Tetrahedron Vol. 26, pp. 4131 to 4138. Pergamon Press 1970. Printed in Great Britain

MECHANISM OF THE PRINS REACTION OF STYRENES

THE PRINS REACTION OF *TRANS*-β-DEUTEROSTYRENE[1]

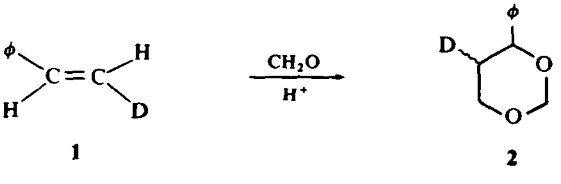
C. L. WILKINS and R. S. MARIANELLI
Contribution from Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

(*Received in the USA* 23 *March* 1970; *Received in the UK for publication* 15 *May* 1970)

Abstract—*Trans*-β-*d*-Styrene has been prepared and allowed to undergo the Prins reaction in both dioxane and acetic acid solutions. The stereochemistry of the product 5-*d*-4-phenyl-1,3-dioxane has been determined by both proton and deuterium nuclear magnetic resonance spectroscopy. It has thus been shown that the Prins reaction of styrene under the conditions used is almost totally non-stereoselective. The implications of these results are discussed. A general reaction scheme which satisfactorily explains the stereochemical behaviour of styrenes in the Prins reaction is presented. The potential usefulness of deuterium magnetic resonance as a probe of reaction stereochemistry has been demonstrated.

THE Prins reaction of styrenes has received much attention.[2–10] In one of the previous studies,[6] it was found that the reaction with several styrenes produced, in all cases, 1,3-dioxanes which were the result of the stereospecific addition of two formaldehyde units. A later study of a number of other styrenes produced dramatically different results, with little stereoselectivity in the formation of 1,3-dioxanes being observed.[5] Kinetic investigations reveal that the Prins reaction of styrene itself is first order in total formaldehyde concentration (summation of concentrations of all species) in water solution.[9] The same result was found by Hellin *et al.* when they studied the Prins reaction of α-methylstyrene,[10] while the order in formaldehyde is said to decrease from first to zero when the reaction of anethole in acetic acid solution is observed.[8] While these results suggest the presence of some kind of intermediate, they do not yield detailed information about its structure.

Interpretation of the previous stereochemical studies has been hampered by a lack of knowledge about the stereochemistry of the Prins reaction of styrene itself and by the wide variety of conditions which have been used. For this reason, we have prepared *trans*-β-*d*-styrene and examined the stereochemistry of its Prins reaction under the two sets of conditions which will best allow comparison with the previous work.



Initially, we intended to determine the stereochemistry of deuterium in the product 5-*d*-4-phenyl-1,3-dioxane by examination of the benzylic proton portion of the NMR spectrum. This seemed an attractive method since the spectrum of the unlabelled material had been analyzed in some detail[11] and it was reasonably easy to pick out the benzylic proton. We anticipated that the deuterated material would show either a doublet or a pair of doublets in this region of the spectrum, and integration would yield the distribution of deuterium between the two possible positions (*cis* or *trans* to the phenyl group). From this, we would infer the stereochemical course of the reaction. It was, in fact, possible to obtain an estimate of the distribution of the deuterium in this manner, but the difficulty of obtaining accurate integrals was such (see Fig 1) that we sought an independent means of confirmation of results obtained in this way. Since we were already interested in the possibility of the use of deuterium magnetic resonance as a tool for following reaction stereochemistry,[12] this method was an obvious choice.

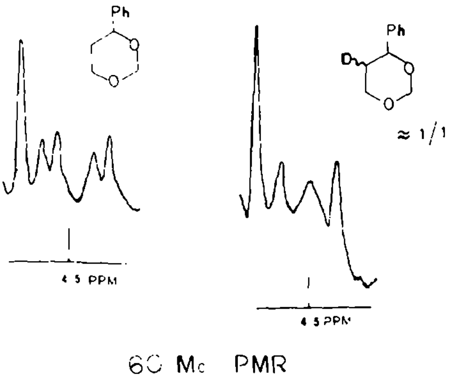


FIG 1. The benzylic proton regions of the 4-phenyl-1,3-dioxane and 5-*d*-4-phenyl-1,3-dioxane NMR spectra.

