

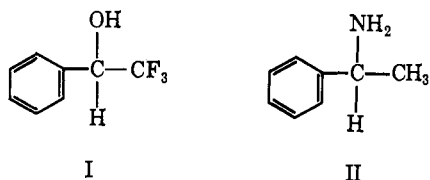
The Nonequivalence of Physical Properties of Enantiomers in Optically Active Solvents. Differences in Nuclear Magnetic Resonance Spectra. I

Sir:

We consider it manifest that enantiomers must be in different average environments when in an optically active solvent. In asymmetrical environments, enantiomers need not possess identical properties toward symmetrical agents. Such differences in behavior toward symmetrical agents may be detected by those physical measurements which are sensitive environmental probes. Nmr spectroscopy falls into this category and we have used this technique to demonstrate spectral differences between enantiomers. A recent postulation¹ of this effect prompts us to give a preliminary account of our findings.

A priori, it was thought that strong solute-solvent interactions, such as hydrogen bonding, dipolar attraction, and charge-transfer interaction, would lead to the greatest difference in average spatial environment of the enantiomers. Moreover, it seemed likely that, for the purpose of nmr measurements, the presence of a group of high diamagnetic anisotropy near the solvent asymmetric center would maximize the probability that a difference in average spatial environment would lead to a difference in average magnetic environment, thus enabling one to distinguish between enantiomers. Incorporation of fluorine into the solute offers a twofold advantage. Not only do the chemical shifts of fluorine resonances occur over a wider range than do those of hydrogen (and hence are expected to be more sensitive environmental probes), but the spectra are uncluttered by solvent proton resonances. These criteria were used in selecting solute-solvent pairs for study.

In carbon tetrachloride, the fluorine resonance of racemic 2,2,2-trifluoro-1-phenylethanol (I) [bp 93° (15 mm), n_D^{25} 1.4593, reported² bp 87° (13 mm) n_D^{25}



1.4590] appears as a doublet ($|J|_{HF} = 6.7$ cps) centered at +4445 cps from internal fluorotrichloromethane.³ No fine structure is evident. In pyridine, the resonance appears as a doublet of triplets ($|J|_{HF} = 7.3$ cps $|J|_{H'F} = 0.7$ cps) centered at +4387 cps from internal fluorotrichloromethane. The fine structure must result from long-range coupling of the fluorines with protons on the aromatic ring.⁴ However, in optically active α -

(1) M. Raban and K. Mislow, *Tetrahedron Letters*, No. 48, 4249 (1965).

(2) R. Stewart and R. Van der Linden, *Can. J. Chem.*, **38**, 399 (1960).

(3) All nmr spectra were determined by means of a Varian A-56/60A spectrometer using ca. 25% solutions.

(4) The appearance of long-range coupling in basic solvents and its absence in neutral solvents such as carbon tetrachloride and 2-octanol suggests that the enhanced acidity of the trifluoromethylcarbinol ($pK = 11.8$)² [see also B. L. Dyatkin, E. P. Machalina, and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965)] causes the oxygen to have considerable negative character when solvated by polar basic solvents. Both the consequent change in electronic structure of intervening bonds and possible changes in conformer populations (arising from the increased size of the solvated oxygen atom) could lead to enhanced long-range coupling.

phenethylamine (II) ($[\alpha]_D^{25} -37.0^\circ$ (neat), reported⁵ $[\alpha]_D^{25} -40.3^\circ$) the fluorine resonances appear as two sets of doublets, each of $|J|_{HF} = 7.2$ cps and centered at +4374 and +4376 cps from internal fluorotrichloromethane. The two sets were of equal intensity as expected for a racemate. Additionally, each of the four lines is further split into a triplet ($|J|_{H'F} = 0.7$ cps) by long-range coupling in the basic solvent. The fluoroalcohol can be recovered unchanged.

When racemic α -phenethylamine is used as solvent, only a doublet ($|J|_{HF} = 7.2$ cps) of triplets ($|J|_{H'F} = 0.7$ cps) is observed. The smaller splitting again appears to be long-range coupling with (presumably) the *ortho* aromatic protons. The coalescence of the spectra of the enantiomers suggests that, in this case, the exchange of (+) and (-) solvent partners by solvated fluoroalcohol is sufficiently fast so that all fluoroalcohol molecules have the same average magnetic environment.⁶

A sample of partially resolved⁷ ($[\alpha]_D^{25} +2.19^\circ$ (neat)) fluoroalcohol in *l*- α -phenethylamine again showed two sets of doublets plus triplet fine structure, but now the highest field set was discernibly more intense than the low-field set. When *d*- α -phenethylamine was used as solvent, the low-field set became the most intense. From measurements of the relative intensities of the two sets, it appears that this fluoroalcohol sample is a 47:53 \pm 0.6 mixture of enantiomers. The specific rotation of the dextrorotatory enantiomer is accordingly calculated to be 36.5 \pm 7.5°.⁸

To our knowledge, this is the first reported example of the determination of optical purity by nmr using an asymmetric solvent to render the spectra of the enantiomers nonequivalent.

