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A Stereochemical Study of Some 2,2'-Bridged Biphenyls

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A STEREOCHEMICAL STUDY OF SOME 2,2'-BRIDGED BIPHENYLS

by

Alan J. Quarfoot

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Doctor of Philosophy

Western Michigan University
Kalamazoo, Michigan
August 1975

Sade: For you just as for me
only the most extreme actions matter
Marat: If I am extreme I am not extreme in the same
way as you
Against Nature's silence I use action
In the vast indifference I invent a meaning
I don't watch unmoved I intervene
and say that this and this are wrong
and I work to alter them and improve them
The important thing
is to pull yourself up by your own hair
to turn yourself inside out
and see the whole world with fresh eyes

--Marat/Sade

ACKNOWLEDGEMENTS

An academic faculty which only disseminates knowledge is little more than an animated textbook. It is therefore with sincere gratitude that I wish to acknowledge the efforts of the many members of the Department of Chemistry who not only shared their knowledge with me, but also their sense of scholarship and intellectual curiosity. Additionally I wish to thank the members of my committee for their guidance and aid in this endeavor. I gratefully acknowledge the aid of Dr. George Slomp of the Upjohn Company in obtaining and interpreting some of the spectral data. After numerous years of association with my advisor, Dr. Don C. Iffland, it is both ludicrous and impossible to attempt to acknowledge fully all that I have gained from him over these past years. Therefore, I can now only render token thanks for the benefits of this association.

Alan Quarfoot

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DISCUSSION

INTRODUCTION

In 1922 George Christie and James Kenner published a rather unassuming paper in the Journal of the Chemical Society of London which was to open a vast new area of scientific endeavor.[1] In that paper they described the successful resolution of 6,6'-dinitro-2,2'-diphenic acid. This marked the first time that the separation of stereoisomers, which owed their activity solely to restricted rotation about single bonds, had been achieved. With this work the concept of atropisomerism, and more specifically so-called biphenyl isomerism, was shown to be more than mere speculation. This discovery which was not trivial, was hindered by poor and/or conflicting data from many sources. This can best be appreciated by examining their work in the proper historical perspective.

The first resolution of a compound into its optical isomers occurred in 1848 when Pasteur manually separated the enantiomers of racemic sodium ammonium tartrate. This separation was based on the dissymmetric facets of the enantiomers in the crystalline state. With the recognition by Kekule in 1858 of the quadrivalency of carbon and the postulation of the tetrahedral carbon concept by Le Bel and van't Hoff in 1874, modern structural organic chemistry was born. Armed with a better understanding of molecular architecture, many individuals spent the years preceding the paper of Christie and Kenner working and speculating on the substitution patterns and corresponding properties of various biphenyls.[2,3,4] However, this contribution by Christie and Kenner was not immediately or completely accepted; or completely understood. This was at least in part due to some poor and conflicting data in the literature, but during the five years after publication it was finally accepted that a new and hitherto unknown form of optical activity existed. This acceptance followed a better understanding of the biphenyl system when almost simultaneously Turner and Le Fevre,[5] Bell and Kenyon,[6] and Mills[7] proposed the concept of hindered rotation about single bonds.

Historically, the work of Adams[8] and his students finally and firmly placed biphenyl isomerism within the confines of modern organic chemistry. They prepared numerous biphenyl derivatives where all ortho positions, that is 2,2', 6 and 6', were substituted with groups and/or atoms larger than hydrogen, which were resolvable into optical antipodes.

Subsequent work by numerous workers[9] produced biphenyl derivatives in which only three of the four ortho positions were substituted and yet were still isolable in an optically active state. Typically these trisubstituted biphenyls showed a greater optical lability than similar tetrasubstituted derivatives, but none the less were sufficiently stable to definitively show the presence of optical activity. In extending this work it was even shown that when sufficiently large substituents were used only in the 2 and 2' positions that resolution into enantiomers could be achieved.[9] The effect of substitution in other positions of the biphenyl ring system led to further observations concerning biphenyl isomers. It was shown that 5,5'-octamethylene-2,2'-diphenic acid was resolvable while the decamethylene analog was not under the same conditions.[10] Presumably this was because the hydrocarbon bridge constrains the rings in such a manner that one carboxyl group must pass the other for racemization to occur and the octamethylene chain is too short to allow sufficient bond bending and/or stretching. Finally, it was demonstrated that substituents in the 5 and 5' positions of a 2,2',6'-trisubstituted biphenyl could enhance the optical stability of the molecule relative to the corresponding biphenyl which only had hydrogen atoms in the 5 and 5' positions. This observation, termed the ''buttressing effect'' is thought to result from crowding of the ortho by the adjacent meta substituents during racemization. This crowding occurs because the interfering ortho groups move away from each other as the benzene rings approach a coplanar conformation. However, the presence of the meta substituents limit the extent to which these bond deformations can occur before equally unfavorable crowding occurs between the ortho and meta groups. The more this deformation is restrained the greater will be the interaction of the two ortho groups during racemization and hence an increased optical stability will be observed.

Concomitant with these substitution studied, there was considerable interest in the nature and variation of the ultraviolet spectra of a large number of biphenyls. This was studied in an attempt to correlate changes in the UV spectrum with changes in the biphenyl dihedral angle and thus, obtain an independent measure of optical stability.[11] Unfortunately this proved to be an insufficiently sensitive method to distinguish minor variations in twist angle and when gross changes did occur they were not always readily interpretable.

During this period, work designed to further extend and study the effect of various substitution patterns was continuing. In 1956, Iffland and Siegel[12] prepared the first optically active biphenyl which possessed a 2,2'-three atom bridge, but which was devoid of other ring substituents. This molecule, 6,6-dicarbethoxydibenzo-[a,c] [1,3] -cycloheptatriene, was active due to the constraining effect of the three atom bridge alone, as opposed to the added stability which would be gained by the presence of large substituents in the 1 and 11 positions of the ring system. These workers reported[13] polarimetric data which indicated a half-time for racemization of approximately 80 minutes at 32.5°. This value would correspond to a free energy of activation for the racemization process of approximately 23 kcal/mol. Subsequently, the nuclear magnetic resonance (NMR) spectrum of this compound was examined by Sutherland and Ramsey[14] and their analysis of the data indicated a free energy for conformational inversion of approximately 14 kcal/mol (14.0 in pyridine and 14.5 in pentachloroethane). In addition to the alarmingly large difference in the data from these two groups of workers (even though one is racemization while the other is inversion data), there is the fact that a compound with only a 14 kcal/mol activation energy for inversion, would <u>not</u> be expected to have sufficient optical stability to be isolable in an active state in the context of ''normal'' experimental conditions such as time of handling and ambient temperature.

In an attempt to shed some light on this discrepancy it was decided to examine the temperature dependent NMR spectrum of this compound and to study the kinetics of racemization of the optically active material polarimetrically. As a companion study, it was proposed that the NMR spectra of some 4,8-dihalo analogs also be examined to determine the significance of any buttressing effect which might be present in these compounds.

EXPERIMENTAL

All melting points are corrected and boiling points uncorrected with all temperatures given in degrees Celsius. Melting points were determined by the capillary method.

The infrared spectra were recorded on either a Perkin Elmer Model 21 or a Beckman IR-8 spectrophotometer and the assignment of bands made according to Bellamy.[15]

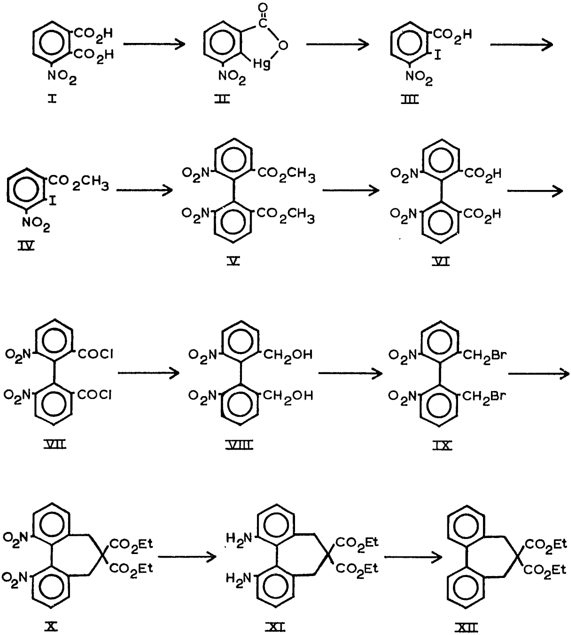
The ultraviolet spectra were obtained with a Cary 14 spectrophotometer in the indicated solvent.

The nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer as approximately 10% solutions in chloroform-d or cyclohexane-d_{12}. Chemical shifts are, in all cases, reported relative to tetramethylsilane as an internal standard, and a Varian Model V-6040 temperature controller was used for the variable temperature work. The probe temperature was measured directly using a Chromel-Constantan thermocouple immersed in methanol or ethylene glycol and a Honeywell Portable Precision Potentiometer Model 2745. The 100 MHz spectra were generously provided by Dr. George Slomp of The Upjohn Company.

Measurements of optical activity were obtained with a Rudolph Model 62 polarimeter. The angle of rotation being measured with a precision of ±0.02° and the average of five readings was used to calculate the specific rotation. All kinetic measurements were made in a two decimeter tube which was thermostatically controlled at ±0.2°.

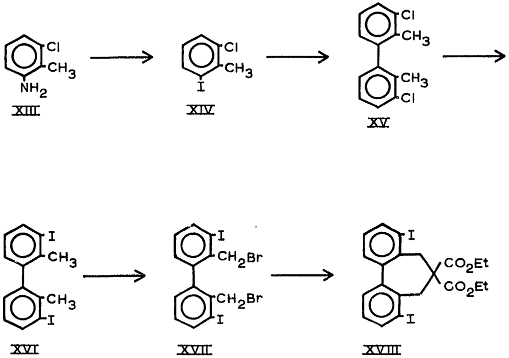
SCHEME I

Synthesis of Active
6,6-dicarbethoxydibenzo-[a,c] [1,3]-cycloheptadiene



SCHEME II

Synthesis of 6,6-dicarbethoxy-4,8-diiodo-dibenzo-[a,c] [1,3]-cycloheptadiene



Synthetic Sequence for Active 6,6-Dicarbethoxydibenzo[a,c][1,3]-cycloheptadiene

Preparation of anhydro-2-hydroxymercuri-3-nitrobenzoic acid(II)[16,17]

To a solution of 120.0 g (3.00 mol) of sodium hydroxide in 1200 ml of water was added 316.7 g (1.50 mol) of 3-nitrophthalic acid(I) with stirring. A solution of mercuric acetate was prepared by dissolving 357.4 g (1.65 mol) of mercuric oxide in 216 ml (3.75 mol) of glacial acetic acid and diluting with 1100 ml of water. The mercuric acetate was added in one portion to the dissolved 3-nitrophthalic acid and the resultant milky white slurry was vigorously stirred while heating to reflux temperature. After approximately 100 hours of refluxing with stirring, the slurry was allowed to cool slightly and filtered. The filter cake was washed twice with hot water and dried to constant weight. Yields typically exceeded 90% and essentially quantitative yields were obtained in some cases. Since the product chars, but does not melt, no suitable criterion of purity could routinely be determined.

Preparation of 2-iodo-3-nitrobenzoic acid(III)[18]

With vigorous stirring, 548.5 g (1.50 mol) of anhydro-2-hydroxymercuri-3-nitrobenzoic acid(III) was dusted into 2000 ml of water containing 63.4 g (1.58 mol) of sodium hydroxide. When the benzoic acid had dissolved completely, a solution of 135 ml (1.57 mol) of concentrated hydrochloric acid and 48 ml (0.84 mol) of glacial acetic acid was added in one portion. A solution of 253.8 g (1.58 mol) of iodine and 166.0 g (1.58 mol) of potassium iodide in 500 ml of water was added with vigorous stirring. The solution was heated to reflux and an additional 68.7 g (1.72 mol) of sodium hydroxide was added. After refluxing for 15 minutes the heating was discontinued, but vigorous stirring was continued for 48 hours. At that time the solution was filtered to remove the mercuric iodide and residual iodine. The filtrate was acidified with 400 ml of concentrated hydrochloric acid and chilled. The flocculent yellow precipitate which formed was filtered and washed three times with 5% aqueous sodium bisulfite and twice with water. The moist cake was crystallized from aqueous ethanol using activated charcoal to clarify the solution. Yields of about 45% were consistently obtained: mp 203-6° [lit.: 204-6°[19] and 210-12°[13]].

Preparation of methyl 2-iodo-3-nitrobenzoate(IV)

After bubbling anhydrous hydrogen chloride into 3500 ml of anhydrous methanol for approximately three hours, 362.9 g (0.75 mol) of 2-iodo-3-nitrobenzoic acid(III) was added. After refluxing for 36 hours the solution was poured, in small portions, into water. The ester was collected by filtration and washed with 5% aqueous sodium bicarbonate until there was no further gassing on bicarbonate addition. The ester was recrystallized from methanol to yield 362.0 g (85%) of the benzoate ester: mp 64-6° [lit.: 64-6°].[13]

Preparation of (±)-dimethyl 6,6'-dinitrodiphenate(V)[20]

A stirred flask containing 362.0 g (1.18 mol) of the benzoate ester(IV) was heated to 170-5° in an oil bath. To the molten ester, 187.3 g (2.95 mol) of copper dust (electrolytic grade) was added in small portions over the course of 90 minutes and stirring and heating was continued for an additional one hour. The reaction mixture was allowed to cool to approximately 100° and poured into 2000 ml of chloroform. The chloroform solution was filtered through Celite and concentrated, by distillation, to approximately 200 ml. On refrigeration an initial crop of the desired biphenyl derivative was obtained. Further concentration and cooling yielded other crops of crystals which were combined with the first crop for a total of 154.7 g (73%): mp 123-6° [lit.: 132-3°].[21]

Preparation of (±)-6,6'-dinitrodiphenic acid (VI)

In spite of published reports[13,20] of base hydrolysis of (±)-dimethyl 6,6'-diphenate, a pilot run using sodium hydroxide led to a dark and heavily contaminated product in poor yield. Therefore, 93.5 g (0.26 mol) of (±)-dimethyl 6,6'-dinitrodiphenate was added to 500 ml of 10% aqueous sulfuric acid and refluxed for 24 hours. Since some solid was still present which was not soluble in base the residual solid material was removed by filtration and added to 200 ml of water containing 22.0 g (0.55 mol) of sodium hydroxide. Ethanol was added (approximately 350 ml) until a homogeneous system was obtained. The ethanolic sodium hydroxide solution was refluxed for 12 hours, at which time 250 ml of solvent was removed by distillation. The remaining solution was acidified with sulfuric acid and cooled to refrigerator temperature. The precipitate which formed was combined with that which formed from cooling the original sulfuric acid solution. On recrystallization of the combined precipitates from an ethanol-water mixture (3:1), 68.8 g (80%) of the desired acid was obtained: mp 258-63° [lit.: 258-61°[13] and 263°[1]].

