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STEREOCHEMICAL APPLICATIONS OF DEUTERIUM MAGNETIC RESONANCE. I.

THE PRINS REACTION OF TRANS-β-DEUTEROSTYRENE

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Nuclear magnetic resonance spectroscopy has become a common tool for the determination of the stereochemistry of electrophilic addition reactions to olefins.(1,2) In many cases the proton magnetic resonance spectra are sufficiently complex that it becomes difficult or impossible to use this method to determine product stereochemistry. We therefore have begun initial investigations on the use of deuterium magnetic resonance for this purpose. Our preliminary results have been encouraging and we now wish to report of the efficacy of this method.

The reaction we chose for the initial studies was the Prins reaction of styrene. We chose this reaction for a number of reasons. First, there has been a great deal of interest in the stereochemistry of the Prins reaction in recent years.(3-6) Much of the controversy has centered around the question of whether the "normal" course of addition of formaldehyde to aromatic olefins is *cis* or *trans*. Since styrene itself is the simplest aromatic olefin, information about the stereochemistry of its Prins reaction would be valuable. Second, the product of the Prins reaction of *trans*-β-*d*-styrene was one which displayed a complex proton magnetic resonance spectrum (7,8) and offered some difficulty in the stereochemical analysis.

Trans-β-*d*-styrene was prepared by the method of Yoshino, Manabe, and Kikuchi(9). The material thus prepared was shown by proton nmr to contain less that 10% of the *cis*- isomer and no detectable amount of the unlabeled compound. These results were confirmed by the deuterium nmr spectrum of the β-*d*-styrene, which showed only the resonance at 16.8 cps (at 9.2 Mc, relative to $CDCl_3$), with J_{HD} = 1.75 cps, of the *trans*- isomer.(9). This labeled styrene was allowed to react with excess formaldehyde in acidic (*ca*. 0.1 n H_2SO_4 in dioxane) *p*-dioxane solution for four days at room temperature. At the end of that time, the reaction mixture was worked up in the usual manner and the organic materials isolated were analyzed by deuterium magnetic resonance, proton magnetic resonance and gas liquid phase chromatography. In this way, it was possible to determine the stereochemistry of the product 5-*d*-4-phenyl-1,3-dioxane as well as that of the recovered starting styrene. Concurrently, we were able to compare the results of the different methods of analysis, thus allowing a test of the accuracy and usefulness of deuterium nmr for this purpose. The reaction was repeated a number of times, using different batches of starting styrene and the results were found to be quite reproducible. Typical analytical data for one such run are tabulated in Table I.

Table I

STEREOCHEMICAL ANALYSIS OF PRINS REACTION PRODUCTS
OF *TRANS*-β-STYRENE IN DIOXANE SOLVENT

Method	β-d-Styrene[a]	A/B[b]	A+B/β-d-Styrene
Glpc[c]	-	-	3.0
H^2NMR	90% *trans*[d]	0.7	3.0
H^1NMR 100Mc	90% *trans*	0.8	-
H^1NMR 60Mc	90% *trans*	0.8	-

a) Recovered from reaction mixture.

b) A is *cis*-5-*d*-4-phenyl-1,3-dioxane and B is the *trans*- isomer.

c) Using a 5' x 1/4" column of SE 30 on acid-washed Chromosorb W at a column temperature of 130° and a helium flow rate of 30 cc/min.

d) *I.e.* no detectable isomerization of the starting material had occurred.

This data clearly shows that the deuterium nuclear magnetic resonance analysis gives reliable values which are in good agreement with those obtained by other methods. As in the case of *cis*- and *trans*-β-d-styrenes(9), the deuterium resonance of the *cis*- isomer of 5-*d*-4-phenyl-1,3-dioxane appears at slightly lower field than that of the *trans*-. The separation of the two signals is less than in the styrene case however, with the *cis*- resonance appearing as a clearly defined shoulder on the low field side of the peak due to the *trans*- isomer. Comparison of the total product/styrene ratios obtained by glpc and H^2 nmr shows the validity of this interpretation of the spectrum. By assuming normal line shapes for both resonances, it is possible to obtain an estimate of the relative amounts of the isomers by merely comparing the peak heights found in the deuterium resonace spectrum. There is quite reasonable agreement between estimates obtained this way and those made by integretion of the pair of doublets centered at 5.52τ in the proton nuclear magnetic resonance spectra of the products. The deuterium magnetic resonance parameters of the product mixture are summarized in Table II.

Table II

H^2 Magnetic Resonance Parameters[a]

Compound	Chemical shift (cps)[b]	J_{H-D}(cps)
trans-β-*d*-Styrene	18.4 ± 0.2	1.75
trans-5-*d*-4-Phenyl-1,3-dioxane[d]	52.5 ± 0.4	--
cis-5-*d*-4-Phenyl-1,3-dioxane[d]	47 ± 1[c]	--

a) These values are for the neat product mixture with sufficient $CDCl_3$ added to serve as an internal standard. Measurements were performed with a Varian DP-60 spectrometer equipped with a variable frequency probe(10).

b) Relative to internal $CDCl_3$, which appears at lowest field.

c) There is greater uncertainty in this value due to its appearance as a shoulder on the *trans* peak.

d) The resolution did not allow the determination of coupling constants.

The interpretation of the data is straightforward and their implications regarding the mechanism of the Prins reaction are clear. The reaction under these conditions shows an almost total lack of stereoselectivity. Previous studies (3) show that a number of styrenes undergo the Prins reaction with little stereoselectivity not only in dioxane and water solutions, but also in the much less nucleophilic solvent-acetic acid. Attempts (6) to rationalize the stereochemical results on the basis of solvent nucleophilicity would, therefore, seem to be unwarranted. The present results are in full accord with the earlier study of 1-phenylpropene under a variety of conditions (3). It is therefore evident that the "normal" course of this reaction under the present conditions is one of non-stereospecificity. This is the result that might be anticipated if steric interactions with β-substituents are of importance in determining the stereochemistry of addition. It is of interest to note that the ratio of *cis*-/*trans*-dioxane was reproducible and, even though there may be a 10-15% uncertainty in the value of this ratio, it appears that the product of *cis* addition to the starting *trans-d*-styrene is always present in larger quantities in the reaction mixture. Isomerization of the *cis*-product seems unlikely, so the implication is that possibly there are two routes to the products - one stereospecific, the other not. In any case, the importance of such a stereospecific route is obviously minor. We now hope to extend the technique developed here to studies of the same reaction under other conditions and in other solvents where our method may be the only feasible way to follow the stereochemistry of this Prins reaction.

In conclusion, we have demonstrated that deuterium magnetic resonance spectroscopy is a valuable and reliable tool for the study of the stereochemical course of chemical reactions. Currently, effort is underway in our laboratories to extend this technique to the study of other reactions which have been difficult or impossible to analyze by proton nmr spectroscopy.

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