(5) W. Theilaker and H. G. Winkler, *Chem. Ber.*, **87**, 691 (1954).

(6) Should this exchange be slowed, a more complex spectrum might arise. In the simplest case, racemic solvent, (\pm), and racemic solute, DL, could form four 1:1 solvates: (+)-D, (-)-L, (+)-L, and (-)-D. The first and second solvates are enantiomeric as are the third and fourth. Each set could have different spectra however, for the sets are diastereomeric. Being diastereomeric, their stabilities may differ and the populations of the two sets may be unequal. Interactions more complex than 1:1 could give rise to additional spectrally nonequivalent species ((+) (+)-D, (+) (+)-L, (+) (-)-D, etc.). Temperature studies and labeling experiments are being carried out to elucidate this point further.

(7) This sample was produced by reduction of the trifluoroacetophenone with a complex of lithium aluminum hydride-*l*- α -phenethylamine in tetrahydrofuran.

(8) Professor Harry Mosher has informed us that the maximum possible rotation of this enantiomer is 41.2°.

W. H. Pirkle

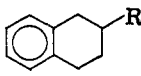
Noyes Chemical Laboratory
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The Reductive Amination of Polynuclear Aromatic Hydrocarbons. A Side Reaction of the Birch Reduction

Sir:

We wish to report the discovery of conditions which allow reductive amination of polynuclear aromatic hydrocarbons to tertiary or secondary amines under Birch reduction conditions as shown for the preparation of N-(1,2,3,4-tetrahydro-2-naphthyl)perhydroazepine (I) from naphthalene using hexamethylenimine and sodium. Birch reduction has been widely applied to aromatic hydrocarbons, using as reducing systems alkali

Table I. Reductive Amination of Naphthalene

Amine	Metal	Reductive amination product (R =) and yield, %	% yield		
			Recovered naphthalene	1,2-Dihydro-naphthalene	1,2,3,4-Tetrahydro-naphthalene
					
Tertiary Amines					
Ethylenimine	Na	1-Aziridiny, 28	14	...	54
Pyrrolidine	Na	1-Pyrrolidiny, 65 ^a	18
Piperidine	Na	Piperidino, 70	...	3	16
Hexamethylenimine	Na	Hexamethylenimino, 55	5	13	20
Morpholine	Na	Morpholino, 52	43
2,6-Dimethyl-morpholine	Na	2,6-Dimethylmorpholino, 86	...	4	8
N-Methylpiperazine	Na	4-Methyl-1-piperaziny, 73	1	2	9
Dipropylamine	Na	Dipropylamino, 7	4	67	20
Hexamethylenimine	Li	No tertiary amine observed	93
Hexamethylenimine ^b	K	Hexamethylenimino, 4	1	1	4
Hexamethylenimine	Ca	No reaction	100
Secondary Amines					
Cyclohexylamine ^c	Na	Cyclohexylamino, 45	13	4	14
<i>n</i> -Hexylamine ^d	Na	<i>n</i> -Hexylamino, 43	25
Ethylamine ^e	Na	Ethylamino, 17 ^f	24

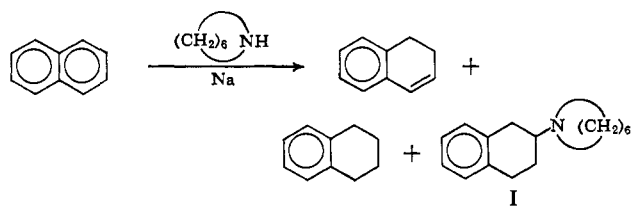
^a Contains 43% 1 isomer. ^b An 87% yield of unidentified polymeric hydrocarbon resulted. ^{c,d,e} 19, 14, and 44% yields, respectively, of 1,2,3,4,1',2',3',4'-octahydro-2,2'-dinaphthyl resulted: L. Reggel, H. W. Sternberg, and I. Wender, *Nature*, **190**, 81 (1961). ^f 6% 1 isomer.

