseline resolved with 1 and 2 ppm separation.

3. For first time, pyramidal inversion has been observed by using the NMR spectroscopy. The ethylmethyl-*p*-tolylsulfonium ion was the sulfonium used for this study.

REFERENCES

1. Wade, L.G. Jr. *Organic Chemistry*. 3rd ed., Prentice Hall, Englewood Cliffs, NJ, **1995**, pp 174-224.

2. Eliel, E.L.; Wilen, S.H. *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp 49-71.

3. Parker, P. *Chemical Reviews*. **1991**, 91, 1441-1457.

4. Perozzi, E.F.; Paul, I.C. *The Chemisrty of Sulphonium Group*. Ed. C.J.M. Sterling and S. Patai., Wiley, New York, **1981**, pp 16-76.

5. Markham, G.D.; Bock C.W. *J. Phys. Chem.* **1993**, 97, 5562-5569.

6. a. Darwish, D.; Scott.C. *Can. J. Chem.* **1973**, 51, 3647-3648.
   b. Darwish, D.; Hui, S.H.; Tomilson, R. *J. Am. Chem. Soc.* **1968**, 90, 5631.

7. Carey, F.A. *Organic Chemistry*, 3rd ed., McGraw Hill, New York, **1996**, p 669.

8. Lewin, B. *Genes V*, 5th ed., **1994**, pp 605-628

9. Trost, B. *Sulfur Ylides: Emerging Synthetic Intermediates*, Academic Press, New York, **1975**.

10. Kikkawa, A.; Toshikazu, T.; Endo, T. *Makromol.Chem.* **1991**,192,655-662.

11. Hamazu, F.; Akashi, S.; Koizumi, T.; Takata, T.; Endo, T. *Journal of Polymer Science: Part A: Polymer Chemistry*. **1991**, 29, 1845-1851.

12. Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. *J. Org. Chem.* **1989**, 54,10, 2374-2383.

13. Acheson, R.M.; Harrison, D. R. *J. Chem. Soc.* **1970**, 1764-1776.

14. Acheson, R.M.; Stubbs, J. K. *J. Chem. Soc.* **1971**, 899-903.

15. Anderson, K. K; Caret, R. L.; Ladd, D. L. *J. Org. Chem.* **1976**, 41, 3096-3100.

16. Krause, E. *Ber.* **1917**, 50, 1813-1822.

17. Wenzel, T. J.; Zaia, J. *Anal. Chem.* **1987**, 59, 562-567.

List of Figures

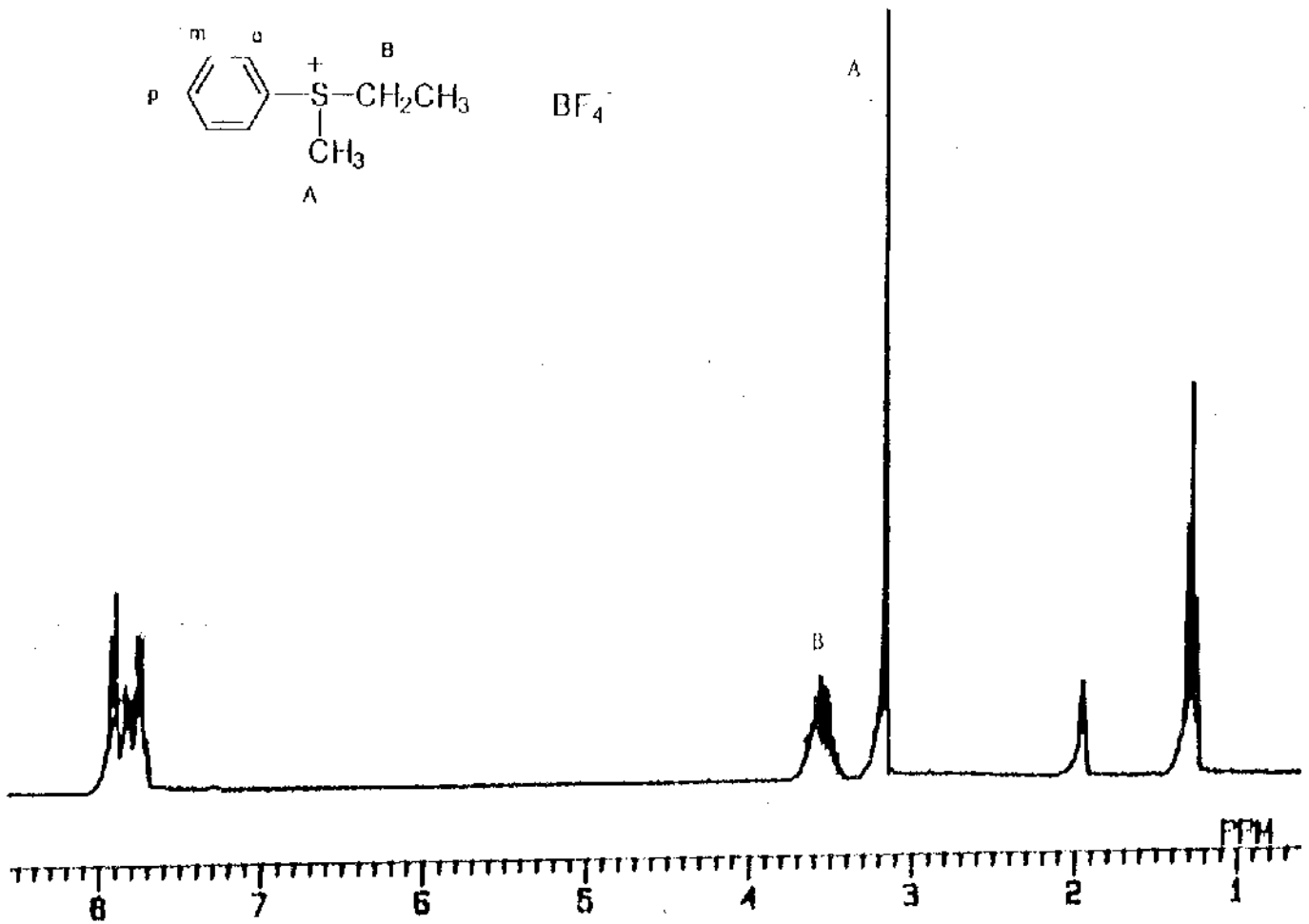


Figure 2. Unshifted ^1H NMR Spectrum of Ethylmethylphenylsulfonium Tetrafluoroborate in d_6-acetone.