Resolution of (±) 6,6'-dinitrodiphenic acid(VI)[20]

A solution was prepared by dissolving 60.7 g (0.18 mol) of (±)-6,6'-dinitrodiphenic acid in 400 ml of acetone and heated to approximately 50°. To the racemic diacid, a solution of 22.1 g (0.18 mol) of (-)-α-phenethylamine ($[\alpha]_D^{20}$ -39°, neat, 97% optical purity)[22] in acetone (85 ml) was added, and the solution immediately placed in a one gallon water bath at 50°. The water bath and solution were allowed to cool simultaneously to room temperature. The crystals which formed on cooling were filtered, washed with boiling acetone and dried for two hours at 90° to remove acetone of recrystallization.[20] The resolution yielded 38.2 g (46%) of the 1A1B diastereomer. The salt softened at 208°, melted at 215° and decomposed with bubbling at 220° [lit.: 217-9°].[20] $[\alpha]_D^{26}$ -143.6° (c = 9.5 mg/ml, 1 = 1, methanol) [lit.: $[\alpha]_D^{28}$ -157.1° (c = 30.4 mg/ml, 1 = 2, methanol)].[20]

The free acid was obtained by dissolving 38.2 g of the 1-α-phenethylammonium-1-6,6'-dinitrodiphenate in 500 ml of water with the aid of heat and acidifying the solution with concentrated hydrochloric acid. After cooling to room temperature, the acidified solution was refrigerated for 48 hours. The crystalline acid was filtered, washed with cold water, air dried and finally dried for two hours at 95°. In this manner 25.3 g (90%) of S-(-)-6,6-dinitrodiphenic acid[23] was obtained from the diastereomeric salt or a 41% yield based on the initial racemic acid: mp 224-7° [lit.: 230-1°][1], $[\alpha]_D^{24}$ -126.5° (c = 4.9 mg/ml, 1 = 1, methanol) [lit.: $[\alpha]_D^{27}$ -126.0° (c = 20.4 mg/ml, 1 = 2, methanol)].[20] Since both enantiomeric amines were available in a high degree of optical purity, both enantiomeric acids could also be obtained in a high degree of optical purity.

Preparation of R-(+)-6,6'-dinitrodiphenic diacid chloride(VII)

Following a published procedure[13] 16.6 g (0.05 mol) of R-(+)-6,6'-dinitrodiphenic acid ($[\alpha]_D^{24}$ +124.9°, methanol) was added to 59.5 g (0.50 mol) of thionyl chloride and the solution was allowed to reflux for 30 hours (Siegel: 24 hours[29]). The reaction mixture was evaporated under reduced pressure and the residue dissolved in a minimum volume of hot chloroform, clarified with charcoal and allowed to crystallize. After drying under vacuum 17.2 g (93%) of the desired diacid chloride was obtained: mp 155° [lit. 155-7°].[13,24] The material was stored in a brown bottle at room temperature prior to determining its optical purity.

When the preparation of a second batch of the diacid chloride was attempted as above, except that the thionyl chloride solution was refluxed for 25 hours, the product was found to be only poorly optically active. Examination of the previously prepared material showed that within 72 hours in the crystalline state it too was racemic.

The racemization in solution has analogies and explanations in the literature,[25,26,27] but the solid state racemization was not expected.

The racemic batches were pooled, hydrolyzed in 10% aqueous hydrochloric acid and purified by recrystallization from aqueous ethanol.

Examination of the rate of acid chloride formation was carried out by spotting small aliquots from a small exploratory run on silica gel TLC plates at various time intervals and developing them in chloroform. Under these conditions only two spots could be seen, that of the unreacted diacid (R_f approximately 0) and that of the diacid chloride (R_f approaching unity). At no time was a third spot corresponding to the half acid chloride seen, but possibly this overlapped with that of the diacid or diacid chloride. In the presence of refluxing thionyl chloride the reaction was judged to be complete in 2-3 hours as indicated by the absence of a diacid spot on the TLC plate. All subsequent diacid chloride preparations therefore employed a three hour reflux time.

Racemization of partially resolved 6,6'-dinitrodiphenic acid

To minimize losses and effort in subsequent reactions, it was decided to racemize the acid of lowest optical purity obtained from the resolution and then resolve that material. In this manner, at least in principle, all of the acid could ultimately be converted to a single configuration. The partially resolved 6,6'-dinitrodiphenic acid was routinely mixed with 10 molar equivalents of thionyl chloride and refluxed for 30 to 36 hours. At that time the residual thionyl chloride was removed under reduced pressure and a convenient volume of 10% hydrochloric acid added. Hydrolysis was achieved by refluxing this solution for approximately 24 hours. On cooling in the refrigerator the diacid would crystallize in sufficiently pure form to be filtered, dried and resolved directly. Yields of racemic acid from partially resolved material were typically of the order of 85%.

Preparation of R-(+)-2,2'-bis(hydroxymethyl)-6,6'-dinitrobiphenyl (VIII)

To circumvent the possible racemization of the acid chloride it was prepared just prior to use and immediately reduced. As above, 22.9 g (0.069 mol) of R-(+)-6,6'-dinitrodiphenic acid was added to 82.1 g (0.69 mol) of thionyl chloride and the solution refluxed for three hours. The solution was evaporated to dryness under reduced pressure and used without further purification. The reduction was carried out using a modification of the procedure of Hall and Poole.[28]

A solution of lithium borohydride in tetrahydrofuran was prepared by slowly adding 15.0 g (0.69 mol) of lithium borohydride to 150 ml of tetrahydrofuran (dried over calcium hydride) with cooling. The solution was stirred and maintained under a dry nitrogen atmosphere. The freshly prepared diacid chloride (theoretically 0.069 mol) was dissolved in 125 ml of dry tetrahydrofuran and added dropwise with stirring to the hydride solution still under nitrogen. Two hours were required to complete the addition such that the reaction temperature could be maintained between 20° and 25°.

When the addition was complete the solution was allowed to stir for one additional hour. At that time the nitrogen atmosphere was removed, the solution was cooled in an ice bath and the reaction mixture quenched by the slow addition of 150 ml of water followed by 10 ml of concentrated hydrochloric acid to dissolve inorganic salts. The reaction mixture, which was homogeneous, was extracted with three 100 ml portions of diethyl ether. The ethyl ether solution was twice washed with 10% aqueous potassium hydroxide to remove acidic impurities and dried over anhydrous sodium sulfate. Evaporation of the ether solution to dryness followed by two recrystallizations from chloroform yielded 11.9 g (56% based on the starting diacid) of the desired dinitrodiol: mp 116-18°, α_D^{24} +58.9° (1 = 1, c = 10.4 mg/ml, methanol) [lit.: mp 120-2°, $[\alpha]_D^{25}$ +55.6° (methanol)].[13]

Preparation of R-(+)-2,2'-bis(bromomethyl)-6,6'-dinitrobiphenyl(IX)[13]

Seven milliliters of concentrated sulfuric acid was slowly added to 88.5 ml (0.78 mol) of concentrated hydrobromic acid and the solution cooled to 3°. To the cold acid mixture was added 11.9 g (0.039 mol) of dinitrodiol(VIII) and the mixture swirled to dissolve the diol. The solution was refluxed for 2.5 hours and after cooling to room temperature poured into 300 ml of water. The precipitate was filtered, washed with water and dissolved in approximately 100 ml of benzene. The benzene solution was clarified with Norite, filtered and dried over anhydrous sodium sulfate. After evaporation of the solution to dryness the resultant solid was recrystallized from benzene. Two crops of crystals were obtained yielding 13.9 g (83%) of the bromomethyl compound: mp 165-8°, $[\alpha]_D^{30}$ +43.6° (1 = 1, c = 15.2 mg/ml, 1,4-dioxane) [lit.: mp 168-70°, $[\alpha]_D^{29}$ +45.3° (1,4-dioxane)].[13]

Preparation of R-(-)-1,11-dinitro-6,6-dicarbethoxydibenzo-[a,c][1,3]-cycloheptadiene(X)[13]

A solution of sodium ethoxide was prepared by slowly adding

2.19 g (0.095 mol) of sodium metal to 150 ml of absolute ethanol. After the sodium had dissolved completely, 7.61 g (0.048 mol) of diethyl malonate was added to the alkoxide solution. The dibromide(IX) was dissolved in 50 ml of dry 1,4-dioxane (over calcium hydride) and to this the ethoxide-ester solution was added dropwise at room temperature with vigorous stirring. Addition required one hour and this was followed by three hours of heating on a steam bath while stirring was maintained. At that time 250 ml of cold water was added to the reaction mixture[29] causing the cyclized material(X) to precipitate from solution. The product was filtered, washed with water and air dried. The crude material (approximately 12 g) was recrystallized from 95% ethanol to yield 9.70 g (71%) of the desired dinitrodiester: mp 141-2°, $[\alpha]_D^{32}$ -512.6° (l = 1, c = 7.9 mg/ml, methanol) [lit.: mp 141-3°, $[\alpha]_D^{32.5}$ -443°, methanol)].[13]

Preparation of R-(-)-1,11-diamino-6,6-dicarbethoxydibenzo[a,c][1,3]-cycloheptadiene(XI)

A suspension of 4.28 g (0.01 mol) of the dinitrodiester(X) and 430 mg of 5% palladium on charcoal in 150 ml of 95% ethanol was shaken with hydrogen (at approximately three atmospheres) in a Parr low pressure hydrogenation apparatus. Within two hours, approximately 80% of the theoretical amount of hydrogen had been absorbed and the reaction was stopped, an additional 200 mg of catalyst was added and the reduction resumed. After a total of six hours, 0.06 mole of hydrogen had been absorbed and the reaction was stopped. The straw-yellow solution was filtered through Celite to remove the catalyst and evaporated to dryness under reduced pressure. The crude diamine was dissolved in a minimum volume of hot cyclohexane, clarified with Norite and allowed to cool. A small first crop of crystals ($[\alpha]_D^{27}$ -18.7° in 95% ethanol) formed on cooling to room temperature. After cooling the filtrate overnight in the freezer a large second crop of crystals formed: mp 111-2°, $[\alpha]_D^{28}$ -29.3° (95% ethanol) [lit.: mp 111-3°, $[\alpha]_D^{32}$ -25.4°, (95% ethanol)].[13] Combined yield: 66%.

Diamine of still larger specific rotation ($[\alpha]_D^{25}$ -45.2°, 1 = 2, c = 5.84 mg/ml, 95% ethanol) could be obtained by very carefully recrystallizing the material from cyclohexane a second time, however, the melting point indicated no change.

Preparation of S-(+)-6,6-dicarbethoxydibenzo-[a,c][1,3]-cycloheptadiene(XII)[13]

Since the numerous deaminations were carried out with a variety of different modifications only the basic procedure will be discussed here.

The diamine, typically $[\alpha]_D^{25}$ approximately -40° in ethanol, was dissolved in excess hypophosphorous acid in a flask equipped with a stirrer and the copper(I) oxide was then added to the solution. In all but two runs the solution was purged with nitrogen gas which was maintained during the course of the reaction. The vigorously stirred reaction mixture was cooled to between -15° and -10° and then an aqueous solution of sodium nitrite was added dropwise. When nitrite addition was completed the reaction mixture was stirred for an additional two hours. At that time the solution was warmed to approximately 10° and extracted with cyclohexane. The cyclohexane solution was twice washed with 5% aqueous sodium hydroxide and finally with water. After drying over anhydrous magnesium sulfate the solution was checked for the presence of optical acitivity. On checking the ultraviolet spectrum of this solution it was found to be identical to that of the racemic compound prepared in an unambiguous manner.[29] Evaporation of the solvent at reduced pressure and temperature yielded a white solid whose infra-red spectrum was again the same as that of the known material, except for the occasional presence of bands presumably attributable to residual cyclohexane (~3100 and ~1450 cm^{-1})[15] and on one occasion a very weak band at ~2120 cm^{-1} (diazo group ?).[15] To further compare this material to that previously prepared[13,29] the solid was dissolved in a minimum volume of cyclohexane and placed on a 1.5 x 9.0 cm neutral alumina column maintained at 20°. The purified product was eluted from the column using cyclohexane containing 2% absolute ethanol. With the exception of the above noted diazo band, the infra-red and ultra-violet spectra of the column purified material was identical to that of the non-chromatographed material. On the basis of this observation this last step was subsequently dropped to minimize handling and thus racemization. The non-chromatographed material thus produced possessed a melting point of 62-64° [lit.: 64-6°].[13] The specific experimental conditions and results are summarized and examined further during the discussion of the entire synthetic sequence. Summaries of the reaction conditions appear in Tables II and III and the kinetic data appear in Appendix C.

Synthetic Sequence for 6,6-Dicarbethoxy-4,8-diiododibenzo-[a,c][1,3]-cycloheptadiene

Preparation of 2-chloro-6-iodotoluene(XIV)[30]

Two moles (282.2 g) of 3-chloro-2-methylaniline was added to 800 ml (9.28 mol) of concentrated hydrochloric acid and 800 ml of water in a five gallon glass container and cooled to 2° with ice. With vigorous stirring, 165.6 g (2.40 mol) of sodium nitrite in 400 ml of ice water was added over the course of approximately 30 minutes so that the temperature remained between 0° and 3°. Approximately 30 g (approximately 0.5 mol) of urea was then added to destroy excess nitrous acid. With continued vigorous stirring, 332.0 g (2.00 mol) of potassium iodide in a minimum volume of ice water was added in small portions to the diazonium salt solution. Addition required approximately 30 minutes with the temperature remaining between 0° and 3°. The potassium iodide addition caused a red-brown precipitate to form, such that the mixture became moderately viscous. The slurry was allowed to warm to room temperature (approximately 22°) during the next 90 minutes while stirring was continued. During this warming, a two phase system developed; a red-brown upper phase and a black oily lower phase. Steam was now directed onto the surface of the reaction mixture and the temperature soon rose to 35°. At this time decomposition of the diazonium iodide was assumed to be complete and the heating was stopped. The addition of solid sodium bisulfite caused the upper aqueous phase, but not the lower oily layer, to lighten in color. The layers were separated and the aqueous phase was extracted with 1000 ml of benzene which was combined with the organic phase. This benzene solution was washed first with water and then with 5% aqueous sodium bicarbonate. After drying over anhydrous sodium sulfate the solution was distilled to yield the following fractions:

Frac. No.	bp	Pressure	n_D^{25}	Weight
1	73-75°	2 mm	1.6204	1 g
2	75-76.5°	2 mm	1.6243	140.2 g
3	76.5-78°	2 mm	1.6248	52.7 g
4	78-80°	2 mm	1.6250	30.9 g
5	80-82°	2 mm	1.6255	18.9 g
6	62-	0.3 mm	1.6269	1 g

(Approximately 125 g of tarry material remained in the distillation flask at the end of the distillation.) The yield obtained from combining Fractions 2, 3, 4 and 5 above was 242.7 g (48%) [lit.: bp 132-3° at 25 mm[31] and bp 99-100° at 5 mm,[30] n_D^{25} 1.6255[30]].