Table II. Reductive Amination of Alkylated Naphthalenes with Hexamethylenimine and Sodium

Starting hydrocarbon	Reductive amination product and yield, %	% yield	
		Recovered hydrocarbon	Reduced hydrocarbon ^a
1-Methylnaphthalene	R ₁ = CH ₃ ; R ₂ , R ₃ , R ₄ , R ₅ = H, 28 ^b	13	39
2-Methylnaphthalene	R ₂ = CH ₃ ; R ₁ , R ₃ , R ₄ , R ₅ = H, 45 ^b	1	38
2- <i>r</i> -Butylnaphthalene	R ₂ = <i>r</i> -butyl; R ₁ , R ₃ , R ₄ , R ₅ = H, 72 ^b	1	24
1,4-Dimethylnaphthalene	R ₁ , R ₄ = CH ₃ ; R ₂ , R ₃ , R ₅ = H, 50	5	27
2,3-Dimethylnaphthalene	R ₂ , R ₃ = CH ₃ ; R ₁ , R ₄ , R ₅ = H, 42	12	14
1,4,5-Trimethylnaphthalene	R ₁ , R ₄ , R ₅ = CH ₃ ; R ₂ , R ₃ = H, 48	8	42

^a A mixture of various 1,2- and 1,2,3,4-tetrahydronaphthalenes. ^b A definite assignment at position 2 or 3 has not been made.

or alkaline earth metals and ammonia or amines as well as combinations of amines.¹ To our knowledge, there



has been no report of formation of a carbon-nitrogen bond involving the aromatic hydrocarbon during the Birch reduction.² However, the metal-catalyzed addition of amines to conjugated hydrocarbons is well

(1) (a) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. I, Part 2, Interscience Publishers, Inc., New York, N. Y., 1963; (b) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958); (c) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955); (d) R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964); (e) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *ibid.*, **28**, 1094 (1963).

(2) L. Reggel, J. P. Henry, and I. Wender, *ibid.*, **26**, 1837 (1961).

documented.³ We suggest that this latter reaction is the final stage of reductive amination of aromatic hydrocarbons; whether amination takes place depends upon the effectiveness of competition of this reaction with the Birch reduction. The mechanism of reductive amination of aromatic hydrocarbons and its relationship to the competing Birch reduction is being studied.

We have examined a variety of metals, amines, and aromatic hydrocarbons in the reductive amination reaction. In our experience, sodium and hexamethylenimine are the most effective combination of reagents, while the alkylated naphthalenes are the most receptive hydrocarbons. The data are presented in Tables I and II.

Variations in the reactants in Tables I and II may result in alteration of yield and position of nitrogen substitution on the reduced ring or may shift the reac-

(3) (a) H. Bestian, *Ann.*, **566**, 210 (1950); (b) A. P. Stuart and C. E. Scott (to Sun Oil Co.), U. S. Patent 3,118,938 (1964), *Chem. Abstr.*, **60**, 9167 (1964); (c) I. G. Farbenind., French Patent 662,431 (1928), *Chem. Abstr.*, **24**, 377 (1930).

tion to produce products of Birch reduction to the exclusion of those due to reductive amination.

A typical reductive amination, that of naphthalene with sodium and hexamethylenimine, may be carried out as follows. To 6.4 g (0.05 mole) of naphthalene and 4.6 g (0.2 g-atom) of dispersed sodium contained in a 500-ml, three-necked flask equipped with a stirrer, air condenser, and nitrogen inlet tube was added 100 ml of hexamethylenimine. A red color developed within 20 min. The mixture was stirred at 25° for 12 hr, and the unreacted sodium, which had agglomerated, was removed. The remaining solution was cooled and treated cautiously with water until the reaction mixture became colorless, then acidified with 10% aqueous hydrochloric acid. After the hydrocarbons had been removed by extraction with ether, the aqueous layer was basified with dilute sodium hydroxide, and surplus hexamethylenimine was removed by steam distillation. The steam distillation residue was extracted with ether. Drying over anhydrous sodium sulfate and distillation yielded 6.2 g (55% yield) of I.

Acceptable C, H, and N analyses⁴ were obtained for each amine in Tables I and II. The structures of these amines were unequivocally established through nmr and mass spectroscopic⁵ studies except as noted in Tables I and II.

Since the reductive amination is generally selective as to position of attachment of nitrogen to the tetralin nucleus⁶ and proceeds in reasonable yield, it offers an attractive synthetic route to novel secondary and tertiary amines.