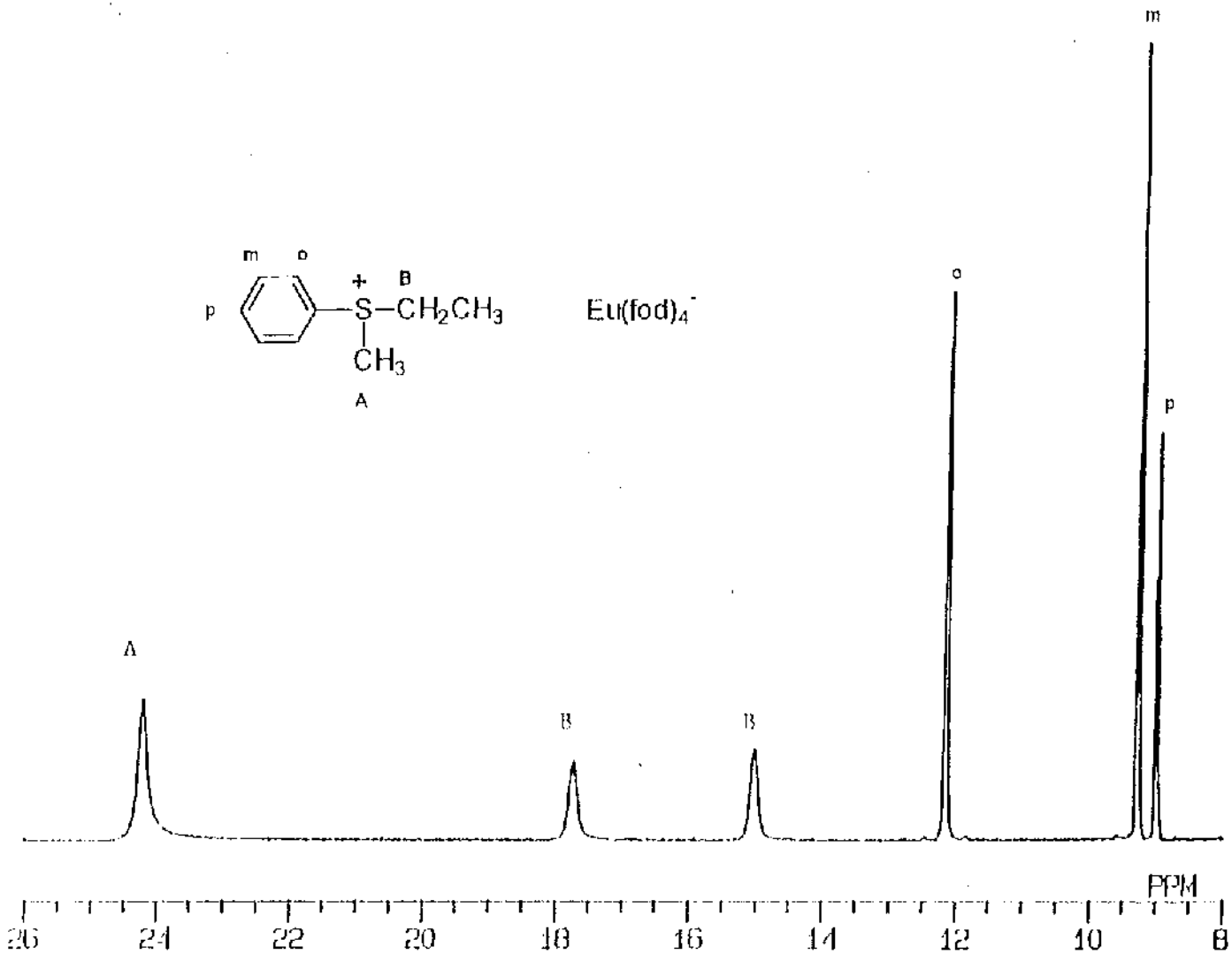


Figure 3. ^{1}H NMR Spectrum of Ethylmethylphenylsulfonium Cation with $Eu(fod)_4^-$ Anion in *d*-chloroform at 0.10 M.

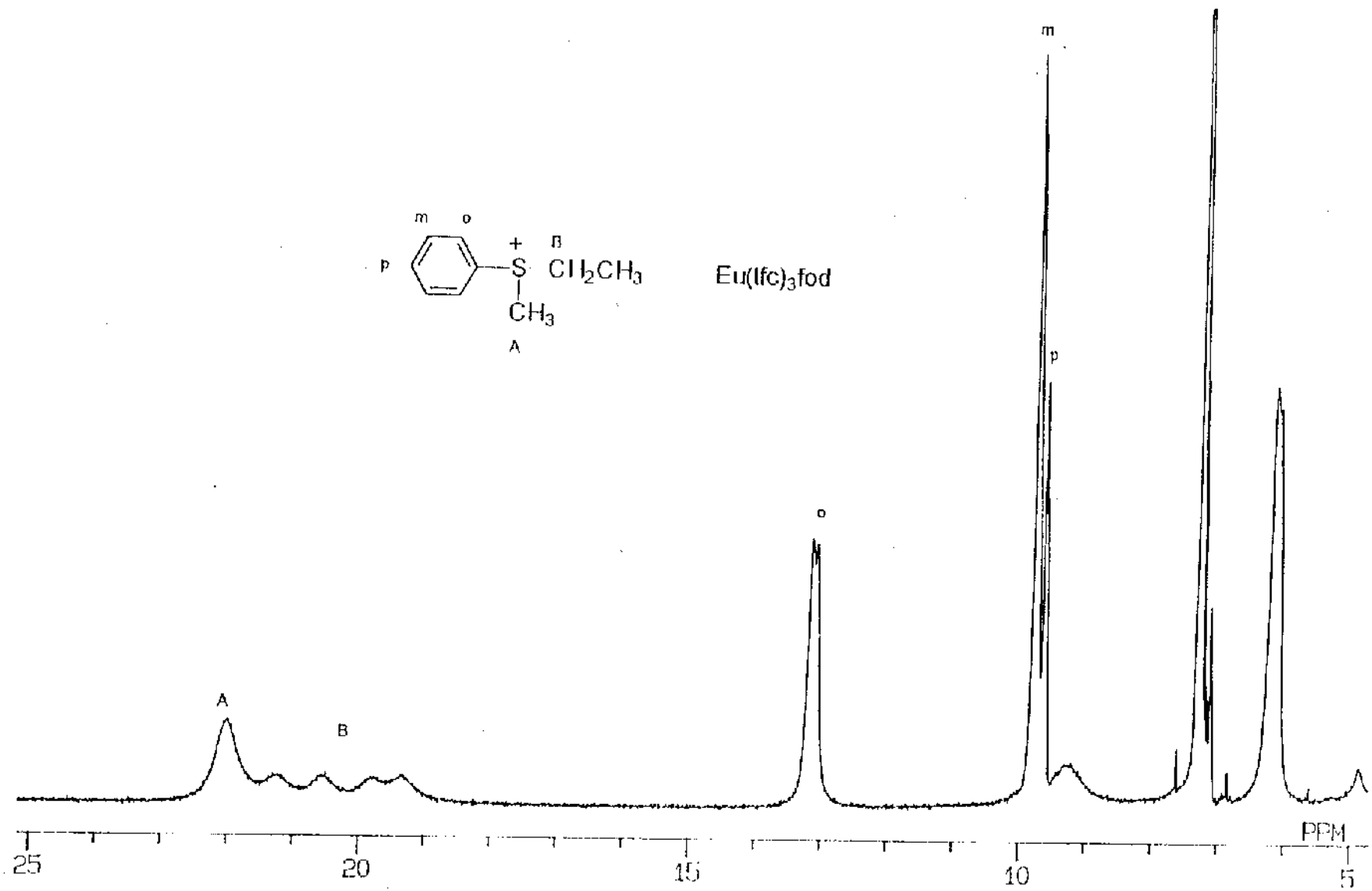


Figure 4. ^{1}H NMR Spectrum of Ethylmethylphenylsulfonium Cation with $Eu(tfc)_3fod^-$ Anion in *d*-chloroform at 0.10 M.