There are a number of advantages in using deuterium magnetic resonance rather than PMR for work of this type. First, the interpretation of spectra are, in general, much more simple than in PMR spectra. The chemical shifts are almost the same as for the proton spectra, but the ratio of coupling constant to chemical shift is reduced by a factor of about 6·5.[13] Furthermore, it is possible to selectively introduce D atoms stereospecifically at known positions in materials to be analyzed, thus producing quite simple spectra when compared to the complex spectra which may arise from the large numbers of H atoms normally present in organic compounds. Thus, the rather complicated pattern for the 5e and 5a protons in the proton NMR spectrum of 4-phenyl-1,3-dioxane is replaced by two overlapping peaks in the deuterium NMR spectrum of a mixture of the corresponding deuterated compounds (Fig 2). By assuming the heights of these peaks are proportional to the peak areas, we may then estimate the percentage of deuterium in the 5a and 5e positions. Reference to Table 1 shows the excellent agreement between the estimates obtained in these two different ways. This agreement gives us considerably more confidence in the accuracy of our estimates, since, not only are they obtained in different ways, but they are measurements of the relative abundance of axial and equatorial atoms attached to two *different* C atoms in the product. While this represents a marginal case, it nevertheless clearly demonstrates the potential of deuterium magnetic resonance as a probe of reaction stereochemistry.

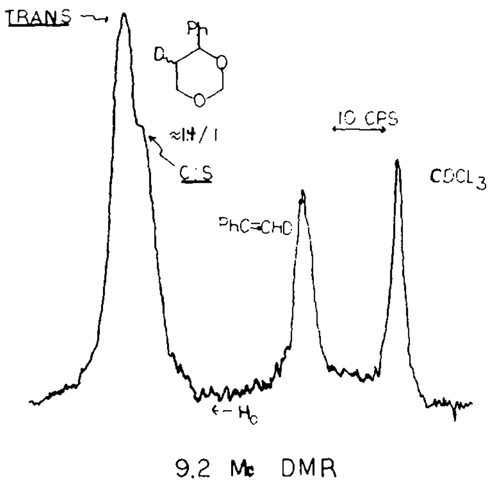


FIG 2. Deuterium magnetic resonance spectrum of a typical crude product mixture.

Since most of the previous determinations of stereochemistry for styrene Prins reactions had been carried out in either acetic acid or dioxane as solvent, we chose to examine the stereochemistry of the β-*d*-styrene Prins reaction in these two solvents.

TABLE 1. COMPARISON OF PROTON AND DEUTERIUM NMR RESULTS

Run	Solvent	Ratio of *cis*/*trans* Addition to form Dioxane	
		H^1 NMR	H^2 NMR
1	Dioxane[a]	1·2	—
2	Dioxane	1·2	1·4[c]
3	Dioxane	1·3	1·4[c]
4	Acetic acid[b]	1·1	—
5	Acetic acid	1·2	1·0[c]
6	Acetic acid	1·2	1·0[c]

[a] Dioxane conditions: 3-fold excess paraformaldehyde, 0·8 N H_2SO_4, 25 degrees

[b] Acetic acid conditions: 10-fold excess paraformaldehyde, 0·9N H_2SO_4, 25 degrees

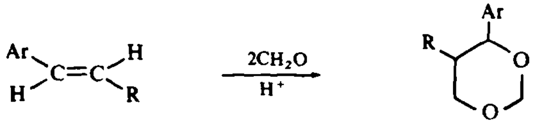
[c] Due to experimental difficulties, this ratio has an uncertainty of about 15%

The reaction conditions were chosen to allow comparison with the previous studies of the 1-phenylpropenes.[5] After the present work was completed, another report of some careful studies of the stereochemistry of the Prins reaction of the 1-phenylpropenes appeared.[14] The data reported there seem to support our formulation of the general reaction mechanism for the Prins reaction of styrenes.

RESULTS AND DISCUSSION

One notable fact emerges from a study of the results tabulated in Table 2. When simple *trans*-β-substituted styrenes are examined under comparable conditions in the two solvents, there is no marked solvent effect on the apparent stereochemistry of the addition. This suggests that the involvement of the solvent is not an important determinant of this aspect of the reaction. Perhaps even more significant is the finding that the reaction stereochemistry in these cases shows a remarkable parallelism with the free energy differences found for the dioxane products (i.e. the amount of net *cis* addition to give substituted dioxane closely follows the stability of that product as determined by equilibration studies).[15] These facts are summarized in Table 3. In their recent work, Bocard *et al.* found no such parallelism for a series of 1-arylpropenes[14] but they did clearly demonstrate the complex dependence of reaction stereochemistry upon both acidity and formaldehyde concentration, a fact which had been noted qualitatively before.[5] Our present results reveal the intriguing fact that, when a mixture of *cis* (*ca* 10%) and *trans*-β-*d*-styrene were subjected to the Prins reaction conditions, a small, but reproducible, amount of stereoselectivity was found.