Preparation of 3,3'-dichloro-o,o'-bitolyl(XV)[30]

Fractions 2 through 5 (above) of 2-chloro-6-iodotoluene (242.7 g, 0.96 mol) were mixed with 122.0 g (1.92 mol) of copper dust (electrolytic grade) and 30 g of acid-washed and ignited sand. With stirring the mixture was heated to reflux and maintained for 74 hours (heating bath temperature: 220-240°). After cooling to room temperature a residual oil which was present was poured off and the reaction solid exhaustively extracted with benzene. The benzene solution was combined with the oily layer and the resultant solution clarified with Norite. The benzene was removed by distillation and the residue purified by vacuum distillation.

The following fractions were obtained:

Frac. No.	bp	Pressure	n_D^{25}	Weight
1	73-75°	2 mm	1.6244	3.40 g
2	133-40°	2 mm	-	74.53 g
3	residue	-	-	50 g

Fraction 2, which solidified on cooling, was recrystallized from methanol to yield 59.1 g (mp 75-9°) of the desired dichlorobitolyl. A second crop of 8.5 g (mp 73-6°) was also collected for a total yield of 67.6 g (56%) [lit.: bp 133-39° at 2 mm, mp 75-6°].[30]

Preparation of 3,3'-diiodo-o,o'-bitolyl(XVI)[30]

Under an atmosphere of dry nitrogen gas, 13.7 g (0.57 mol) of Grignard grade magnesium turnings were heated with 0.2 g of iodine. After cooling, 500 ml of dry (over calcium hydride) tetrahydrofuran was added and the mixture heated to reflux. At that time, 67.6 g (0.27 mol) of 3,3'-dichloro-o,o'-bitolyl(XV) in 250 ml of dry tetrahydrofuran was added in one portion. After one hour of stirring at reflux, 0.56 g (1 mole percent) of aluminum isopropoxide was added.[32] Stirring and heating were resumed and 20 hours after commencing the reaction 0.56 g (1 mole percent) of aluminum isopropoxide was again added (Total: 1.12 g or 2 mole percent). Stirring and heating were continued for a total of five days, at which time most of the magnesium had been consumed.

A solution of 143.5 g (0.57 mol) of iodine in dry tetrahydrofuran was prepared and placed in a stirred flask under a nitrogen atmosphere. The di-Grignard reagent from above was added dropwise with stirring to the iodine solution over the course of one hour.

After addition was complete the solution was stirred for 2.5 hours. The reaction was then quenched by the addition of 200 ml of water followed by the addition of approximately 25 g of sodium bisulfite to remove free iodine. The reaction volume was reduced to approximately 1000 ml under vacuum and 300 ml of benzene was added. After mixing, the aqueous and benzene layers were separated and the aqueous portion extracted with fresh benzene. The benzene solutions were pooled, washed with water and partially dried over anhydrous sodium sulfate. This solution was clarified with Norite, dried over anhydrous magnesium sulfate and evaporated to dryness. The crude residue so obtained was recrystallized from a 1:1 mixture of benzene and methanol. The crystalline product, which was somewhat dark, was pulverized, washed with methanol and dried to yield 49.6 g (43%) of the desired diiodobitolyl based on the starting dichlorobitolyl: mp 113-18° [lit. 119-20°].[30]

Preparation of 2,2'-bis(bromomethyl)-3,3'-diiodobiphenyl(XVII)[30]

Bromination was achieved by dissolving 49.6 g (0.11 mol) of 3,3'-diiodo-o,o'-bitolyl and 46.8 g (0.26 mol) of N-bromosuccinimide in 400 ml of carbon tetrachloride. This solution was heated to reflux and 1.0 g of dibenzoyl peroxide was added. After 24 hours of refluxing another 1.0 g of peroxide was added. After a second 24 hour reflux period a final 1.0 g of peroxide (total peroxide: 3.0 g) was added. By the time the bromination had proceeded for a total of 75 hours, the solution was red-brown in color from excess bromine and was cooled to room temperature. The solution was filtered to remove the succinimide and washed with aqueous sodium bisulfite to remove free halogen. The solution was dried by distillation and finally evaporated to dryness under reduced pressure. The crude product was recrystallized from carbon tetrachloride to give a first crop of 38.6 g (mp 160-3°) and a second crop of 12.8 g (mp 150-4°) or a total yield of 76% [lit.: mp 159.5-60.5°].[30]

Preparation of 6,6-dicarbethoxy-4,8-diiododibenzo[a,c][1,3]-cycloheptadiene(XVIII)

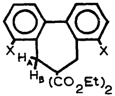
A solution of sodium ethoxide was prepared by dissolving 0.9 g (0.04 mol) of metallic sodium in 25 ml of absolute ethanol. When all of the sodium had dissolved, 1.6 g (0.01 mol) of diethyl malonate was added in one portion and within ten minutes a white turbidity developed. The ethoxide-malonate solution was added dropwise with stirring and at room temperature to a solution of 5.9 g (0.01 mol) of 2,2'-bis(bromomethyl)-3,3'-diiodobiphenyl in 60 ml of dry (over calcium hydride) 1,4-dioxane. Addition required one hour and then stirring was continued for an additional 18 hours. At that time the solution was heated to reflux, allowed to cool and poured into 100 ml of water. The precipitate was filtered and the aqueous dioxane solution extracted with chloroform. The chloroform and solid were combined, washed twice with water and clarified with Norite. After evaporation of the chloroform solution to dryness the residue was recrystallized from a 1:1 mixture of chloroform and absolute ethanol. A crop of white needles weighing 2.76 g (46%) was obtained: mp 221-4° [lit.: 227.8°].[33]

The corresponding 4,8-difluoro-,[34] -dichloro-[30] and -dibromo-[35]

compounds were previously prepared by generally similar routes by other workers and were generously supplied for this work. A very brief summary (Table I) of some physical properties of all of the compounds studied is provided here for the sake of comparison. Each of the compounds to be discussed is, for convenience, designated in shortened form to indicate the nature of the 4,8-substituents. The first letter(s) gives the chemical symbol of the 4,8-substituents while the second portion of the code is E2 indicating the compound to be the diester at position 6. Thus, the parent hydrocarbon, i.e. 4,8-dihydrogen, is designated as H2E2, the analogous 4,8-dibromo-compound as Br2E2 and the other derivatives accordingly.

TABLE I

SUMMARY OF PHYSICAL PROPERTIES OF SELECTED BIPHENYLS



X	MP	$\lambda^{\star}$max	log $\epsilon^{\star}$max			NMR[‡]	
H (H2E2)	64-6°	249 mμ	4.228	δ_A=2.90	δ_B=3.29	J_{AB}=-13.8 Hz	($CDCl_3$)
H (H2E2)	64-6°	249 mμ	4.228	δ_A=2.79	δ_B=3.21	J_{AB}=-12.8 Hz	(C_6D_{12})
F (F2E2)	114-6°	247 mμ	4.14	δ_A=2.82	δ_B=3.57	J_{AB}=-14.7 Hz	J_{HF}=-2.4 Hz ($CDCl_3$)
Cl (Cl2E2)	150-1°	250 mμ	4.176	δ_A=2.96	δ_B=3.70	J_{AB}=-14.6 Hz	($CDCl_3$)
Br (Br2E2)	167-8°	250 mμ	4.180	δ_A=3.04	δ_B=3.68	J_{AB}=-14.5 Hz	($CDCl_3$)
I (I2E2)	227-8°	252 mμ	4.167	δ_A=3.18	δ_B=3.52	J_{AB}=-14.5 Hz	($CDCl_3$)

[★] In 95% ethanol.
[‡] Low temperature limits from this work assuming a simple AB spin system.
δ values are calculated relative to TMS and expressed in ppm.

DISCUSSION

Synthetic Results

Although the synthetic routes to these biphenyl derivatives is lengthy and somewhat tedious, they are none the less relatively straightforward and thus require but few comments.

Since the synthetic method of Iffland and Siegel[13] (See Scheme I) had been shown to be successful for preparation of the parent compound, it was decided to follow the same route with minor variations.

The preparation and resolution of 6,6'-dinitrodiphenic acid(VI) was achieved by standard literature methods without undue difficulties. However, the preparation of the corresponding diacid chloride proceeded along quite unexpected lines. Although previous workers[21,13] with this system have not indicated significant racemization during its preparation, it was found to be a quite facile process during preparation and in the crystalline state. This latter observation is even more surprising when it is remembered that it occurred in recrystallized material as opposed to a crude unpurified product. Conceivably, the racemization may be explained on the basis of an intramolecular interaction which facilitated a co-planar conformation of the two aromatic rings and thereby aided inversion. Another plausible explanation may involve the interaction of the acid, or more likely the acid chloride, with an impurity in the thionyl chloride used in the reaction. The presence of iron and other heavy metals can readily be demonstrated in commercial thionyl chloride and the in situ generation of an acylium ion and a chlorometal anion is not inconceivable. Once formed, the acylium ion presumably would have a lesser steric requirement than its corresponding acid or acid chloride analog and thus inversion followed by ion pairing to produce the acid chloride of opposite configuration to that of the starting material is again not inconceivable. This, and other types of rearrangements of acid halides, has in fact considerable precedent in the literature.[27]

Once having made this at best unfortunate observation it was decided to take advantage of the reaction in subsequent work. When 6,6'-dinitrodiphenic acid is resolved using α-phenethylamine the dextro acid-dextro base (dAdB) and levo acid-levo base (lAlB) diastereomeric salts are found to be much less soluble in the acetone solvent than the ''mixed'' salts, i.e. dAlB and lAdB. Thus, the supernatant from the resolution was evaporated to dryness and the resultant diastereomeric salt decomposed with mineral acid to yield a diphenic acid to lower than desired optical purity. Intentional racemization of this material was achieved by refluxing in excess thionyl chloride followed by hydrolysis. In this manner, the less pure enantiomer from a resolution could be converted into a racemic modification and subsequently resolved. By repeating this procedure several times virtually all of the racemic diphenic acid could be converted to a single enantiomer. In this way all subsequent reactions need only be performed once, as opposed to once for each enantiomer; or if more than one run had to be made, mother liquors and the like could be pooled and worked up together since only enantiomer was being handled.

The reduction of the freshly prepared acyl halide was carried out using a modification of the published procedure of Hall and Poole[28] involving lithium borohydride. The choice of lithium borohydride in tetrahydrofuran in preference to sodium trimethoxyborohydride[13] was made in hopes of achieving a better yield than that previously described (56%). The overall yield of diol by this method was the same 56%, but that is based on the starting diacid and therefore combines the acid chloride yield with that of the reduction. Using typical thionyl chloride yields, the yield for the reduction was only approximately 60%. Even though this is a small increase in the overall yield, the method would appear, at least subjectively, to be the preferable procedure. That is because the lithium borohydride reaction is homogeneous and occurs quite rapidly unlike the slower reduction in the 1,4-dioxane-sodium trimethoxyborohydride suspension. Therefore, short reaction times are preferable to minimize possible racemization of the unreacted acyl halide. At no time was the presence of amine, due to nitro group reduction, observed.

Conversion of the α,α'-diol(VIII) to its corresponding dibromide(IX) and ring closure occurred readily as previously described. Reduction of the dinitro compound(X) to the diamine(XI) was carried out in the presence of palladium on charcoal as opposed to platinum oxide, in an attempt to minimize the presence of products containing nitrogen-nitrogen bonds. When platinum oxide was used the presence of some dark colored material was reported,[13] and since this might indicate the presence of a benzocinnoline and/or the corresponding azoxy compound the precaution of using palladium was taken. This is because palladium shows a greater activity toward hydrogenolysis of nitrogen-nitrogen bonds than does platinum.[36]

Unfortunately, the deamination reaction did not proceed as well as it had been hoped. A summary of the several deamination runs is given in Tables II and III since numerous variables were examined in an attempt to obtain material of high optical purity. With the exception of one run (No. 1) in which the reaction temperature was too low, the yield of deaminated hydrocarbon was good, but only one run (No. 3) produced material of high specific activity. Variation of the ratio of copper catalyst ranged from 10 moles of copper(I) oxide per mole of amino group down to 0.05 moles per mole of amino group with no apparent effect. This is not surprising however, if the copper ion is truly acting as a catalyst in the reaction. The sodium nitrite was always used in excess and likewise would not be expected to significantly alter the reaction. Even in the presence of a large amount of copper ion the influence of an oxygen atmosphere on a reaction which is known to be free radical in nature[37] could not be predicted with certainty so a nitrogen atmosphere was adopted as a standard precaution.

The possible occurrence of a photochemically induced racemization was considered after some preliminary results seemed to indicate that the deaminated compound racemized faster when the rotation was measured near the 249 mμ biphenyl band than when it

TABLE II

SUMMARY OF REACTANT RATIOS FOR THE DEAMINATION OF DIAMINE(XI)

Run No.	Moles Diamine	$\frac{\text{Moles } H_3PO_2}{\text{Moles Diamine}}$	$\frac{\text{Moles } NaNO_2}{\text{Moles Diamine}}$	$\frac{\text{Moles } Cu_2O}{\text{Moles Diamine}}$
1	0.005	100	2.50	2.0
2	0.0025	100	2.50	2.0
3	0.002	100	3.00	2.0
4	0.0005	500	3.00	2.0
5	0.0005	500	3.00	2.0
6	0.0005	500	3.00	2.0
7	0.00025	500	3.00	0.1
8	0.00065	25	3.00	0.5
9	0.00028	56	3.00	1.0

TABLE III

SUMMARY OF REACTION CONDITIONS FOR THE DEAMINATION OF DIAMINE(XI)

Run No.	Under N_2	In Dark	% Yield	Comments
1	-	-	10	Temperature: -20 - -15°
2	-	-	33	Low activity, Racemization kinetics at 25.0° attempted
3	+	±	66	At night, lights on, white solid-high activity, racemization kinetics at 25.0° attempted
4	+	-	65	Low activity, afternoon, racemization kinetics at 25.0°
5	+	+	62	Low activity, at night, lights off, racemization kinetics at 35.2°
6	+	+	Low	No activity, at night, lights off
7	+	+	70	No activity
8	+	+	49	Low activity, very crude, unable to purify
9	+	+	60	Low activity, racemization kinetics at 15.8°

was measured at the D ''line'' of sodium (589 mμ). This is consistent with the observation that at least some bridged biphenyls can be racemized photochemically.[38] With this in mind some reactions were run during the daylight hours with room fluorescent lights on, some at night with the lights on and still others at night or in a darkened room with the lights off. Although these precautions do not logically seem detrimental in nature, it likewise does not appear to have had a clear cut or pronounced favorable effect upon the course of the reaction.