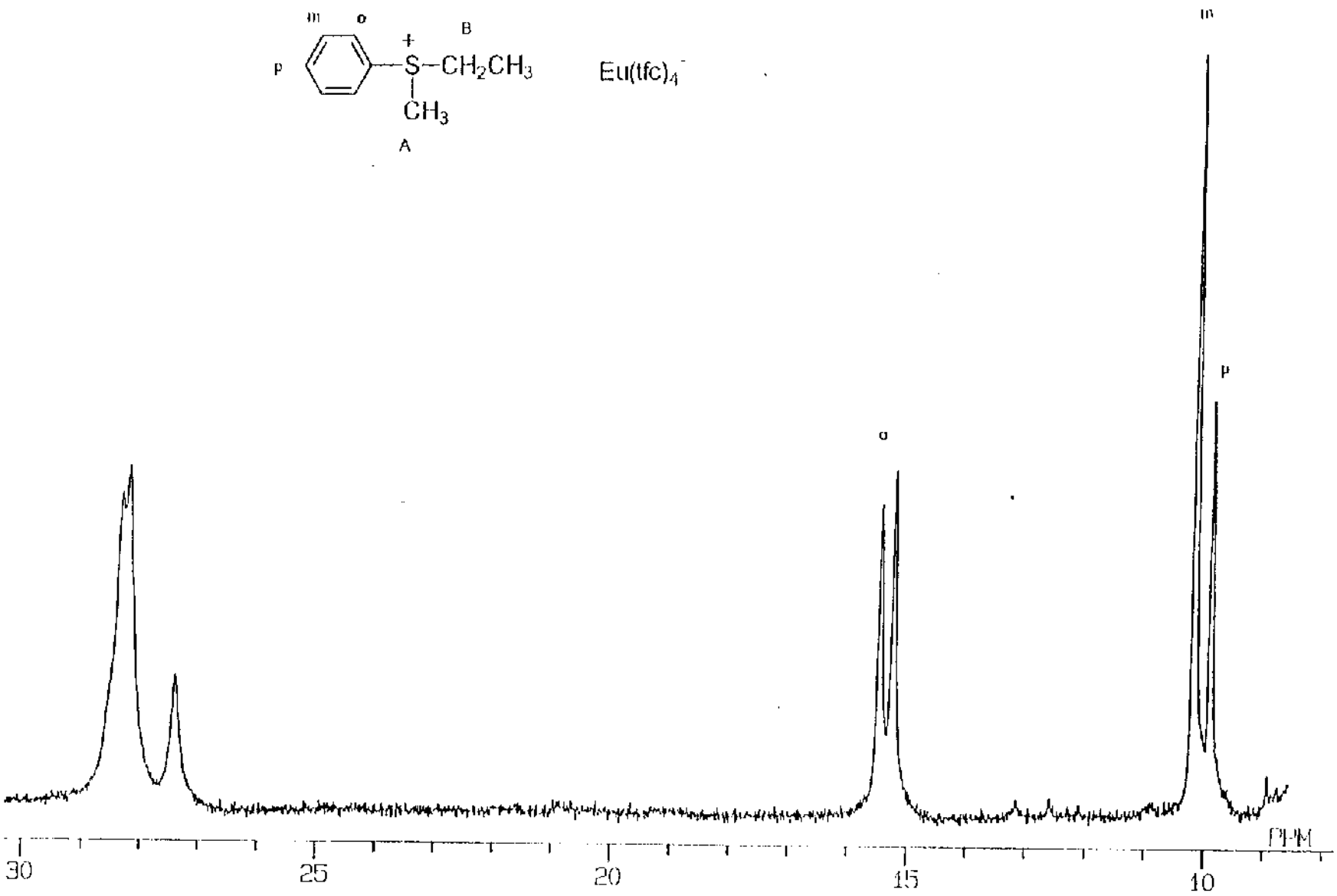


Figure 5. ^{1}H NMR Spectrum of Ethylmethylphenylsulfonium Cation with $Eu(tfc)_4^-$ Anion in *d*-chloroform at 0.10 M.