TABLE 2. STYRENE PRINS REACTIONS



Ar	R	Conditions	Solvent	*cis*/*trans* addition ratio
*p*OMe	—CH_3	2 fold excess P[e] no added acid, 125°	HOAc	all *cis*[a]
φ	—CO_2H	3 fold excess P 4 N H_2SO_4, 125°	HOAc	all *cis*[c]
φ	—Br	3 fold excess P 4 N H_2SO_4, 100°	HOAc	4·2[b,c]
φ	—CH_3	10 fold excess P 0·9 N H_2SO_4, 25°	HOAc	1·7[b,c]
φ	—D	10 fold excess P 0·9 N H_2SO_4, 25°	HOAc	1·1
φ	Cl[d]	2 fold excess P 3·0 N, 100°	Dioxane	5·0
φ	Br[d]	4 fold excess P 1·5 N, 85–100°	Dioxane	7·7
φ	CH_3[d]	3 fold excess P 0·8 N, H_2SO_4, 25°	Dioxane	1·2
φ	D	3 fold excess P 0·8 N, H_2SO_4, 25°	Dioxane	1·2

[a] Ref. 6

[b] The *trans* addition product isomerizes slightly under the reaction conditions (25% for the Br compound, 5% for the methyl)

[c] Ref. 5

[d] *cis* isomers of these compounds gave approximately equal amounts of *cis* and *trans* addition products (Ref. 5)

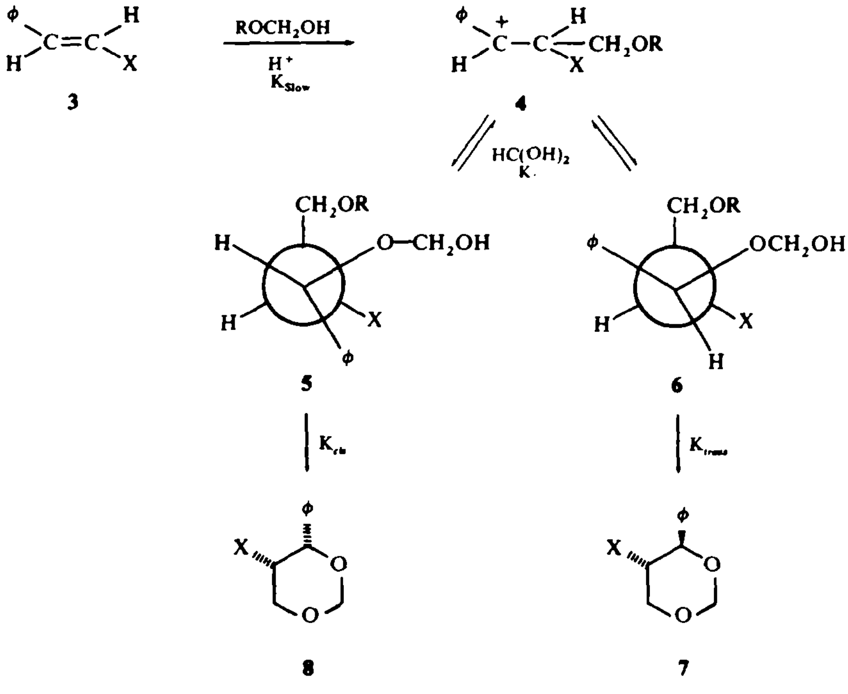
[e] P = paraformaldehyde

TABLE 3. QUALITATIVE CORRELATION OF PRINS REACTION STEREOCHEMISTRY FOR TRANS-β-SUBSTITUTED STYRENES WITH PRODUCT DIOXANE STABILITY

β-Substituent	$-\Delta F$ (kcal/mole)[a]	Approx equilibrium % *trans* dioxane at 25°	Approx % *cis* addition	
			HOAc	Dioxane
$-CO_2H$	6·1[e]	96	100[c]	—
—Br	1·8	91	81[d]	89
—Cl	1·6	88	—	83[d]
$-CH_3$	1·4	82	63[d]	55
—D	0[b]	50	52	53

[a] Determined at 128·5°
[b] Assumed
[c] Ref. 7
[d] Ref. 5
[e] Determined at 95·2°

In light of all the available data, it now seems to us that the explanation for the seemingly inconsistent and often puzzling stereochemical behavior of various styrenes, as they undergo the Prins reaction, lies in a careful consideration of the complex interplay of a number of factors. Such a consideration had led us to formulate the following scheme which, we believe, has the attractive merit of offering a relatively simple explanation which is consistent with all known data on the Prins reaction of styrenes. This is outlined below.