Acknowledgment. We are grateful to the American Petroleum Institute for generous support of this research, and to the Research Foundation, Oklahoma State University, for their assistance. We wish to thank Dr. O. C. Dermer for valuable discussions and for having read the manuscript.

(4) Galbraith Laboratories, Inc., Knoxville, Tenn.

(5) We are indebted to Mr. M. C. Hamming, Continental Oil Co., Ponca City, Okla., for these data.

(6) The majority of the amines were found to have nitrogen attached at the 2 position of the 1,2,3,4-tetrahydronaphthyl nucleus. Nitrogen attachment at both the 1 and 2 positions was observed in some cases.

(7) American Petroleum Institute Research Project 58A Graduate Research Assistant, 1962-present.

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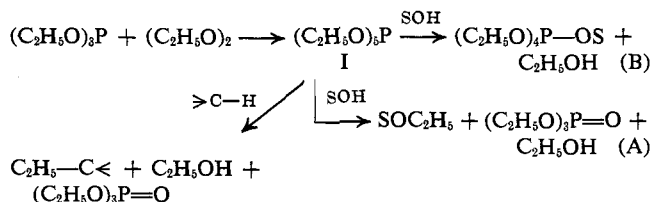
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Reactions of Pentaethoxyphosphorane¹

Sir:

Recently it was reported that pentaalkoxyphosphoranes can be prepared by the reaction of a trisubstituted phosphite and a dialkyl peroxide such as diethyl or dimethyl peroxide.² The only other synthetic method leads to pentaalkoxyphosphoranes containing five-membered rings,³ and thus this new method is poten-

tially of much greater generality. Recent work has suggested that this is the case.⁴ Moreover, it has become increasingly clear that the pentaalkoxyphosphoranes are extremely reactive substances and that some of these reactions may have considerable synthetic value. It is the purpose of this report to elaborate on some of these reactions. These studies have been conducted with pentaethoxyphosphorane (I). This compound has been chosen because of its ready availability and the ease of characterization of the products of its reactions.



Pentaethoxyphosphorane is most conveniently prepared by allowing triethyl phosphite to react with diethyl peroxide at room temperature. After 15 days the content of I in the reaction mixture reaches ca. 60%. Subsequent standing at room temperature leads to a steady diminution in the content of I.⁵ Storage at low temperatures inhibits the decomposition. The crude reaction mixture can be enriched in I by distillation at reduced pressure. The major contaminants are triethyl phosphate, triethyl phosphite, and ethanol. These substances do not interfere with the reactions being reported and thus they have been conducted using the crude reaction mixture of I.

Several modes of reaction are available to I depending upon the coreactant. These include reactions in which alkylation (A) occurs and also those in which exchange (B) between the reactant and ethoxy groups takes place.

The alkylation reactions are most facile with acidic materials. For example, carboxylic acids are rapidly and quantitatively converted to the corresponding ethyl ester. Triethyl phosphate and ethanol are also formed. Of greater interest are the reactions with phenols. Hydroquinone reacted exothermically with I to give *p*-ethoxyphenetole, triethyl phosphate, and ethanol. No other major products were detected by glpc. Similarly *p*-nitrophenol reacted vigorously with I to give *p*-nitrophenetole in quantitative yield.⁶ *p*-Methoxyphenol yielded *p*-methoxyphenetole. Reaction of I with 2,6-di-*t*-butyl-*p*-cresol was slow, and after 15 days only a small amount of the corresponding ether was formed.

Of particular interest are the reactions of I with enolic substances. Acetylacetone reacted vigorously at room temperature or 0° to give mainly the enol ether of acetylacetone. A small amount of 3-ethyl-2,4-pentanedione was also formed. Reaction with diethyl malonate was not exothermic at room temperature. After 14 days analysis by glpc showed that the major products were diethyl ethylmalonate (88%), triethyl phosphate, and ethanol. Little or none of the dialkylated product was formed. When diethyl ethylmalonate

(3) F. Ramirez, *Pure Appl. Chem.*, 9, 337 (1964).

(4) Unpublished results from these laboratories.

(1) This research has been supported by the National Science Foundation under NSF GP202 and GP4997.

(2) (a) D. B. Denney and H. M. Relles, *J. Am. Chem. Soc.*, 86, 3897 (1964); (b) D. B. Denney and S. T. D. Gough, *ibid.*, 87, 138 (1965).

(5) The percentage of I in a reaction mixture can be determined by adding excess benzoic acid and measuring the amount of ethyl benzoate formed by glpc or by titrating unreacted benzoic acid.

(6) Yields were determined by glpc on the reaction mixtures.