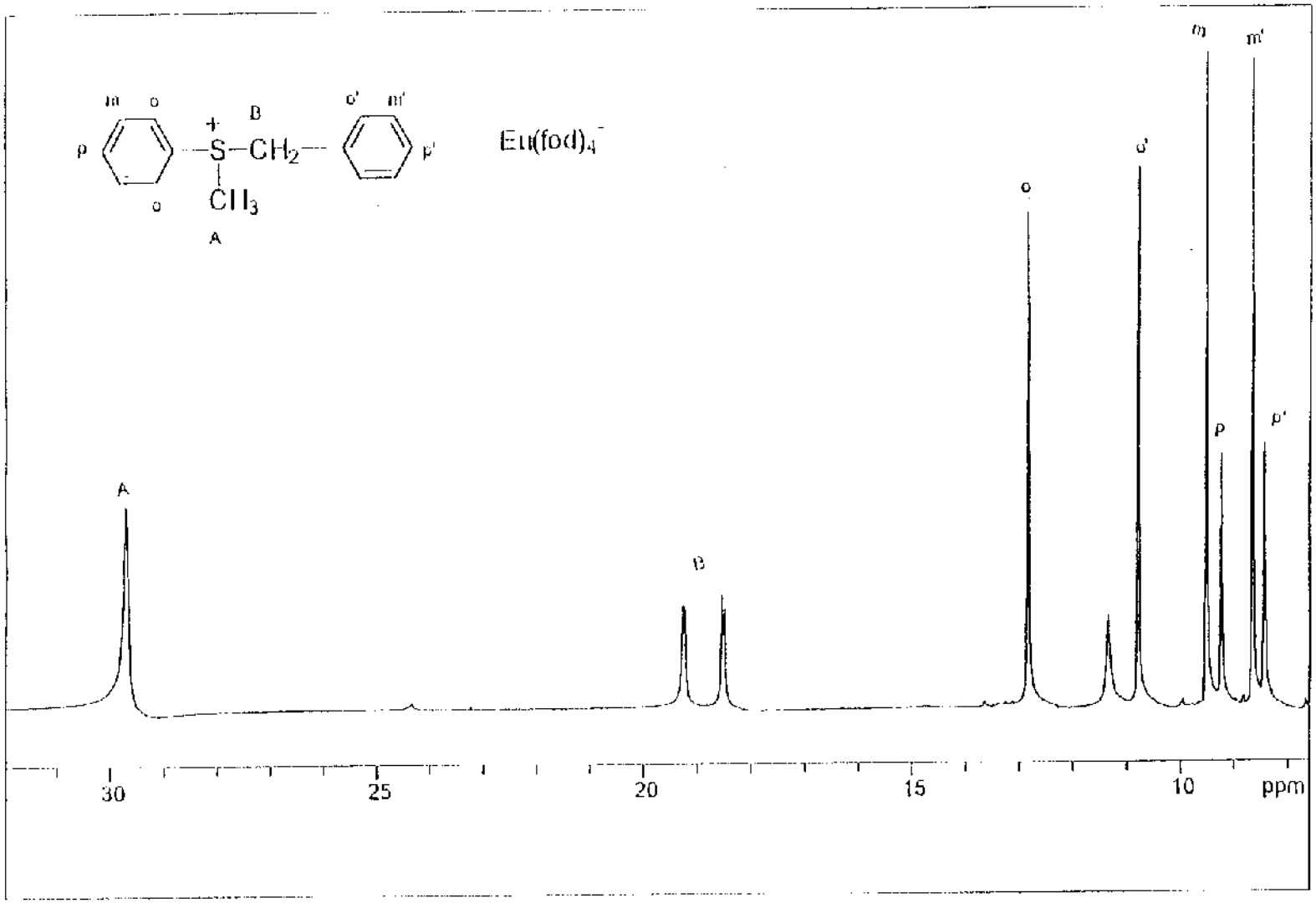


Figure 6. ^{1}H NMR Spectrum of Benzylmethylphenylsulfonium Cation with $Eu(fod)_4^-$ Anion in *d*-chloroform at 0.10 M.

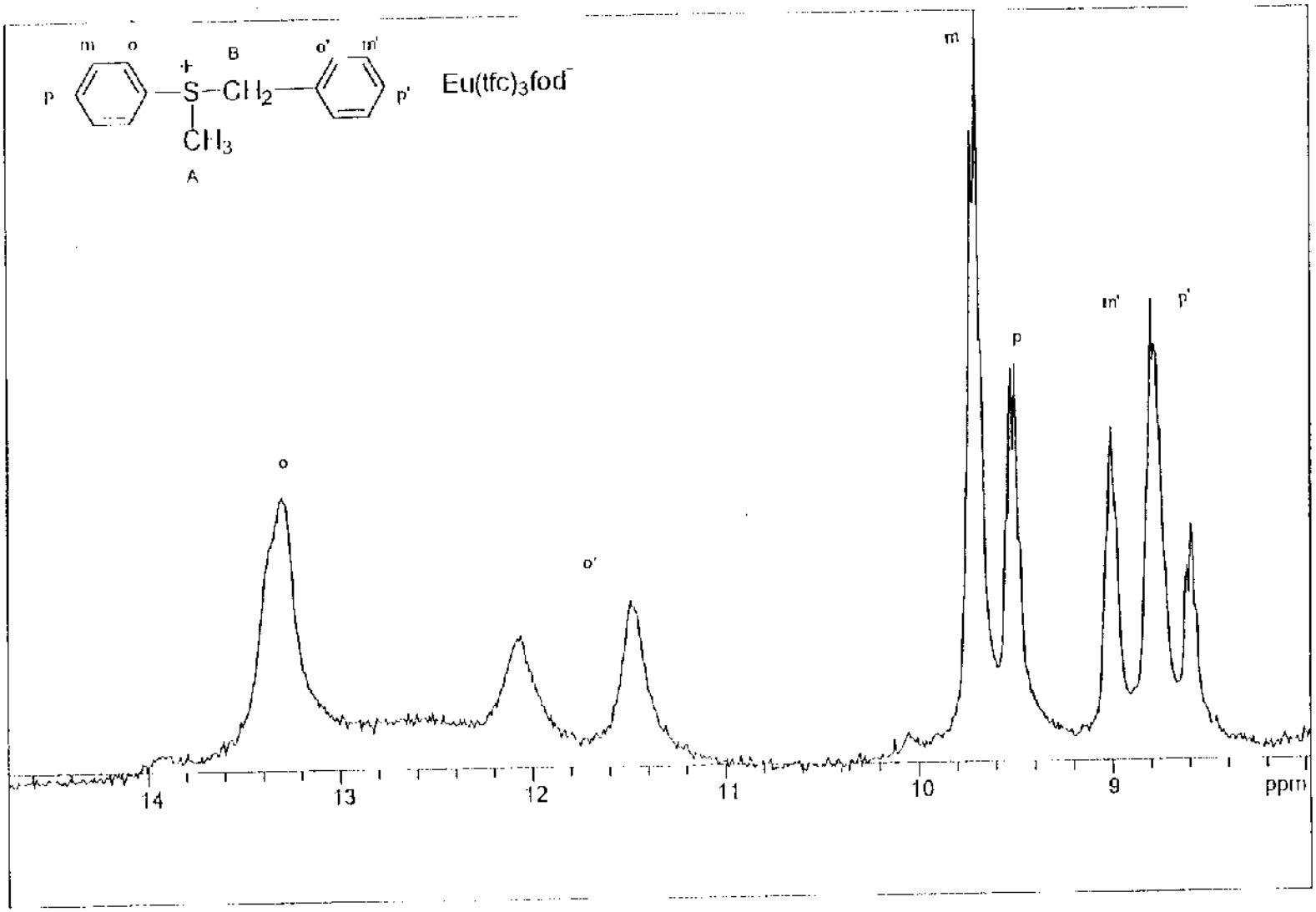


Figure 7. ^{1}H NMR Spectrum of Benzylmethylphenylsulfonium Cation with $Eu(tfc)_3fod^-$ Anion in *d*-chloroform at 0.05 M.