The final parameter studied was the ratio of hypophosphorous acid to diamine. Since the acid serves both as solvent and reactant, at least superficially the presence of an excess versus the presence of a vast excess of acid would seem to make little or no difference. At least in this particular circumstance that ''logical assumption'' may not be entirely justified. Between 5 and 15 moles of acid per mole of amine has been suggested as a possible guideline[39] and considering the low cost of 50% hypophosphorous acid this does not appear extravagant (particularly in light of the relative value of the amine used). Further it has been stated that:

> ''In general, when amines that are deaminated smoothly with only 5 moles of hypophosphorous acid are treated with 15 moles, the yield is increased another 5 to 15%.''[39]

With this in mind as well as the difficulty of working with small solution volumes, no attempt was made initially to keep the ratio of acid to amine low. During the course of one early run (No. 3), the observation was made that a white solid was being deposited on the upper walls of the flask as the solution was stirring. When the cyclohexane from extraction of the aqueous reaction mixture was subsequently examined for optical activity, it was found to show a rather large experimental rotation considering the fact that this solution was quite dilute. From the ultraviolet spectrum of the solution the concentration was calculated and using that value, the specific rotation, at 589 mμ was found to be 218°. Evaporation of a small volume of solution yielded a sample that showed a good melting point (62-4°) and in time the rotation of the main body of the solution went to zero indicating the absence of an impurity which was optically stable. The infra-red spectrum of a sample obtained by simple evaporation of the solvent was identical to that of the authentic hydrocarbon except for the presence of a very weak absorbance at ~2120 cm^{-1} (diazo group ?). Although this sample exhibited a rather large specific rotation, it must be remembered that the molecule is an inherently dissymmetric chromophore and systems of this nature have been prepared with much larger rotations, e.g. hexahelicene, $[\alpha]_D$ ~3700°.[40] Since this highly active material was obtained in a reaction where presumably the product crystallized from solution as it was formed, and subsequently deposited on the flask walls, racemization would be expected to be impeded by the constraints of the crystal lattice. However, if the solvent volume is very large, i.e. a high acid to amine ratio, the hydrocarbon product would be in solution a larger percentage of the time and so there would be more time for racemization to occur.

Whether or not the preceding reasoning is valid cannot readily be determined at this point, but the role of the solvent/reactant hypophosphorous acid in this reaction at the very least appears to be somewhat more complicated than initially expected. Unfortunately a lack of additional amine precluded the possibility of pursuing this variable any further.

NMR DATA

The study of conformational changes of molecules has been greatly extended by the use of nuclear magnetic resonance (NMR) spectroscopy. This powerful tool is particularly advantageous for processes occurring with an activation energy in the range of approximately 6 to 25 kilocalories per mole. By applying line shape analysis to the exchange averaging of NMR signals, the rate constant of the process may be determined.[41,42,43] The range of rate constants most amenable to study by NMR is that of the order of 1 to 10^4 sec^{-1}.[44,45] An additional and highly significant advantage to the method is that, unlike polarimetric measurements, optically active material need not be used and thus repeated use of the same sample is possible.

The price that is required of the experimenter for these advantages is twofold. First, the precise nature and complexity of the spin system in question must be understood, for without this knowledge the appropriate mathematical treatment cannot be applied. Secondly, once having determined the nature of the spin system, the existence of the appropriate mathematical formulations and computing techniques must be available. Due to the extensive and continuing work of numerous workers in this field, the mathematical description of many spin systems has been developed; however, the choice of which treatment is appropriate still rests in the hands of the individual experimenter.

The NMR spectrum of the parent hydrocarbon, at least superficially, appears to be what would be expected (Figure 1). It consists of a somewhat complex aromatic region, the typical quartet and triplet of an ethyl group representing the methylene and methyl resonances respectively and finally a doublet of doublets centered at approximately δ 3 and corresponding to the diastereotopic benzylic hydrogen atoms at positions 5 and 7. These observations are consistent with those of other workers.[11]

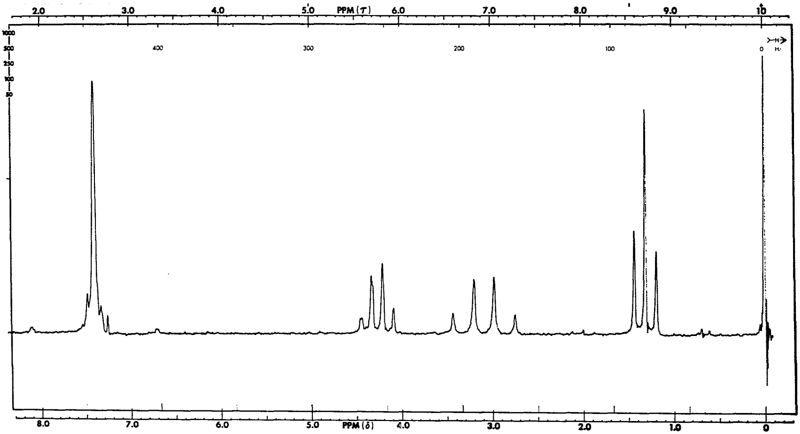
The reaction under study here is the intramolecular rotation of a biphenyl molecule about its 1,1' or pivot bond such that it is converted into its mirror image configuration. This may be represented as follows:

$$\mathrm{d} \underset{k_{INV}}{\overset{k_{INV}}{\rightleftharpoons}} \mathrm{l} \tag{1}$$

where d and l represent the dextro- and levorotatory configurations respectively, and k_{INV} is the rate constant for the inversion process. Examination of molecular models indicates that the two hydrogen atoms of position 5 exist in grossly different electronic and/or magnetic environments, relative to each other, and thus it is not surprising that each atom should give rise to an NMR signal which is separate and distinct from that of the other. These signals appear not as two singlets, as would be the case in an AX spin system but rather as a doublet of doublets due to a significant geminal coupling constant (approximately -13 Hz). Exactly the same situation exists for the hydrogen atoms at position 7 and thus it is seen that each of the doublets integrates for two hydrogen atoms relative to the remainder of the spectrum.

FIGURE 1

NMR Spectrum of H2E2 (60 MHz, $CDCl_3$)



Temperature: -30.7°

Filter Band Width: 2 Hz
R.F. Field: .015 G

Sweep Time: 500 sec
Sweep Width: 500 sec

Since NMR spectroscopy is an achiral method of investigation, the sample being studied need not be optically active. Despite this lack of optical activity in the sample, Eq. 1 is still valid since we are interested in determining what conditions are required for a given set of atoms to undergo an inversion, such that they achieve a final ''equilibrium'' position in space which is enantiomeric relative to their intial ''equilibrium'' position. The manner in which the hydrogen atoms on the benzylic carbon atoms of compound XII achieve this, is for the molecule as a whole to undergo an intramolecular rotation about its pivot bond so as to be converted into its optical antipode. Thus, the rate constant obtained via NMR for the dextro-levo inversion should be ''about'' the same as that which may be obtained from polarimetry data.

Based on literature precedent and the apparent simplicity of the temperature dependent spectra, the analysis used was that of a simple AB system. A quantitative description of this system has been presented by Alexander.[46] This formulation[46,47] correlates the half-life for exchange with the AB coupling constant, the difference between the chemical shifts of the two signals and the experimental line widths at half height. In this treatment the mathematics assumes one of three forms depending upon the temperature region being examined. At low temperatures, where exchange is slow, the following relationship is observed

$$\tau = \frac{1 \pm J_{AB} \Big/ \sqrt{\delta_{AB}^{2} + J_{AB}^{2}}}{\pi \, (\omega - \omega_{0})} \qquad (2)$$

where $2\delta_{AB}$ represents the difference between chemical shift H_A and that of H_B and J_{AB} is the H_A-H_B coupling constant with both δ_{AB} and J_{AB} expressed in units of radians per second. The line-widths at half height for the exchanging signal selected from the AB system and any convenient non-exchanging signal, in units of Hertz, are represented as ω and ω_o respectively. The plus and minus signs above are used respectively, with the outer and inner lines of the AB ''quartet'' depending upon which is chosen for use in the analysis. Finally, τ represents the average residence time in seconds of the molecule in a specified conformation.

As the sample temperature is increased, exchange becomes more rapid and at the very point at which the individual signals coalesce into a single broad band, the average residence time is calculated as follows

$$\tau_c = \frac{\sqrt{2}}{\pi\sqrt{\delta_{AB}^2 + 6J_{AB}^2}} \qquad (3)$$

This equation is valid, at the coalescence temperature, so long as the natural line-width, in the absence of exchange, is negligible relative to that at coalescence.[48,49] Although highly reliable, a few percent systematic errors will occur when using Eq. 3 due to approximations made during its derivation.[50] At temperatures above that of coalescence, a new equation may be derived[49,51] from Eq. 2 to describe the observed spectral changes as a function of the change in residence time

$$\tau = \frac{2(\omega - \omega_o)}{\pi\delta_{AB}^2} \qquad (4)$$

Once having analyzed the temperature dependent spectra and calculated the average residence times, the calculation of the activation parameters is relatively straightforward. Since τ represents the average residence time of a molecule in a given state, the reciprocal of that quantity represents the rate constant for change to or from that state. That is, if k_{INV} represents the rate of conformational inversion of the molecule then

$$k_{INV} = 1/\tau \tag{5}$$

Application of the Absolute Reaction Rate Theory[52,53,54] to this type of data may be readily achieved. According to this theory, the rate constant for a reaction is related to the free energy of activation in the following manner

$$k = \frac{\kappa k_B T}{h} \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right) \tag{6}$$

But since

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \tag{7}$$

substitution of Eq. 7 into Eq. 6 yields

$$k = \frac{\kappa k_B T}{h} \exp\left(-\frac{\Delta H^{\ddagger}}{RT}\right) \exp\left(\frac{\Delta S^{\ddagger}}{R}\right) \tag{8}$$

In this expression, k is the rate constant; κ, the transmission coefficient; k_B, Boltzmann's constant; T, absolute temperature; h, Planck's constant; $\Delta H^{\ddagger}$, the enthalpy of activation; $\Delta S^{\ddagger}$, the entropy of activation; and R, the gas constant. Rearrangement and substitution of known values into Eq. 8 yields the following relationship

$$\log_{10}\left(\frac{k}{\kappa T}\right) = 10.319 - \left(\frac{1}{T}\right)\left(\frac{\Delta H^{\ddagger}}{4.574}\right) + \left(\frac{\Delta S^{\ddagger}}{4.574}\right) \qquad (9)$$

It may be readily seen that if κ equals unity, then a linear plot of $\log_{10}(k/T)$ versus $1/T$ will have as its slope $-\Delta H^{\ddagger}/4.574$ and $\Delta S^{\ddagger}$ may be calculated as well since the y-intercept corresponds to $10.319 + (\Delta S^{\ddagger}/4.574)$.

Since there is neither an obvious reason nor an apparent need to assume a more complex mechanism for this reaction, a simple first order reversible reaction was assumed. The calculations were performed in the following manner for each of the compounds examined. First, the low temperature spectrum for each compound-solvent pair was analyzed by use of the LAOCN 3 computer program of Castellano and Bothner-By.[55] Using this program the accurate values for the chemical shifts, the AB coupling constant and the theoretical line intensities were obtained from the individual line frequencies. Using these values, the line-widths at half height of the non-exchange broadened TMS line and one broadened benzylic hydrogen line, the average residence time, τ, was calculated for each compound at each temperature. This was done using Eq. 2, 3 or 4 depending upon the temperature region under examination. The taking of reciprocals of the residence times yielded the appropriate first order rate constants. A least squares regression analysis of the rate constant-temperature data points was performed by the ACTENG program of DeTar.[56] Since only one spectrum was recorded for each compound at each temperature, a standard deviation for the temperature and rate constant could not be calculated. Instead however, the largest probable errors based on the limits of instrument precision and human measuring error were used in place of the standard deviations in the ACTENG calculations. The results of these calculations are given in Tables IV and V along with a tabulation of Arrhenius activation energies and pre-exponential factors which are also calculated by the program. The ''standard deviations'' given are those obtained using the above stated errors.

Plots of $\log_{10}$ (k_{INV}/T) versus 1/T are shown in Figures 2-7 to indicate the nature of the data from which the values in Tables IV and V were obtained (the circled data points in these figures were not included in the calculations). Complete tables of the temperature-rate constant data are given in Appendix B along with approximate coalescence temperatures. A number of interesting observations may be made upon examining this data and the subsequent calculations. First is the apparent discontinuity in the data for the parent hydrocarbon irrespective of solvent. In both chloroform and cyclohexane the inversion rate appears to be affected by one or more factors on one side of the coalescence temperature ($T_c \approx 16°$) which are either not operative or are of reduced importance on the other side of the coalescence temperature. In these data sets it could not be readily determined which of the three possible equations (Eq. 2, 3 or 4) for τ was applicable at one temperature very near the coalescence temperature. As a result the rate was calculated using each equation and these values are given in Appendix B and designated by squares in Figures 2 and 3.