The initial rate-determining attack upon the styrene **3** by formaldehyde or one of its polymeric forms may take place to form the carbonium ion **4**. Next, a reversible addition of a nucleophilic species (such as methylene glycol) can take place to form one of the two possible diastereomers **5** or **6**. Since these additions are reversible, isomerization of the diastereomers is possible. Further reaction of either one will lead, irreversibly, to the corresponding product dioxanes, **8** or **7**. If we consider the conformation necessary for cyclization to take place, it is seen there is likely to be a severe interaction between the aryl group and the β-substituent in **5** while no such interaction occurs in **6**. Thus, when β-substituents are present, the dioxanes formed from intermediates such as **6** could reasonably be expected to predominate.

If the reaction stereochemistry is considered in terms of the scheme presented, it is clear that, most generally, the composition of the product mixture will depend on the stereochemistry of the initial addition step and on the relative rates of interconversion of **5** and **6** and product formation (to give **7** and **8**). However, closer consideration suggests two important limiting cases. The first is a case where the isomerization step (represented by the composite rate constant k_1) is much faster than the product forming step (represented by the rate constant k_{products}). In this case ($k_1 \gg k_{\text{products}}$), the product distribution will be governed by the ratio of the rates k_{cis} and k_{trans}. For *trans*-β-substituted styrenes, k_{trans} might well be significantly greater for the reasons suggested above and thus, rather stereoselective *cis* addition to yield the *trans*-substituted dioxane may be observed. Alternately, the reverse might be the case (i.e. the isomerization could be much slower than product formation). In that case, the stereochemistry of the addition to **4** would control the stereochemical outcome (as reflected in the composition of the dioxane mixture **7** and **8**).

Viewed in these terms, it seems entirely reasonable that the presence of a substituent which can stabilize carbonium ion **4** and thus, presumably, enhance the rate of isomerization of **5** to **6** would lead to a shift in stereoselectivity to favor a more stable product. This is precisely the result found with anethole where all *cis* addition was observed.[6, 8] More recently, this same effect was demonstrated with a series of 1-arylpropenes[14] where the products progressively shifted toward the equilibrium composition as the carbonium ion-stabilizing ability of the substituent increased. Our proposal also predicts non-stereospecific formation of products resulting from solvent interception of the ion **4**, something which is also observed experimentally in the case of anethole.[6] The data of Table 3 may also be accommodated by this interpretation, as a direct correspondence between product stability and reaction stereochemistry may be noted.

That there is a degree of stereoselectivity in the formation of the diastereomers **5** and **6** is illustrated by the data obtained from the reaction of the β-deuterostyrene mixture. Here, the complicating influence of different product forming rates has been eliminated, and a small but reproducible stereoselectivity is noted. This may be accounted for by comparable rates of product formation and isomerization. While stereospecific addition to the styrenes would yield a 9:1 product ratio for the dioxanes, a ratio of approximately 1·2:1 is observed. This is readily explained using the present scheme.

In conclusion, we feel the present mechanism adequately explains the data and even though there is no direct evidence for the structures of the second intermediates, **5** and **6** are attractive possibilities. This interpretation suggests that in no case does the stereochemistry we observe represent the actual stereochemistry of the rate-determining step, but rather is a result of a complex interplay of a number of rate constants. In other words, previous difficulties in rationalizing experimental data for individual styrenes have arisen largely as a result of neglecting to consider the entire array of available data.

EXPERIMENTAL

Materials. Chemicals were used as obtained, without further purification unless otherwise stated. Reagent grade glacial AcOH and Mallinckrodt reagent grade dioxane (stabilized) were used as reaction solvents. Paraformaldehyde was obtained from Eastman Organic Chemicals Department and 99·77% D_2O from Columbia Organic Chemicals. Reagent grade sulfuric acid was used in all cases. A mixture of *trans*- and *cis*-β-*d*-styrene* was prepared by the method of Yoshino *et al.*[16]

Apparatus. Proton NMR measurements were obtained with a Varian A-60D spectrometer, while deuterium NMR measurements were performed with a Varian DP-60 spectrometer equipped with a variable frequency transmitter and receiver.[17] $CDCl_3$ was solvent for all NMR measurements. TMS was used as an internal standard for the proton NMR spectra and the $CDCl_3$ peak for the deuterium NMR spectra. The mass spectral D analysis was performed with a double focussing Hitachi RMU-6D mass spectrometer. The GLPC analysis was done with a Varian-Areograph 90-P3 gas chromatograph, equipped with a disc integrator, using a 5′ × ¼″ column of SE-30 on acid-washed Chromosorb W at a column temp of 130° and a helium flow rate of 30 cc/min.