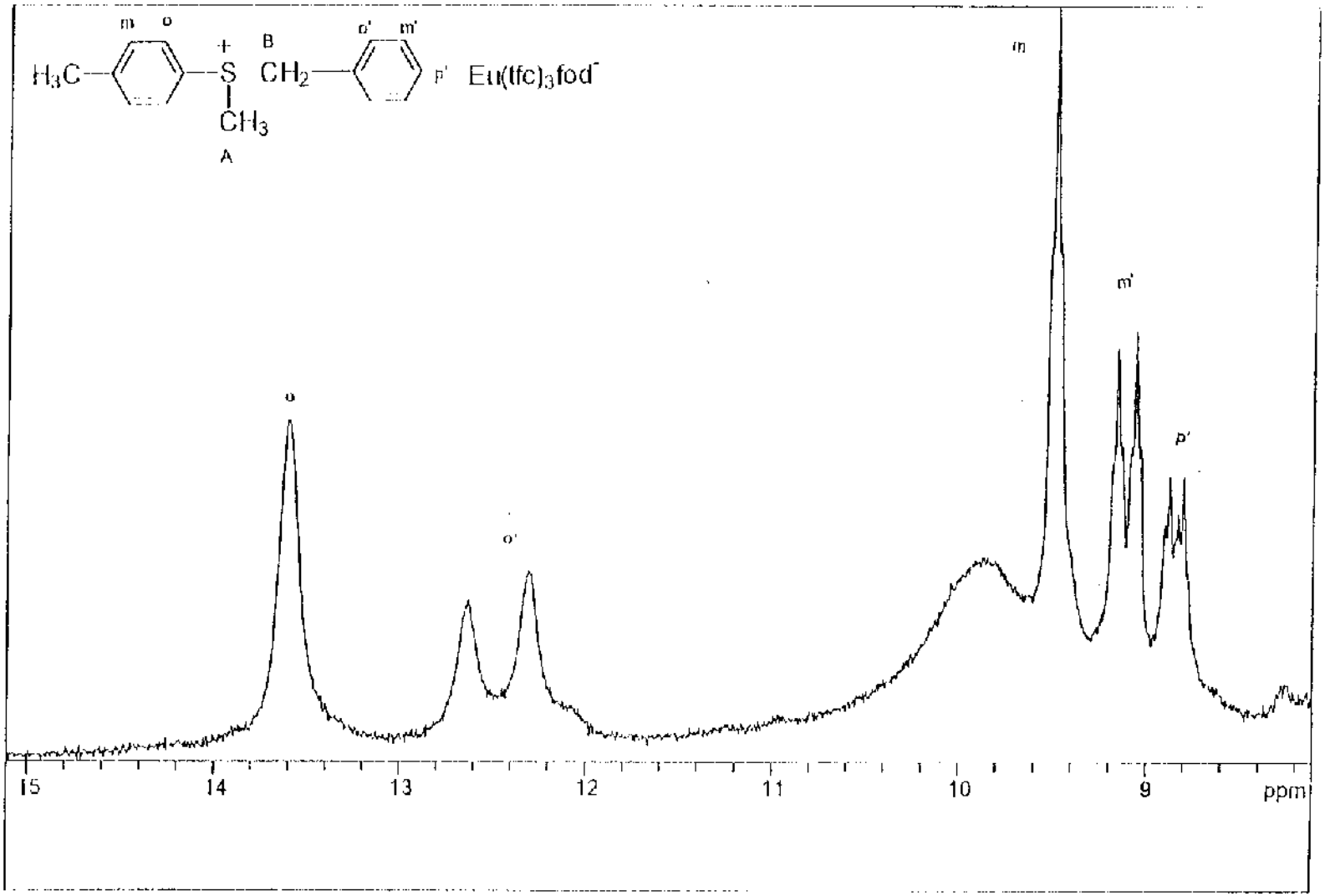


Figure 8 ^{1}H NMR Spectrum of Benzylmethyl- *p*-tolylsulfonium Cation with $Eu(tfc)_3fod^-$ Anion in *d*-chloroform at 0.10 M.

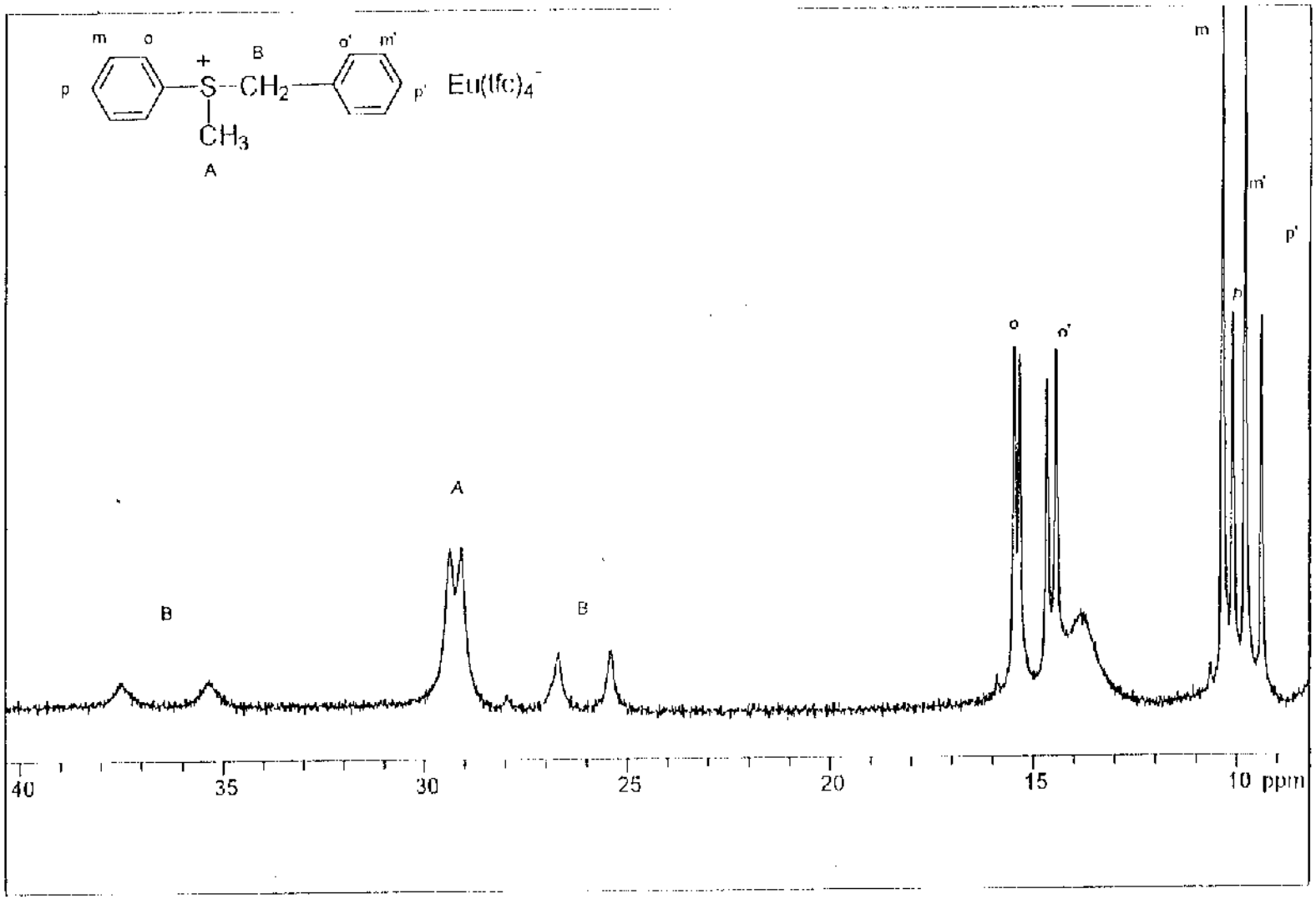


Figure 9. ^{1}H NMR Spectrum of Benzylmethylphenylsulfonium Cation with $Eu(tfc)_4^-$ Anion in *d*-chloroform at 0.10 M