If a compound is behaving in a predictable manner, one would

TABLE IV

NMR THERMODYNAMIC ACTIVATION PARAMETERS

Compound[1]	ΔH_{INV}(kcal/mol)	"Std. Dev."	ΔS_{INV}(e.u.)	"Std. Dev."
H2E2[2]	9.66	0.87	-18.56	3.56
H2E2[3]	12.52	1.22	-2.03	6.12
H2E2[2,4]	10.28	2.58	-16.67	15.86
H2E2[3,4]	12.39	0.88	-3.36	3.36
F2E2	20.96	0.63	19.93	3.16
Cl2E2	37.62	1.26	58.77	6.14
Br2E2	38.71	1.11	60.10	3.72
I2E2	40.39	0.81	64.04	2.00

[1] All in chloroform-d unless otherwise specified

[2] Temperature: -9.6° to 15.6°

[3] Temperature: 22.0° to 99.6°

[4] Run in cyclohexane-d_{12}

TABLE V

NMR ARRHENIUS ACTIVATION PARAMETERS

Compound[1]	Arrhen. A_{INV}	"Std. Dev."	Arrhen. E_{INV} (kcal/mol)	"Std. Dev."
H2E2[2]	6.20×10^{9}	9.38×10^{9}	10.23	0.87
H2E2[3]	9.93×10^{12}	1.97×10^{13}	13.19	1.22
H2E2[2,4]	8.46×10^{10}	4.16×10^{11}	10.81	2.58
H2E2[3,4]	1.72×10^{13}	2.53×10^{13}	13.00	0.88
F2E2	2.13×10^{13}	1.49×10^{13}	21.87	0.63
Cl2E2	2.18×10^{18}	2.54×10^{18}	38.70	1.26
Br2E2	1.00×10^{22}	1.23×10^{22}	39.60	1.11
I2E2	1.60×10^{30}	1.95×10^{30}	41.04	0.81

[1] All in chloroform-d unless otherwise specified

[2] Temperature: -9.6° to 15.6°

[3] Temperature: 22.0° to 99.6°

[4] Run in cyclohexane-d_{12}

FIGURE 2

NMR Kinetic Data of H2E2 in $CDCl_3$

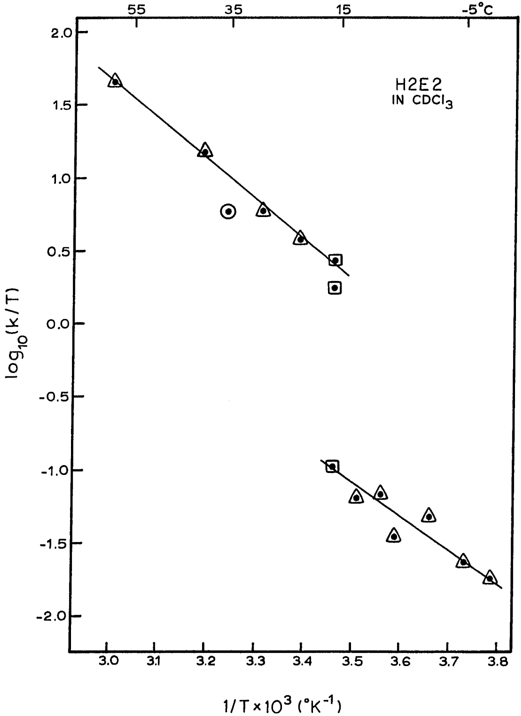


FIGURE 3

NMR Kinetic Data of H2E2 in C_6D_{12}

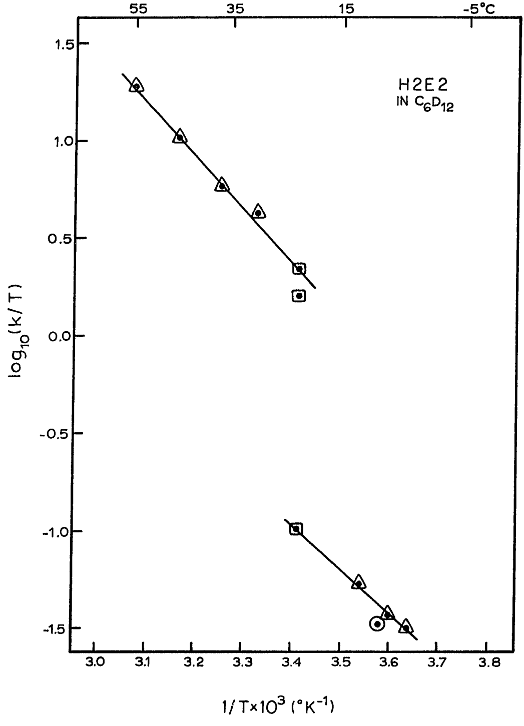


FIGURE 4

NMR Kinetic Data of F2E2

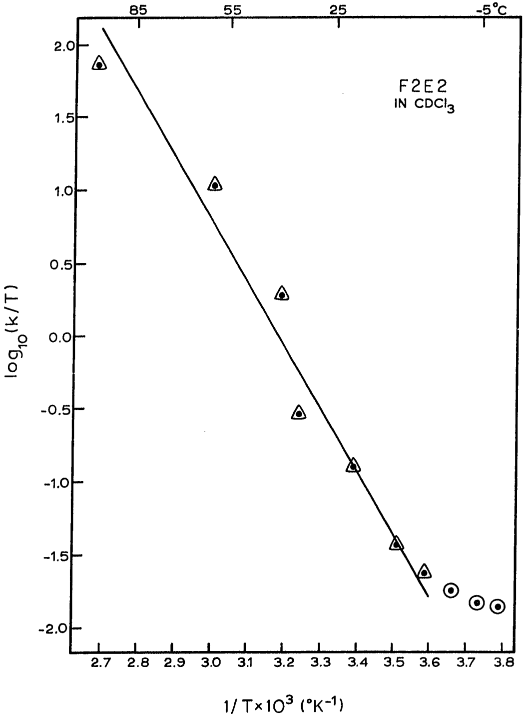


FIGURE 5

NMR Kinetic Data of C12E2

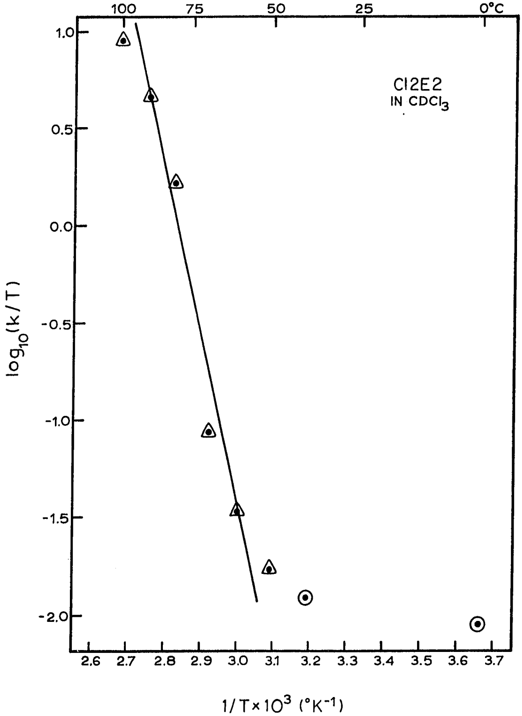


FIGURE 6

NMR Kinetic Data of Br2E2

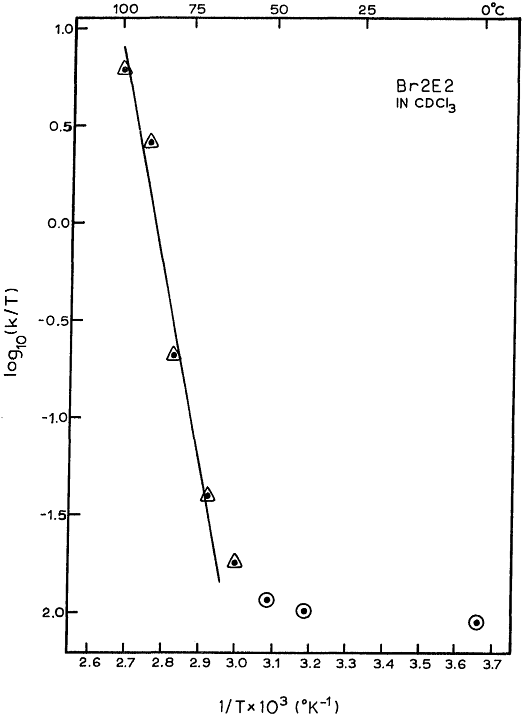
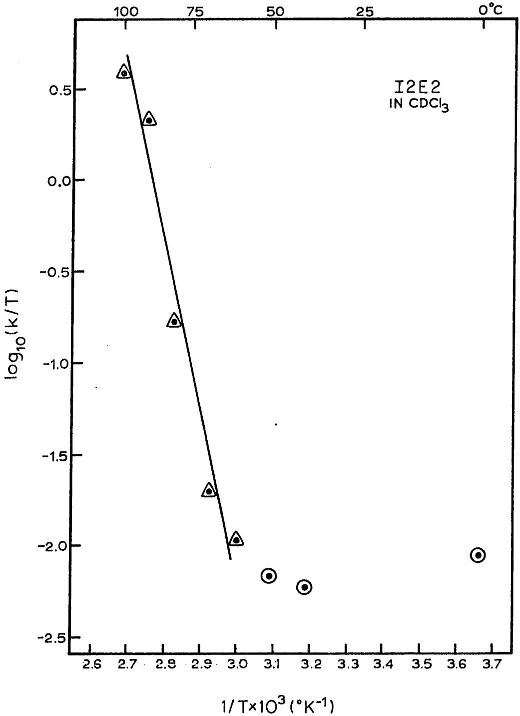


FIGURE 7

NMR Kinetic Data of I2E2



expect a gradually changing and overlapping set of rates from Eq. 2,3 and 4 when moving stepwise from below to above the coalescence temperature. Unfortunately this is not observed with the parent compound and the cause(s) of this observation lay somewhat in the realm of speculation. Possible explanations might include temperature dependent changes in the solution viscosity or the degree of solvation of the biphenyl molecules. Since the sample is contained in a sealed tube, the pressure as well as the temperature is changing and thus conceivably this might be explained as a pressure effect. Further speculation however seems quite unwarranted due to the lack of additional information.

In general the plots show relatively little scatter except perhaps for a smooth deviation from linearity at low temperatures by all systems and again for reasons of unexplained origin. The reason(s) for this deviation may include one or more of the previously discussed factors such as changes in viscosity, degree of solvation or pressure. Additionally it might be attributable to heterogeneity of the sample as a result of the presence of crystalline material due to a decreased solubility at the lower operating temperatures. Besides these deviations there remain at least three and perhaps more points which bear upon the reliability of these calculations. The first relates to the relative heights of the peaks of the AB spin system. As previously mentioned the LAOCN 3 calculations yield theoretical line intensities in addition to chemical shifts and coupling constants. The ratios of the inner to outer line intensities of the AB portion of the spectrum, were consistently found to be larger in the experimental spectra than the ratios obtained from the theoretical calculations. As can be seen in Table VI these discrepancies are, in most cases, quite sizable. Although this deviation from theory may seem of trivial importance there are ample precedents in the literature for the value of this and similar types of correlations when studying rate processes by NMR spectroscopy.[57] Since the experimental ratios are in all cases larger than expected, as determined by comparing them to the calculated values, one would expect the rate constants to likewise be larger than expected. In fact this is precisely what is observed as will be seen later when the polarimetry results are considered. The reason(s) for these departures from the calculated values are not clear cut, but possible explanations will be discussed after further consideration of the data.

Specifically turning to an examination of the range and progression of values in Table V we first observe the enormous range of values for the Arrhenius pre-exponential term. To place these values in perspective it should be noted that examination of a large number of bridged biphenyls indicated a typical value for this factor of between approximately 10^{12} and 10^{15} sec^{-1}.[28] Therefore, unless a rather extreme explanation can be found for the enormity of these values, the calculations and/or data as a whole must again be considered suspect.

Finally, the range of values for the enthalpy and entropy of activation do not appear reasonable. In spite of the fact that those compounds which bear bulky halogen groups are severly crowded,

TABLE VI

COMPARISON OF PEAK HEIGHT RATIOS

Compound (Solvent)	Intensity Ratios (Inner/Outer)		$\frac{\text{Experimental Ratio}}{\text{Calculated Ratio}}$
	Calculated	Experimental	
H2E2 ($CDCl_3$)	3.14	4.96	1.58
H2E2 (C_6H_{12})	2.64	4.65	1.76
F2E2 ($CDCl_3$)	1.89	1.98	1.05
Cl2E2 ($CDCl_3$)	1.92	2.46	1.28
Br2E2 ($CDCl_2$)	2.09	2.86	1.37
I2E2 ($CDCl_3$)	3.79	7.00	1.85

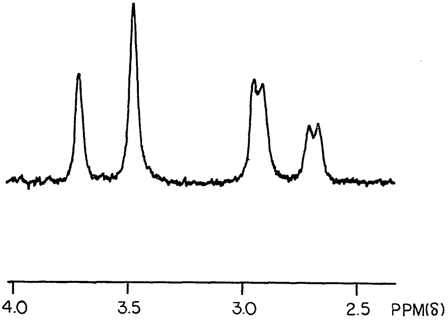
it is still difficult to rationalize entropies of activation as large as those obtained in these calculations. The magnitude of the enthalpies as well are not readily understood or explained. If in fact the parent hydrocarbon has an enthalpy of activation to racemization of only 10 or 12 kilocalories per mole then that is in sharp contrast to the value of approximately 23 kilocalories per mole previously obtained by Iffland and Siegel[13] via polarimetric techniques. Although it is in moderate agreement with the value of about 14 kilocalories per mole obtained by Sutherland and Ramsey[14] it is well below that normally required for isolation of optically active material under normal laboratory conditions of temperature and handling time. This would again be in contradiction to the work of Iffland and Siegel[13] as well as data which will subsequently be presented which appears to confirm their basic observations.

It thus appears that on any one or more of several points the NMR data and/or calculations herein presented are significantly vulnerable to criticism. Since the spectra themselves are reproducible the most likely area of concern would be the mathematical handling of the raw data. Since the kinetic treatment itself appears to be beyond reproach the spectral analysis would appear to have been faulty. If in fact this is correct then there are at least two possible explanations. The first is that this is truly an AB spin system, but that there is a perturbing influence upon the spectrum. Although biphenyls are relatively rigid molecules there is no reason to believe that normal torsional oscillations about bonds do not occur. If for example we consider a temperature dependent, torsional vibration about the pivot bond of a biphenyl molecule, it can readily be seen that the dihedral angle formed by the planes of the benzene rings would oscillate slightly about an angle of lowest potential energy. Simply stated the molecule would ''wobble'' slightly causing the dihedral angle to increase or decrease slightly. When the wobble for a given molecule becomes very large it inverts to its enantiomeric configuration. The concept of a wobble then is really only a matter of degrees when comparing it to conformationl inversion. Remembering that when complete inversion occurs, the relative positions of the diastereotopic benzylic hydrogens are interchanged we are presented with a very difficult question. Could the wobble be sufficient, such that although inversion does not occur, the benzylic hydrogen atoms begin to take on some of the character of their diastereotopic counterparts and therefore give rise to a peak whose envelope is really the weighted average of a large number of similar conformational states of the same configuration? Although this question is far more readily asked than answered it has been approached theoretically.[58,59] There can be no question that virtually any given sample of molecules is best described as a collection of molecules, which are distributed in a precise manner over a variety of energy states. However, what is not readily answered is whether or not the distribution, in the bridged biphenyls, is sufficiently wide to significantly and measurably broaden the envelope of the NMR signals in question. In the limit of an extremely broad distribution of energies this might best be described as a system in which the transmission coefficient, κ, is significantly different from unity. Unfortunately this type of consideration immediately becomes quite speculative, although some interesting extensions might be attempted using the reasoning of Glasstone et al.[52] for the cis-trans isomerization of simple olefins.