Acetic acid Prins reactions. Trans-β-*d*-styrene (300 mg, 2·8 mmole) was added to a mixture of glacial AcOH (6 ml), conc H_2SO_4 (256 mg, 3 mmole), and paraformaldehyde (756 mg, 25·2 mmole [as CH_2O]). The resultant mixture was then stirred at room temp, protected from light, for 4 days. At the end of that time, the reaction mixture was poured into a 5% Na_2CO_3 aq (160 ml) and extracted, first with two 30 ml portions ether, then one 50 ml portion. The combined ether layers were washed with several 50 ml portions distilled water. The ether soln was dried over Na_2SO_4 and the ether distilled off to yield 346 mg crude product. This product was shown by GLPC to contain, besides solvent and recovered styrene, about 242 mg (53% yield) 5-deutero-4-phenyl-1,3-dioxane and approximately 20 mg unidentified material. The crude product mixture was then analyzed by NMR to obtain the stereochemical distribution of the D in the product dioxane and the recovered styrene. There had been no detectable isomerization of the starting material. This entire procedure was repeated 3 more times, using separately prepared batches of deuterostyrene with essentially the same results being obtained in each case.

Dioxane Prins reactions. Trans-β-*d*-styrene (219 mg, 2 mmole) was added to a mixture of dioxane (5 ml), conc H_2SO_4 (190 mg, 2·2 mmole), and paraformaldehyde [185 mg, 6 mmole (as CH_2O)]. The mixture was then stirred in the dark for 4 days at room temp. At the end of that time the reaction mixture was poured into water (50 ml) and extracted with three 25 ml portions ether. The combined ether layers were washed with several portions of 5% $NaHCO_3$ aq and then water. The ether soln was dried over Na_2SO_4 and the ether removed by distillation. The material thus isolated was shown by GLPC to contain, besides solvent and recovered styrene, approximately 170 mg (44% yield, uncorrected for recovered starting material) 5-deutero-4-phenyl-1,3-dioxane. Analysis of the crude product by NMR yielded the stereochemical disposition of D in the product. No detectable isomerization was found in the un-reacted styrene. The same procedure was repeated two more times with essentially the same results.

Nuclear magnetic resonance analysis. The crude reaction products were dissolved in a small amount (approximately 20% of their volume) of $CDCl_3$ and placed in a standard NMR sample tube. This sample was then placed in the DP-60 spectrometer and the D resonance spectrum recorded (sample spinning was used). The oscillator frequency used for the measurement was 9·2 Mc. Comparison of the peak heights appearing at 52·5 c/s (*trans*-5-*d*-4-phenyl-1,3-dioxane) and 47 c/s (*cis*-5-*d*-4-phenyl-1,3-dioxane) yielded the relative amounts of deuterium *cis* and *trans* to the phenyl group in the product. Un-reacted *trans*-β-*d*-styrene appeared at 18·4 c/s and examination of the region at slightly lower field, where the *cis* isomer absorbs,[16] allowed a check for isomerization. The $CDCl_3$ resonance, which appears at lowest field, was taken as zero.

An alternate method of determining the position of D in the product was to further dilute the sample

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* Labeled styrene prepared in this way was shown to be greater than 97% monodeuterated (mass spectrometry) and to contain approximately 10% of the *cis*-deuterated isomer (NMR).

which had been used for the D resonance measurement and, after adding TMS, to examine the PMR, using the A-60D spectrometer. Comparison of the benzylic proton doublets centered at 4·48 allows one to determine the relative amount of *cis* and *trans* 5-protons. This, by inference, yields the relative amount of *cis* and *trans* 5-deuterium. The deuterostyrene composition can also be checked by examination of the appropriate part of the spectrum.[16]

Acknowledgments—We gratefully acknowledge the generous support of the Research Council of the University of Nebraska. We would also like to thank Professor Christopher Michejda for helpful discussions.

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