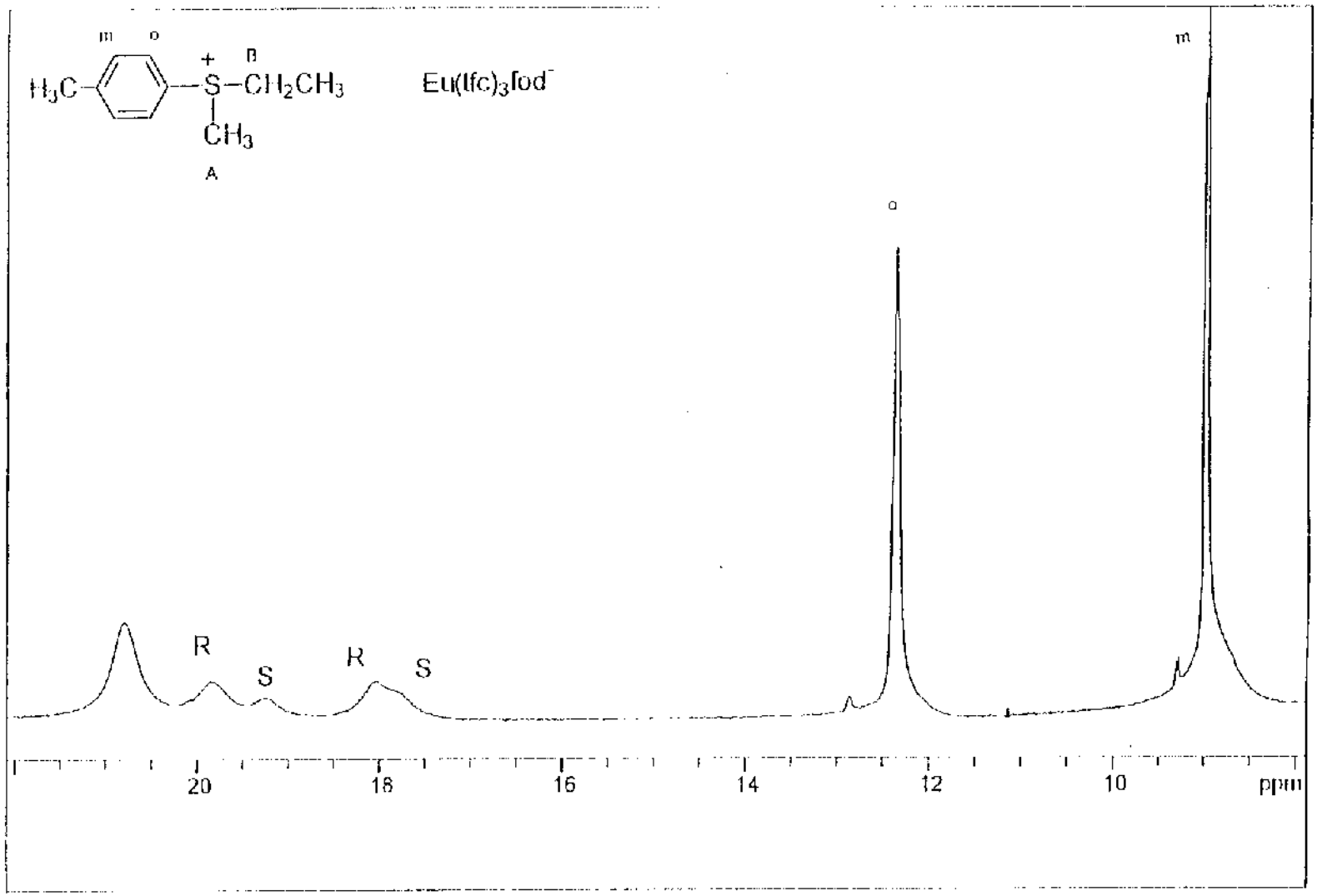


Figure 10. ^1H NMR Spectrum of (R)-enriched Ethylmethyl-*p*-tolylsulfonium Cation with $Eu(tfc)_3fod^-$ Anion in *d*-chloroform at 0.10 M.