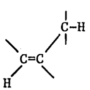
All of the foregoing presumes that the signals seen represent a perturbed, but none the less, a true AB system. As previously stated this was assumed on the basis of literature precedent[11] and the apparent spectral simplicity. It now appears plausible that physically these systems deviate significantly from that description and type of mathematical treatment. This deviation could occur in either or both of two ways. In the first there could be long range coupling of the 4 and 8 hydrogen atoms with their proximal benzylic hydrogens, such that one or both of the AB signals are affected. The extent of coupling would, of course, be a function of molecular geometry and the strength of interaction. A variant of this situation does in fact occur with the 4,8-difluoro compound (F2E2). In this case the interaction manifests itself as a splitting of each line of the high field doublet into a poorly resolved doublet (J_{HF} = -2.40 Hz, Figure 8). This coupling constant agrees well with the cis and trans coupling constants of 2.6 and 3.3 Hz respectively for $|J_{F-H_{Me}}|$ in the isomeric 1-fluoropropenes.[60] Although the lines of the low field doublet do not <u>appear</u> to be affected by this type of coupling, it may be that the coupling is sufficient to broaden the

FIGURE 8

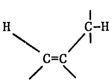
Benzylic Methylene Portion of F2E2 (60 MHz, -9.6°)



lines, but insufficient to cause discernable splitting. Returning to a consideration of the non-ring substituted parent hydrocarbon, it should be noted that there is no <u>observable</u> long-range coupling as in the fluoro compound, but the occurrence of line broadening due to this type of interaction is an unsettling possibility. A similar possibility would presumably exist for the chloro, bromo and iodo compounds as well. If this coupling does occur however, it is probably less significant here than in the fluoro compound based on the magnitude of the corresponding coupling constants



J_{HH} = -1.5 Hz[61]

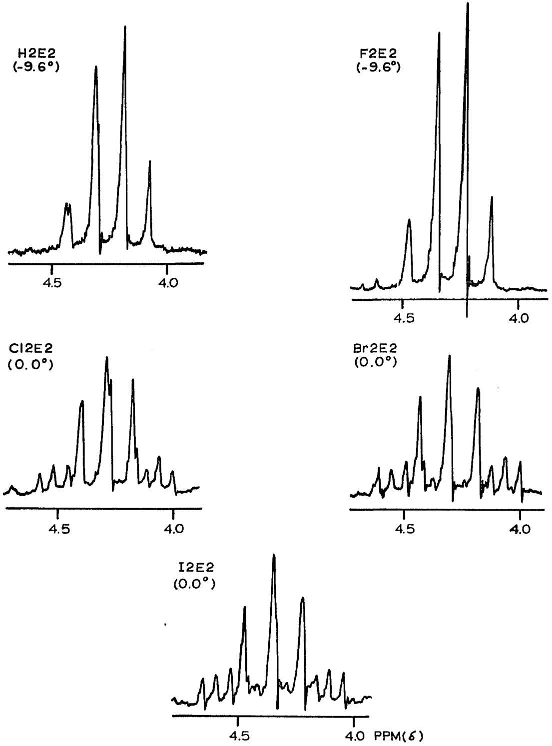


J_{HH} = -2 Hz[61]

Unfortunately, the possible existence or co-existence of a second type of four bond coupling must also be considered. In this second situation spectral complexity is caused by non-equivalence and therefore coupling of the hydrogen atoms of Position 5 with those of Position 7. Using proper nomenclature, the four benzylic hydrogens would be classified as an AA'BB' system which is tending toward the limit of an AB system. Using the method of Barfield[62] approximate values were calculated for $J_{AA'}$ and $J_{AB'}$. These values were used in the LAOCN 3 program in an attempt to refine all of the spectral parameters. Unfortunately no iterations could be performed to achieve this result, because the initially calculated spectrum consisted of numerous closely spaced lines such that specific transitions could not be assigned as would be necessary for a complete analysis of this nature. These calculations did serve to indicate however, that long range coupling constants of only a few tenths of a Hertz may be capable of significantly broadening an otherwise sharp line under these circumstances.

Despite the natural prejudices in favor of one's own data it should be stated at this point that because of a host of objections, the calculations presented and discussed herein do not appear to be trustworthy <u>as presented</u>. This is <u>not</u> to say that the spectra are ''wrong'', but rather, allowing for a bit of speculation, that the mathematical treatment is too simplistic and that a more sophisticated approach is required to properly analyze this group of compounds. Possibly supporting this contention is information obtained from other portions of the spectra. In particular there is the changing character of the quartet arising from the methylene hydrogen atoms of the carboethoxy groups. At ambient temperatures a clear and definite progression in spectral characteristics is observed in this portion of the spectrum in moving from the non-ring substituted parent hydrocarbon through the lower halogens to the 4,8-diiodo compound. In the parent compound these signals appear in an approximate ratio of 1:3:3:1 and seem to be that of a simple methylene which is spin coupled to a methyl group (Figure 9). However, as the size of the 4,8-substituents increases, this portion of the spectrum takes on an increasingly complex nature (Figure 9). In the limit of the iodinated compound,

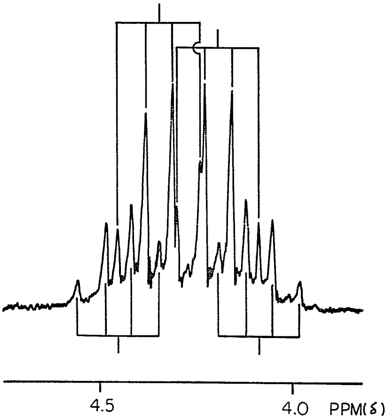
FIGURE 9



Methylene Portion of NMR Spectra of
Compound Studied (60 MHz)

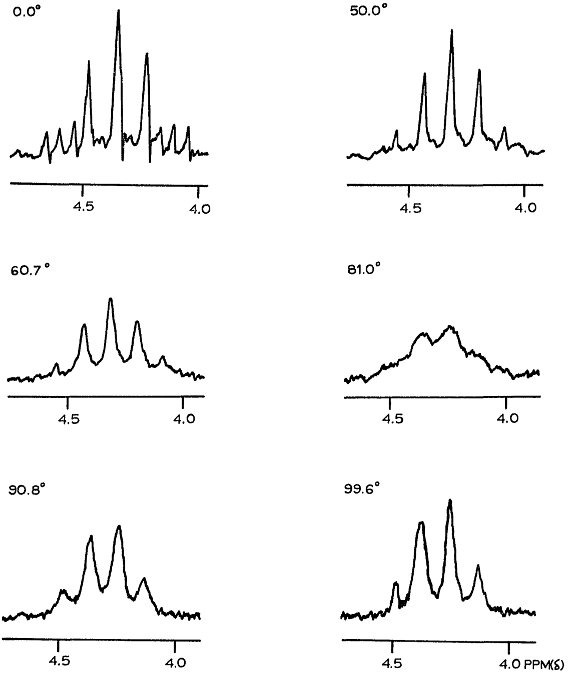
these signals appear as a highly complex series of lines. And yet despite this overall complexity there appears to be four distinct quartets present (Figure 10). Conceivably, these quartets represent a series of well defined and allowable positions for the carboethoxy groups, relative to each other, in a molecule whose large halogen substituents severely restrict the range of movement of these groups. If this is true, then this effect should be temperature dependent and should disappear completely at higher temperatures. Indeed as seen in Figure 11 this portion of the spectrum does become simplified at elevated temperatures and assumes a simple and relatively uncomplicated nature above approximately 90°. This simplification at elevated temperatures is similarly observed with the chloro and bromo compounds. It therefore does not seem to be an overstatement that in addition to any other perturbing influences seen in these spectra, that there may be additional steric factors present, which are altering the signals in a way which has not been considered in these calculations. The relative importance and precise nature of these steric interactions cannot be readily evaluated, but a complete disregard of their existence would seem to be foolish.

FIGURE 10



Ethoxy-Methylene Portion of the NMR Spectrum of I2E2 (100 MHz)
(ambient temperature)

FIGURE 11



Ethoxy-Methylene Portion of the NMR Spectra of I2E2 as a Function of Temperature (60 MHz)

POLARIMETRY DATA

The polarimetric observation of optically active compounds represents perhaps the earliest and least complicated method of examining racemization processes and kinetics. The reason for this becomes apparent upon examination of the equation relating the observed rotation to the concentration of material undergoing racemization. That is

$$\alpha = cl[\alpha]_t^\lambda \tag{10}$$

where, α is the observed rotation; l, the path length of the cell in decimeters; c, the solute concentration in grams per milliliter; and $[\alpha]_t^\lambda$, the specific rotation of the compound in the specified solvent at temperature and using light of wavelength λ to make the observation. Since $[\alpha]_t^\lambda$ is equal in magnitude, but opposite in sign for optical antipodes the observed rotation, α, is in reality the weighted average of these two contributing factors. Since the specific rotation of enantiomers is equal, the observed rotation may be taken as a measure of the relative amounts of the enantiomers present. Thus any changes in the observed rotation reflect changes in the relative amounts of the two isomers present. While NMR and most other instrumental techniques ''look at'' all of the molecules in the sample, polarimetric techniques effectively measure only the absolute quantity of the predominant enantiomer which is present in excess of the lesser enantiomer. Since the stereochemical inversion under consideration here is presumed to be a simple reversible first order reaction with the same rate constant for both the forward and reverse reactions, the rate may be expressed in terms of the initial and instantaneous observed rotations, α_o, and α_t, respectively.[53] That is

$$k_{INV} = \frac{1}{2t} \log_e(\alpha_o/\alpha_t) \qquad (11)$$

where t is the time and k_{INV} the rate constant for inversion. This rate constant for inversion may also be obtained from the NMR data and is related to the rate constant for racemization as follows:

$$k_{RAC} = 2k_{INV} \qquad (12)$$

As previously indicated, unexpected difficulties arose in the course of the deamination reaction which was used to prepare the final material in an active form. As a result, a fewer than desired number of kinetic runs could be performed. The raw data as obtained in these runs are given in Appendix C. The first important consideration with respect to these data, is that the observed rotation in each case goes to zero. This observation supports the position that the material under study was free of optically active, but nonlabile impurities. Examination of Figures 12-14 indicate that the observed rotation changes in a smooth and predictable manner. This observation indicates the absence of a second optically active and labile compound, but whose rate of racemization is significantly different from that of the first. A least squares analysis was performed on these data and the rate constants so obtained are given in Table VII. All runs were carried out in cyclohexane and the rate

FIGURE 12

Racemization Kinetics of H2E2 at 15.8°

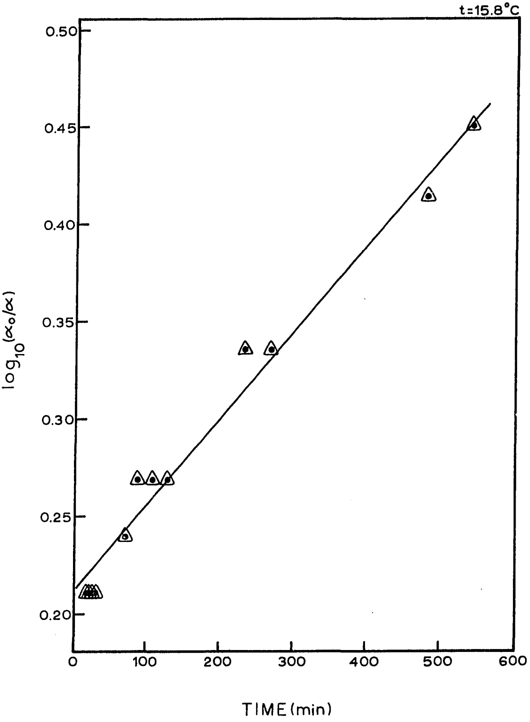


FIGURE 13

Racemization Kinetics of H2E2 at 25.0°

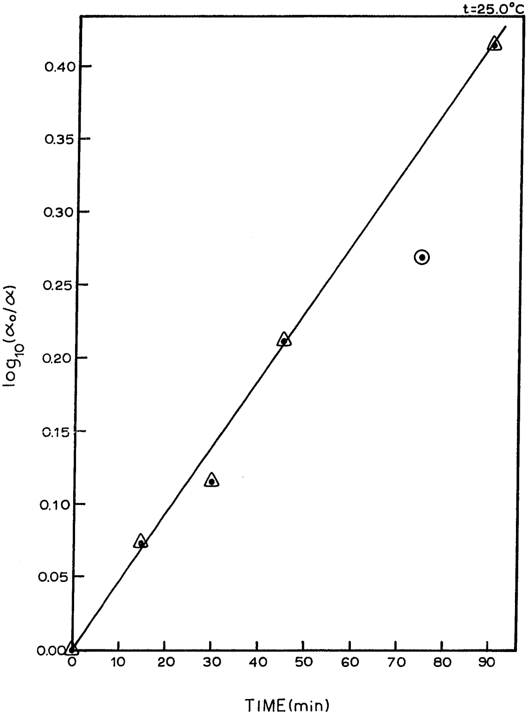
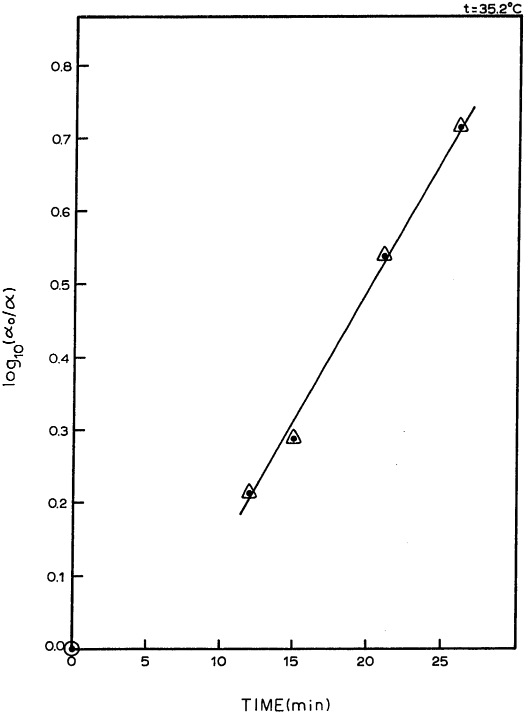


FIGURE 14

Racemization Kinetics of H2E2 at 35.2°



constants presented are those for inversion so as to facilitate comparison with the values obtained from the NMR data.