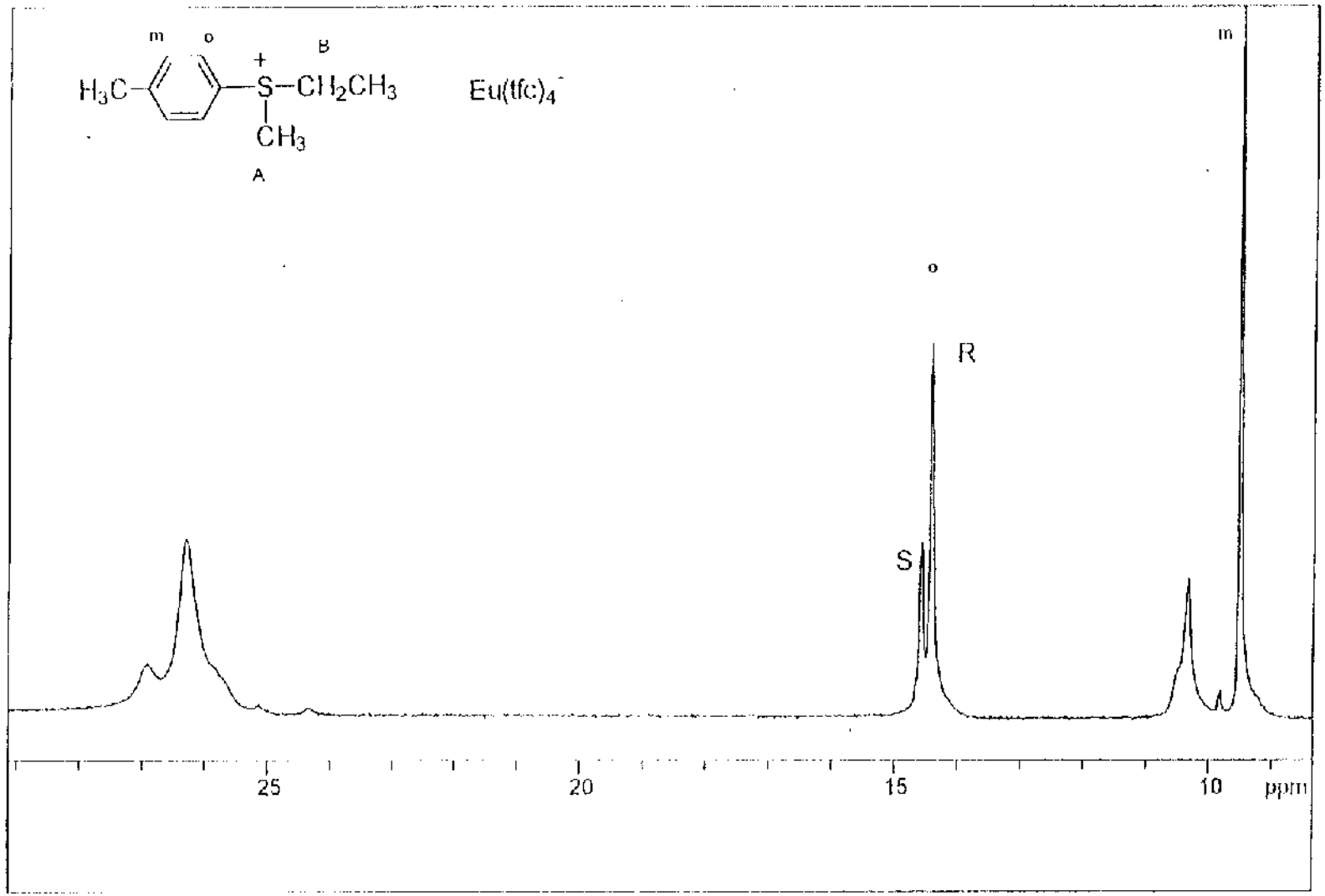


Figure 11. ^{1}H NMR Spectrum of (R)-enriched Ethylmethyl-*p*-tolylsulfonium Cation with $Eu(tfc)_4^-$ Anion in *d*-chloroform at 0.10 M.

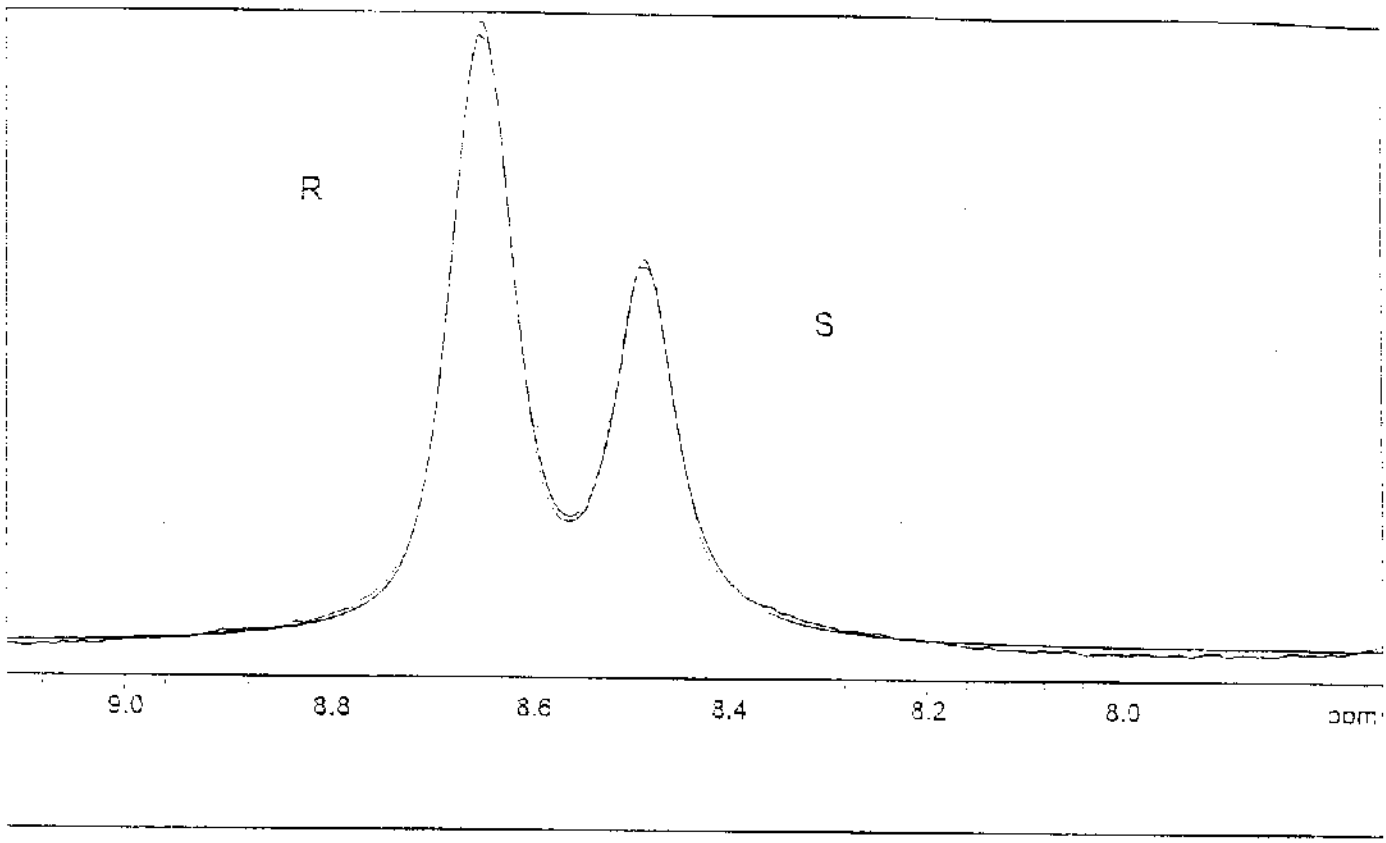


Figure 12. ^{1}H NMR Methyl Signal of CH_3CH_2 Group of (R)-enriched Ethylmethyl-*p*-tolylsulfonium Cation with $Eu(tfc)_4^-$ Anion in *d*-chloroform at 0.10 M. Curve fitting was performed by ACORN Nuts NMR Processing Software; 61% R, 39% S.