TABLE VII

POLARIMETRIC RATE CONSTANTS FOR COMPOUND XII

Temperature (°)	$k_{INV}(\sec^{-1})$
15.8	8.91×10^{-6}
25.0	8.90×10^{-5}
35.2	7.04×10^{-4}

Even a cursory examination of these values indicates that they differ by many orders of magnitude from those which one would expect from the NMR data. As with the NMR data a plot of $\log_{10}$ (k_{INV}/T) versus $1/T$ was prepared and from this plot (Figure 15) the values of $\Delta H^{\ddagger}_{INV}$ and $\Delta S^{\ddagger}_{INV}$ were obtained in the manner of Eq. 9 as before. The calculated values are as follows:

$$\Delta H^{\ddagger}_{INV} = 39.27 \text{ kcal/mol}$$

$$\text{and} \quad \Delta S^{\ddagger}_{INV} = 54.44 \text{ e.u.}$$

Due to the difficulty of interpreting the individual enthalpies and entropies, the free energy of activation at 25° has been calculated for each data set and these are presented in Table VIII. Examination of these values indicate the serious discrepancy between the results of the NMR data and those of the polarimetry data. The values of 13 and 15 kilocalories per mole obtained by

FIGURE 15

Polarimetric Kinetics of H2E2

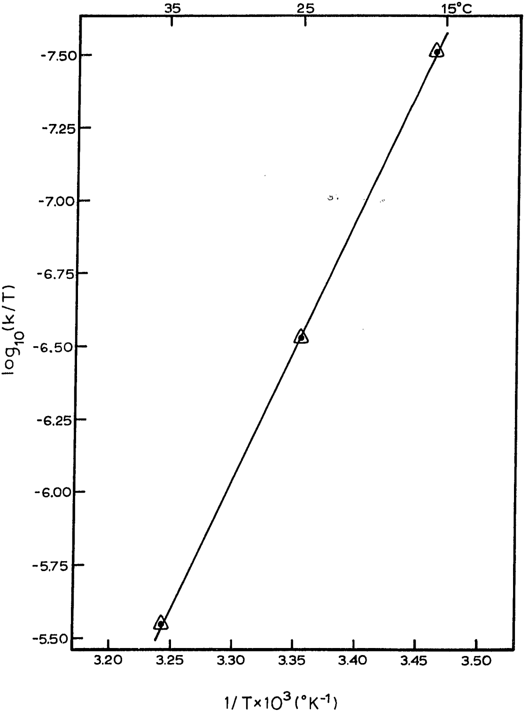


TABLE VIII

FREE ENERGIES OF ACTIVATION FOR INVERSION AT 25°

Compound	$\Delta G^{\ddagger}_{INV}$ (kcal/mol)
H2E2 (NMR, $CDCl_3$)[*]	15.19 ± 1.88
H2E2 (NMR, $CDCl_3$)[**]	13.13 ± 2.59
H2E2 (NMR, C_6D_{12})[*]	15.25 ± 6.19
H2E2 (NMR, C_6D_{12})[**]	13.39 ± 1.89
F2E2 (NMR, $CDCl_3$)	15.02 ± 0.89
Cl2E2 (NMR, $CDCl_3$)	20.10 ± 1.73
Br2E2 (NMR, $CDCl_3$)	20.79 ± 1.78
I2E2 (NMR, $CDCl_3$)	21.30 ± 1.66
H2E2 (Polarimetry, C_6H_{12})	23.04

[*] Temperature: -9.6° to 15.6°

[**] Temperature: 22° to 99.6°

NMR techniques are clearly below those at which one would generally expect to be able to isolate and observe racemization kinetics of an optically active molecule. Conversely, the value of 23.04 kilocalories per mole is entirely reasonable for a molecule of this type[11,28,54] and is also consistent with the apparent ease with which this material racemized.

Since the parent compound (XII) could reproducibly be isolated in an active form, and since the polarimetric calculations require no assumptions of behavior as in the NMR analysis, it must again be concluded that one or more extraneous effects are tainting the reliability of the above NMR analysis and results. Further, it should be noted that these results support the polarimetric work of Iffland and Siegel[13] (ΔG_{RAC} approximately 23 kcal/mol at 32.5°) while casting very serious doubt on the correctness of the interpretation of the NMR data presented by Sutherland and Ramsey[14] and paralleled in this examination.

CONCLUSIONS

Initially the goal of this work was twofold, the first of which was to resolve the apparent conflict between the polarimetry data of Iffland and Siegel[13] and the NMR work of Sutherland and Ramsey.[14] As presented here there now appear to be compelling reasons to distrust any simple AB system analysis of NMR data from these compounds and instead to rely on the polarimetric values. At the very least the polarimetric results appear sufficiently accurate to be used as a standard for the relative success or failure of more sophisticated NMR calculation techniques.

The companion goal of this work was to systematically study and if possible quantify the magnitude of the buttressing effect as observed in a series of closely related compounds. The concept of a buttressing effect,[9,63] which is a subtype of the organic chemist's most invoked of all effects, namely steric hindrance, is undoubtedly sound. The problem, as with so many other ''obvious'' and ''intuitive'' concepts, is that a quantitative backing for these beliefs is not always available. Unfortunately this lack of knowledge makes the use of the concept somewhat difficult since its relative importance is unknown.

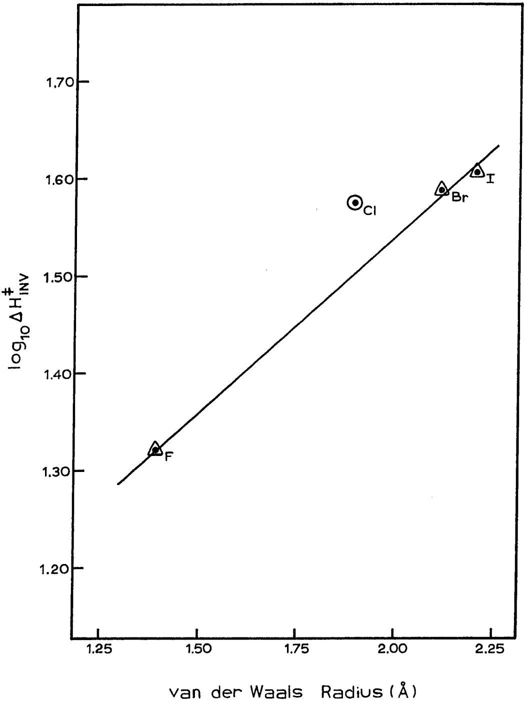
With this realization in mind the temperature dependent NMR spectra of a series of 4,8-dihalo-dibenzo-cycloheptadienes were examined. Unfortunately, as presented above the mode of spectral analysis was faulty and a more accurate analysis was not available. If by making the assumption that the errors are systematic <u>and</u> of approximately the same order of magnitude, then the trend in the values is reasonably valid while the individual values are not.

In a totally serendipitous manner the search for a trend in the data was begun by plotting the enthalpy of activation for inversion versus the van der Waals interference radius[9] of the 4,8 substituents. Upon examination of this plot it was found that the points formed a smooth trend and that in addition a smooth trend was again obtained when the entropies of activation for inversion were plotted against their respective van der Waals radii. In an attempt to linearize this type of plot the logarithm of the enthalpy was used instead of the enthalpy itself and as seen in Figure 16 a straight line was in fact obtained for the points representing fluorine, bromine, and iodine, while the point for chlorine deviated significantly.

Subsequent to this observation, support for this type of mathematical tinkering was received from Nilsson and co-workers.[64] They were examining the NMR spectra of a series of ring substituted 1,3,5-trineopentylbenzenes and found that a plot of the free energy for intramolecular rotation versus the van der Waals volume, V_w, gave ''a smooth curve passing through the points for H, F, Cl, Br, and I.'' Pursuing this further they mention in a footnote that ''a plot of ΔG vs. ln V_w gave an excellent straight line ($r = 0.999$).'' With this in mind we re-examined our data by this

FIGURE 16

Enthalpy of Activation versus Buttressing Atom Radius



technique (Figure 17). Although an excellent straight line (r = 0.999 was obtained in this manner for the Cl, Br, I and some selected H data points, the point for fluorine showed a deviation. Pressing the issue still further it was found that a simple linear plot of ΔG_{INV} at 25° versus V_w (Figure 18) also gave an excellent straight line.

The foregoing discussion was presented with considerable trepidation and with the full realization that virtually anything can be ''proven'' or ''related'' with sufficient mathematical obfuscations. Further no rigid attempt is being made to prove the physical significance, if any, of these plots. Rather a sincere attempt is being made to find an empirically useful relationship which might be of use in a predictive sense. On that basis the relative stability of pairs of compounds might be compared and discussed.

Having obtained this relationship, it now seems that what is needed next is an accurate set of thermodynamic parameters for any of these compounds. This is necessary because at that point the parameters of the other compounds in the series could hopefully be approximated with some degree of accuracy. Without this type of accurate data the magnitude of the buttressing effect can only be discussed in general and relative terms.

FIGURE 17

Free Energy of Activation versus $\log_e V_w$

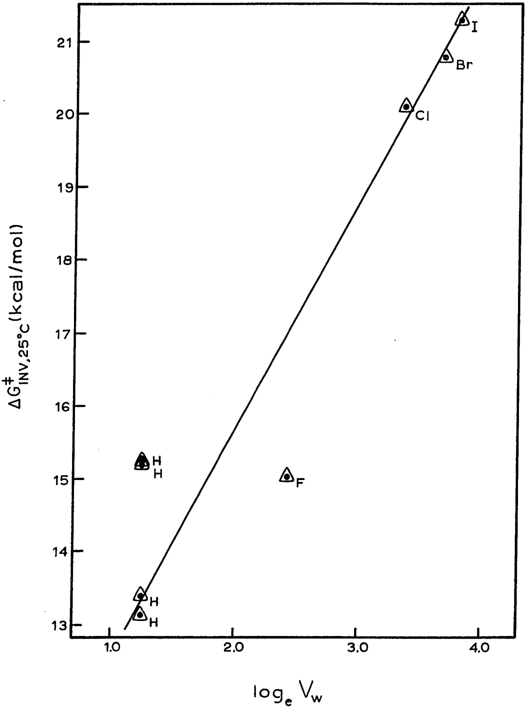
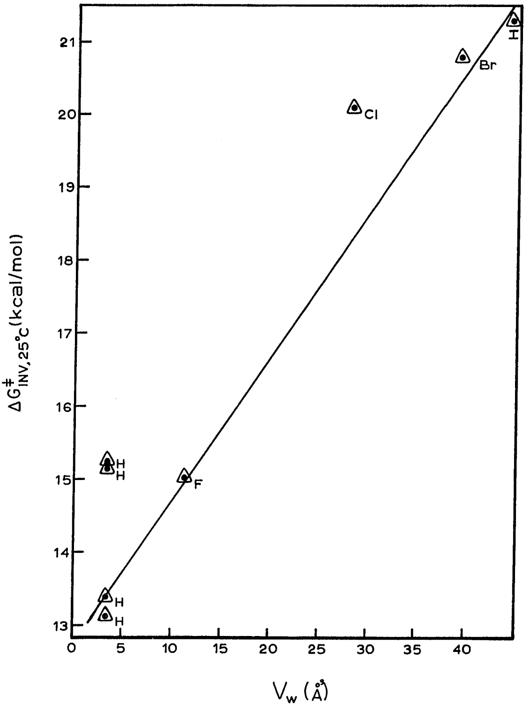


FIGURE 18

Free Energy of Activation versus Buttressing Atom Volume



SUMMARY

The temperature dependent nuclear magnetic resonance spectra of a series of 6,6-dicarbethoxydibenzo-[a,c] [1,3]-cycloheptadienes have been recorded and analyzed. The compounds studied were those bearing hydrogen, fluorine, chlorine, bromine or iodine atoms in the 4 and 8 positions of the ring system and the analysis of the position 5(7) benzylic hydrogen atoms was that of an AB spin system. Concurrently, the parent hydrocarbon, i.e. the 4,8-dihydrogen compound, was prepared in optically active form for racemization studies, from active 6,6'-dinitro-2,2'-diphenic acid.

After computation of the individual NMR rate constants for each compound at each temperature, the enthalpy and entropy of activation for inversion were calculated. Using the active compound, the rate of racemization was polarimetrically determined at three temperatures over the range of 15.8° to 35.2°. Using these data the free energy of activation for inversion at 25° was found to be 23.04 kilocalories per mole while the value obtained from the NMR data was between 13.13 and 15.25 kilocalories per mole. Finally the individual enthalpies and entropies were calculated. The enthalpy, $\Delta H^{\ddagger}_{INV}$, for the parent hydrocarbon as calculated from the NMR data was in the range of 9.66 to 12.52 kilocalories per mole while the entropy, $\Delta S^{\ddagger}_{INV}$, was between -18.56 and -2.03 entropy units. These values were in sharp contrast to the corresponding values of 39.27 kilocalories per mole and 54.44 entropy units obtained from

the analysis of the polarimetric data. After considering several possible explanations it was decided that analysis of the NMR data as an AB spin system was incorrect and that a more sophisticated approach is required. Unfortunately this was not possible at the time.

A comparison of similarly calculated values for the halogenated members of this series showed that by suitable graphical methods the variation of activation parameters with the substituent size could be related. However, since the mathematical method of analysis was overly simplistic, only the general trend and not the exact magnitude of this variation could be discussed.

APPENDIX A

NMR DATA

H2E2 in chloroform-d

Temperature (°)	Line Frequencies (Hz)[*]	ω_0(Hz)[*]	ω(Hz)
-9.6	165.7 179.5 192.4 206.2	0.35	2.02
-4.9	165.7 179.5 192.1 205.8	0.38	2.58
0.0	----- 178.6 190.0 -----	0.38	4.84
5.1	----- 179.4 191.0 -----	0.40	3.80
7.5	----- 180.0 190.0 -----	0.42	7.20
11.9	----- 180.0 190.0	0.43	6.54
15.6	183.8	0.30	10.8
22.0	185.0	0.49	7.82
28.8	185.0	0.39	4.90
35.3	184.3	0.39	4.96
40.8	185.0	0.48	2.19
60.7	184.2	0.38	0.92

[*] In this and following tables in Appendix A, ω_0 is measured at TMS signal (sweep width: 50 Hz; sweep time: 250 sec) and ω (Hz) is average of width of two when members of the AB quartet (sweep width: 100 Hz; sweep time: 500 sec) except for F2E2. Line frequencies are measured from spectra having 500 Hz sweep width and 500 sec sweep time.

H2E2 in cyclohexane-d_{12}

Temperature (°)	Line Frequencies (Hz)	ω_0(Hz)	ω(Hz)
1.9	159.5 172.3 187.9 200.7	0.42	5.12
4.7	160.3 172.7 187.0 199.4	0.44	6.00
6.5	----- 172.5 188.1 -----	0.32	5.30
9.7	----- 173.7 186.5 -----	0.44	8.70
20.5	180.6	0.41	16.6
27.8	180.0	0.42	8.60
34.5	181.2	0.41	6.24
43.0	181.0	0.40	3.60
52.5	181.0	0.31	1.98

F2E2 in chloroform-d

Temperature (°)	Line Frequencies (Hz)	ω_0(Hz)	ω(Hz)
-9.6	159.2 161.6 173.9 176.3 208.2 222.9	0.40	2.20
-4.9	192.5 194.6 207.1 209.3 241.4 256.0	0.40	2.34
0.0	~160.0 ~162.2 ~174.6 ~208.5 223.1	0.41	2.78
5.1	160.6 175.0 208.4 222.8	0.42	3.64
11.9	160.0 174.7 208.0 222.7	0.45	5.58
22.0	----- 204.0 232.2 -----	0.39	18.2
28.8	----- 200.5 216.7 -----	0.38	37.6
35.3	----- ~181 ~201 -----	0.41	43.6
40.8	190.9	0.39	13.5
60.7	191.0	0.42	9.40
99.6	191.1	0.48	2.10

C12E2 in chloroform-d

Temperature (°)	Line Frequencies (Hz)	ω_o(Hz)	ω(Hz)
0.0	169.4 184.0 215.8 230.4	0.48	1.68
40.8	169.0 183.6 216.2 230.8	0.35	2.22
50.0	168.8 183.4 216.0 230.4	0.40	3.11
69.8	----- 184.5 214.5 -----	0.38	14.9
81.0	----- 190.1 204.9 -----	0.41	40.6
90.8	199.3	0.41	18.4
99.6	200.0	0.48	9.46

Br2E2 in chloroform-d

Temperature (°)	Line Frequencies (Hz)	ω_0(Hz)	ω(Hz)
0.0	174.3 189.0 214.5 229.2	0.42	1.66
40.8	173.8 188.3 214.9 229.4	0.33	1.95
50.0	173.7 188.2 214.9 229.5	0.32	2.24
60.7	173.7 188.3 215.0 229.6	0.40	3.46
69.8	----- 187.7 214.0 -----	0.32	7.20
81.0	----- 191.5 211.9 -----	0.38	37.8
90.8	200.3	0.42	24.6
99.6	201.4	0.40	10.4

I2E2 in chloroform-d

Temperature (°)	Line Frequencies (Hz)	ω_0(Hz)	ω(Hz)
0.0	182.1 196.7 206.0 220.6	0.35	1.76
40.8	181.6 196.0 206.2 220.6	0.32	1.40
50.0	181.5 196.0 206.4 220.9	0.32	1.60
60.7	----- 196.0 206.6 -----	0.32	2.38
69.8	----- 196.5 206.7 -----	0.42	4.32
81.0	----- 197.7 204.3 -----	0.38	34.8
90.8	201.0	0.33	8.40
99.6	202.0	0.32	4.72

APPENDIX B

Calculated Rate Constants for Inversion from NMR Data

H2E2 in chloroform-d

$T_c \approx 16°$

Temperature (°)	Rate (sec^{-1})*	
-9.6	4.67 ± 0.23	
-4.9	6.16 ± 0.23	
0.0	$1.25 \pm 0.02 \times 10^1$	
5.1	9.51 ± 0.23	
7.5	$1.90 \pm 0.02 \times 10^1$	
11.9	$1.71 \pm 0.02 \times 10^1$	
15.6	$2.94 \pm 0.02 \times 10^1$	(if $T < T_c$)
	4.98×10^2	(if $T = T_c$)
	$7.71 \pm 0.14 \times 10^2$	(if $T > T_c$)
22.0	$1.11 \pm 0.04 \times 10^3$	
28.8	$1.80 \pm 0.06 \times 10^3$	
35.3	$1.77 \pm 0.13 \times 10^3$	
40.8	$4.74 \pm 1.01 \times 10^3$	
60.7	$1.50 \pm 1.88 \times 10^3$	

* Calculated rate constant for inversion.

H2E2 in cyclohexane-d_{12}

$T_c \approx 21°$

Temperature (°)	Rate (sec^{-1})*	
1.9	8.63 ± 0.55	
4.7	$1.02 \pm 0.06 \times 10^1$	
6.5	9.14 ± 0.55	
9.7	$1.52 \pm 0.06 \times 10^1$	
20.5	$2.97 \pm 0.06 \times 10^1$	(if $T < T_c$)
	4.72×10^2	(if $T = T_c$)
	$6.45 \pm 0.12 \times 10^2$	(if $T > T_c$)
27.8	$1.28 \pm 0.05 \times 10^3$	
34.5	$1.79 \pm 0.09 \times 10^3$	
43.0	$3.26 \pm 0.03 \times 10^3$	
52.5	$6.25 \pm 0.10 \times 10^3$	

* Calculated rate constant for inversion.

F2E2 in chloroform-d

$T_c \approx 41°$

Temperature (°)	Rate (sec^{-1})[*]
-9.6	3.67 ± 0.61
-4.9	3.95 ± 0.61
0.0	4.83 ± 0.61
5.1	6.56 ± 0.61
11.9	$1.05 \pm 0.06 \times 10^1$
22.0	$3.63 \pm 0.06 \times 10^1$
35.3	$8.80 \pm 0.06 \times 10^1$
40.8	5.94×10^2
60.7	$3.57 \pm 0.12 \times 10^3$
99.6	$1.98 \pm 0.31 \times 10^4$

[*] Calculated rate constant for inversion.

C12E2 in chloroform-d

$T_c \approx 81°$

Temperature (°)	Rate (sec^{-1})*
0.0	2.43 ± 0.61
40.8	3.78 ± 0.61
50.0	5.48 ± 0.61
60.7	$1.12 \pm 0.06 \times 10^1$
69.8	$2.94 \pm 0.06 \times 10^1$
81.0	5.86×10^2
90.8	$1.67 \pm 0.03 \times 10^3$
99.6	$3.35 \pm 0.11 \times 10^3$

* Calculated rate constant for inversion.

Br2E2 in chloroform-d

$T_c \approx 86°$

Temperature (°)	Rate (sec^{-1})[*]
0.0	2.43 ± 0.59
40.8	3.18 ± 0.59
50.0	3.77 ± 0.59
60.7	6.00 ± 0.59
69.8	$1.35 \pm 0.06 \times 10^1$
81.0	$7.34 \pm 0.06 \times 10^1$
90.8	$9.53 \pm 0.12 \times 10^2$
99.6	$2.31 \pm 0.07 \times 10^3$

[*] Calculated rate constant for inversion.

I2E2 in chloroform-d

$T_c \approx 91°$

Temperature (°)	Rate (sec^{-1})[*]
0.0	2.43 ± 0.52
40.8	1.87 ± 0.52
50.0	2.21 ± 0.52
60.7	3.56 ± 0.52
69.8	6.73 ± 0.52
81.0	5.95 ± 0.05 x 10^1
90.8	7.87 ± 0.28 x 10^2
99.6	1.44 ± 0.09 x 10^3

[*] Calculated rate constant for inversion.

APPENDIX C

Racemization of H2E2 in Cyclohexane

T = 15.8°

1 = 2 dm, λ = Na D line, conc. = ?

Time (min.)	α^{*}
0	0.26
20	0.16
23	0.16
26	0.16
32	0.16
75	0.15
90	0.14
110	0.14
130	0.14
234	0.12
270	0.12
480	0.10
540	0.09
24 hrs.	0.00

[*] α corrected for instrument error in zero reading.

T = 25.0°

1 = 2 dm, λ = Na D line, conc. = ~100 mg/ml by UV

Time (min.)	α*
0	0.26
15	0.22
30	0.20
45	0.16
75	0.14
90	0.10
12 hrs.	0.00

*α corrected for instrument error in zero reading.

T = 35.2°

1 = 2 dm, λ = Na D line, conc. = ?

Time (min.)	α*
0	0.62
12	0.38
15	0.32
21	0.18
26	0.12
35	0.00
45	0.00

*α correct for instrument error in zero reading.

BIBLIOGRAPHY

1. G.H. Christie and J. Kenner, J. Chem. Soc., 121, 614 (1922).
2. H. Sachse, Ber., 21, 2530 (1880).
3. F. Kaufler, Ann., 351, 151 (1907); Ber., 40, 3250 (1907); Ber., 40, 3253 (1907).
4. J. Schmidt and A. Kämpf, Ber., 36, 3745 (1903).
5. E.E. Turner and R.J.W. LeFevre, Chem. Ind. (London), 45, 831 (1926), Chem. Ind. (London), 45, 883 (1926).
6. F. Bell and J. Kenyon, Chem. Ind. (London), 45, 864 (1926).
7. W.H. Mills, Chem. Ind. (London), 45, 884 (1926).
8. R. Adams and H.C. Yuan, Chem. Rev., 12, 261 (1933).
9. R.L. Shriner, R. Adams and C.S. Marvel in ''Organic Chemistry'', Vol. 1, H. Gilman, Ed., John Wiley and Sons, Inc., New York, New York, 1938, p. 268ff.
10. R. Adams and N. Kornblum, J. Amer. Chem. Soc., 63, 188 (1941).
11. D.M. Hall in ''Progress in Stereochemistry'', Vol. 4, B.J. Aylett and M.M. Harris, Eds., Butterworth and Co., Ltd., London, 1969, Chapter 1.
12. D.C. Iffland and H. Siegel, J. Org. Chem., 21, 1056 (1956).
13. D.C. Iffland and H. Siegel, J. Amer. Chem. Soc., 80, 1947 (1958).
14. I.O. Sutherland and M.V.J. Ramsey, Tetrahedron, 21, 3401 (1965).
15. L.J. Bellamy, ''The Infrared Spectra of Complex Molecules'', 2nd Ed., John Wiley and Sons, Inc., New York, New York, 1959.
16. F.C. Whitmore and P.J. Culhane, J. Amer. Chem. Soc., 51, 602 (1929).
17. F.C. Whitmore, P.J. Culhane, and H.T. Neher in ''Organic Synthesis'', Col. Vol. I, 2nd Ed., Henry Gilman, Ed., John Wiley and Sons, Inc., New York, New York, 1932, pp. 56-8.

18. P.J. Culhane in ''Organic Synthesis'', Col. Vol. I, 2nd Ed., Henry Gilman, Ed., John Wiley and Sons, Inc., New York, New York, 1932, p. 126.

19. C.W. James, J. Kenner and W.V. Stubbings, J. Chem. Soc., 117, 773 (1920).

20. A.W. Ingersoll and J.R. Little, J. Amer. Chem. Soc., 56, 2123 (1934).

21. J. Kenner and W.V. Stubbings, J. Chem. Soc., 119, 593 (1921).

22. W. Theilacker and H. Winkler, Chem. Ber., 87, 690 (1954).

23. P. Newman, P. Rutkin and K. Mislow, J. Amer. Chem. Soc., 80, 465 (1958).

24. J. Kenner and W.V. Stubbings, J. Chem. Soc., 119, 599 (1921).

25. S. Stallberg-Stenhagens, J. Amer. Chem. Soc., 69, 2568 (1947).

26. J. Cason and R.D. Smith, J. Org. Chem., 18, 1201 (1953).

27. D.V. Banthorpe and B.V. Smith in ''The Chemistry of the Acyl Halides'', Saul Patai, Ed., Interscience Publishers, Inc., New York, New York, 1972, Chapter 8.

28. D.M. Hall and T.M. Poole, J. Chem. Soc. (B), 1034 (1966).

29. H. Siegel, Ph.D. Dissertation, West Virginia University, Morgantown, West Virginia, 1956.

30. Y.H. Chiang, M.A. Thesis, Western Michigan University, Kalamazoo, Michigan, 1961.

31. J.B. Cohn and J. Miller, J. Chem. Soc., 85, 1627 (1904).

32. E.B. Blues and D. Bryce-Smith, Chem. Ind. (London), 1533 (1960).

33. D.C. Iffland and B.E. Anderson, 1962, unpublished data.

34. D.C. Iffland and R. O'Boyle, 1967, unpublished data.

35. D.C. Iffland and A.E. Nader, 1963, unpublished data.

36. R.L. Augustine, ''Catalytic Hydrogenation'', Marcel Dekker, Inc., New York, New York, 1965, p. 102.

37. H. Zollinger, ''Azo and Diazo Chemistry'', Interscience Publishers, Inc., New York, New York, 1961, p. 153.

38. K. Mislow and A.J. Gordon, J. Amer. Chem. Soc., 85, 3521 (1963).

39. N. Kornblum in ''Organic Synthesis'', Vol. 2, R. Adams, Ed., John Wiley and Sons, Inc., New York, New York, 1944, p. 278.

40. M.S. Newman and D. Lednicer, J. Amer. Chem. Soc., 78, 4765 (1956).

41. J.A. Pople, W.G. Schneider and H.J. Bernstein, ''High Resolution Nuclear Magnetic Resonance'', McGraw Hill, New York, New York, 1959, p. 220.

42. H. Strehlow in ''Techniques of Organic Chemistry'', Vol. 8, A. Weissberger, Ed., Interscience Publishers, Inc., New York, New York, 1963, p. 865.

43. I.O. Sutherland in ''Annual Reports on NMR Spectroscopy'', Vol. 4, E.F. Mooney, Ed., Academic Press, New York, New York, 1971, pp. 71-235.

44. J.E. Anderson, Quart. Rev. (London), 19, 426 (1965).

45. L.W. Reeves in ''Advances in Physical Organic Chemistry'', Vol. 3, V. Gold, Ed., Academic Press, Inc., New York, New York, 1965, p. 187.

46. S. Alexander, J. Chem. Phys., 37, 967 (1962).

47. M. Oki and H. Iwanura, Tetrahedron, 24, 2377 (1968).

48. R.J. Kurland, M.B. Rubin and W.B. Wise, J. Chem. Phys., 40, 2426 (1964).

49. M. Oki, H. Iwanura and N. Hayakawa, Bull. Chem. Soc. Jap., 37, 1865 (1964).

50. H.G. Schmid, H. Friebolin, S. Kabuss and R. Mecke, Spectrochim. Acta, 22, 623 (1966).

51. P.K. Korver, P.J. van der Haak and Th. J. DeBoer, Tetrahedron, 22, 3157 (1966).

52. S. Glasstone, K.J. Laidler and H. Eyring, ''The Theory of Rate Processes'', McGraw Hill Book Co., New York, New York, 1941.

53. F.W. Cagle, Jr. and H. Eyring, J. Amer. Chem. Soc., 73, 5628 (1951).

54. D.M. Hall and M.M. Harris, J. Chem. Soc., 490 (1960).

55. S. Castellano and A.A. Bothner-By, Quantum Chemistry Program Exchange (Q.C.P.E.), Department of Chemistry, Indiana University, Bloomington, Indiana, 47401, No. 111.

56. D.F. DeTar in ''Computer Programs for Chemistry'', Vol. 3, D. F. DeTar, Ed., W.A. Benjamin, New York, New York, 1969, p. 6.

57. G. Binsch in ''Topics in Stereochemistry'', Vol. 3, E.L. Eliel and N.L. Allinger, Ed., Interscience Publishers, New York, New York, 1968, p. 121.

58. J.O. Halford, J. Chem. Phys., 16, 410 (1948).

59. R.A. Newmark and C.H. Sederholm, J. Chem. Phys., 43, 602 (1965).

60. R.A. Baudet and J.D. Baldeschwieler, J. Mol. Spectrosc., 9, 30 (1962).

61. E.D. Becker in ''High Resolution NMR, Theory and Chemical Applications'', Academic Press, Inc., New York, New York, 1969, p. 97.

62. M. Barfield, J. Chem. Phys., 41, 3825 (1964).

63. E.L. Eliel, ''Stereochemistry of Carbon Compounds'', McGraw Hill Book Co., New York, New York, 1962, pp. 162-163.

64. B. Nilsson, P. Martinson, K. Olsson and R.E. Carter, J. Amer. Chem. Soc., 96, 3190 (1974).

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