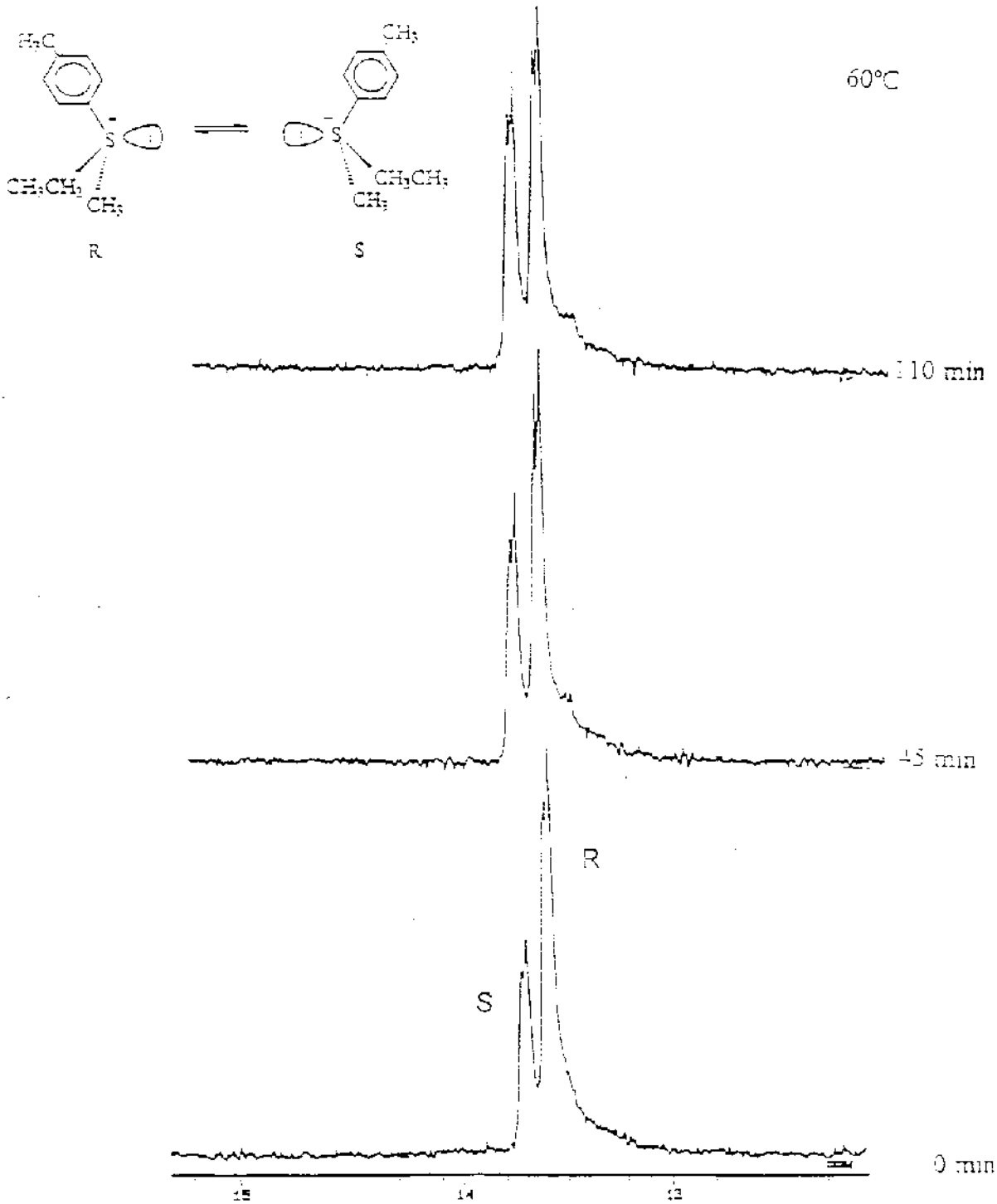


Figure 13. ^{1}H NMR Spectrum of (R)-enriched Ethylmethyl-*p*-tolylsulfonium Cation with Eu(tfc)$_3^-$ Anion in *d*-chloroform at 0.025 M as Function of Time at 60.0 °C.

APPENDIX I

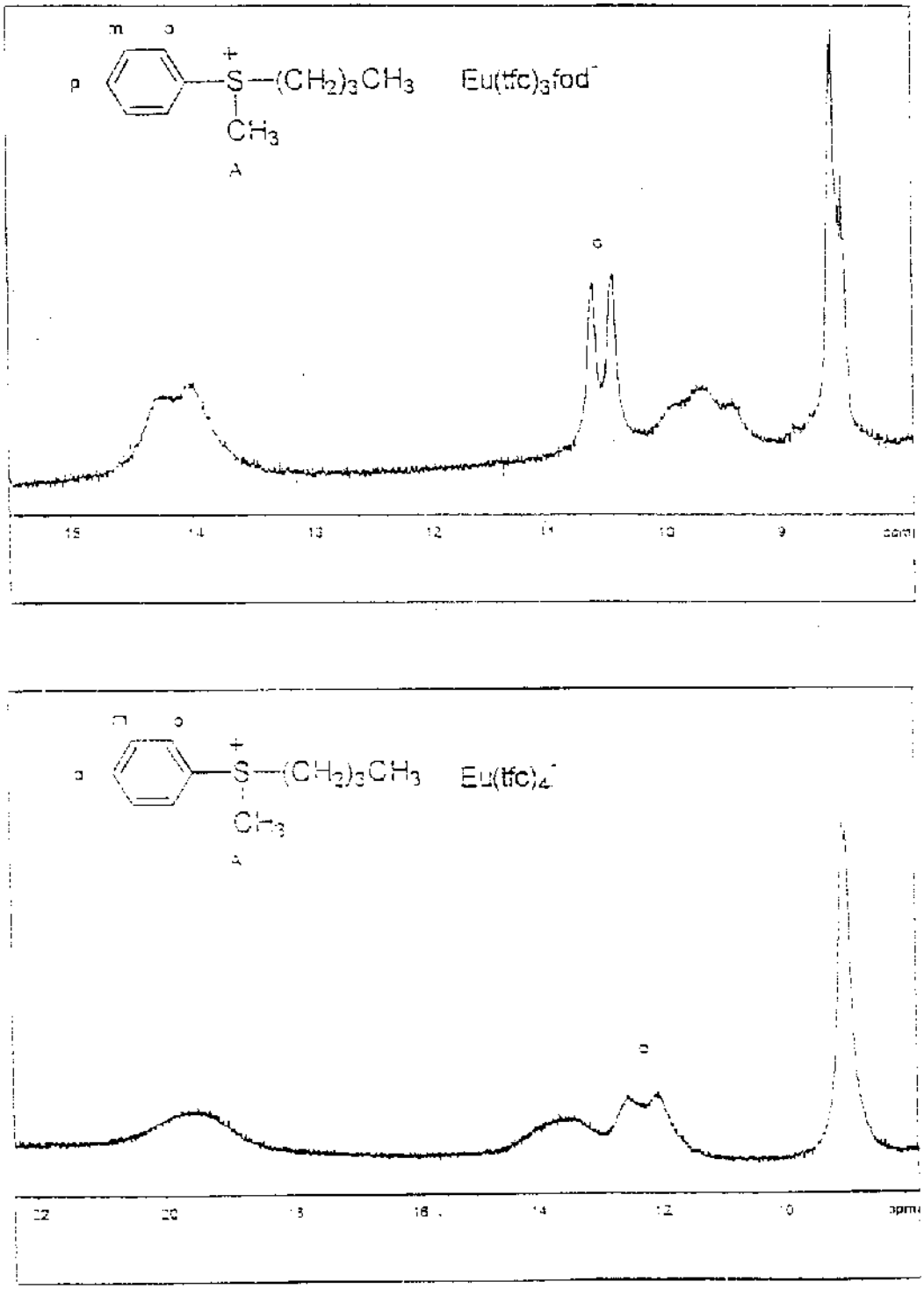


Figure A and B. Comparison of Butylmethylphenylsulfonium Ion with $Eu(tfc)_3fod^-$ and $Eu(tfc)_4^-$ in *d*-chloroform at 0.10 M.