A Kinetic Investigation of the Addition of Diazomethane to Styrenes. Role of Dipolar Aprotic Solvents in Predicting Direction of Dipole Orientation. (1)

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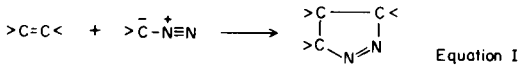
The addition of diazomethane to a series of substituted styrenes has been kinetically investigated with emphasis on polar, solvent, and solvation effects. Although the reaction is generally insensitive to solvent polarity, a sizeable substituent effect (ρ = +0.90) has been observed. Also, a sizeable increase in rate was generally observed in protic solvents such as water, and a considerable rate enhancement occurred in the case of nitrostyrene in the dipolar aprotic solvent, dimethylformamide. The results are discussed in terms of a concerted mechanism involving a partially-charged transition state II, with negative charge formation on the α-carbon of the styrene.

The methoxystyrene offers an exception to the Hammett equation and the unexpectedly high rate constant for this compound could be discussed in terms of a possible participation of the highly nucleophilic resonance form of *p*-methoxystyrene and an α-addition *via* the transition state III. However, solvation effects in dimethylformamide (failure to obtain the anticipated rate increase) and the formation of a 3-substituted pyrazoline adduct from the cycloaddition reaction indicate steric control to predominate over electronic factors and β-addition to prevail unequivocally.

It is proposed that solvation effects in protic solvents can be utilized to advantage in cycloaddition reactions leading to 1-pyrazolines, for which no other routes are available at the present time.

INTRODUCTION

The reaction between diazocompounds and olefinic bonds is a well known method for the synthesis of pyrazolines (Equation I) (4). However, reaction occurs readily only when the double bond is activated, such as in the case of α, β-unsaturated esters, ketones, nitriles, and secondary nitroolefins. Compounds, such as the styrenes,



Equation I

containing double bonds that are not susceptible to nucleophilic attack, often fail to react with diazocompounds or react only very slowly. As a result, few studies have been carried out on the addition of diazocompounds to styrenes.

Recently, Overberger and Anselme investigated the addition of aryldiazocompounds to styrenes in order to determine the generality and scope of this reaction for the preparation of 1-pyrazolines. They observed that while the reaction of phenyldiazomethane with styrene and *p*-chlorophenyldiazomethane with *p*-chlorostyrene yielded the *trans*-3,5-diaryl-1-pyrazolines (5), the addition of *p*-methoxyphenyldiazomethane to *p*-methoxystyrene gave equal amounts of the *cis* and *trans*-3,5-bis(*p*-methoxyphenyl)-1-pyrazolines (6). The mechanism suggested by these authors for the formation of the unanticipated *cis* isomer called for the participation of resonance form B of *p*-methoxystyrene (Scheme B) (6).

The addition reactions of diazocompounds to olefinic double bonds are classified as "1,3-dipolar cycloadditions" (7). A concerted mechanism in which the two new σ bonds are formed simultaneously, although not necessarily developed to the same extent, has been proposed for these additions (7). However, measurements of the rates of addition of an azomethine imine, a sydnone and a nitrone to *p*-substituted styrenes (8) indicate that the rate depended only slightly on the nature of the *p*-substituent; only in the case of the nitrone was the Hammett equation satisfied with a value of ρ = +0.83.

The addition of diazomethane to styrenes has not been reported. The existence of a mesomeric effect of the type shown in *p*-methoxystyrene (Scheme B) would impart a particularly nucleophilic character to the olefinic double bond due to participation of resonance form B. This raises an interesting question as to the direction of addition of diazomethane to this styrene and the extent of simultaneity of bond formation, and charge distribution in the transition state. While β-addition generally prevails among the

styrenes (5,8), an abnormal α-addition might be expected in the case of *p*-methoxystyrene. In order to secure data relevant to these questions, and to determine the generality of this method for the synthesis of aryl substituted pyrazolines, we undertook a kinetic investigation of the addition reaction of diazomethane to substituted styrenes, with particular emphasis on polar, solvent, and solvation effects.

RESULTS AND DISCUSSION

The rate constants for the addition of diazomethane to styrenes were determined using *pseudo* first order techniques (9). Preliminary studies with styrene established the first order kinetic dependence on diazomethane and styrene. First and second order rate constants for the reaction at several different styrene concentrations (always in excess) are presented in Table I. The reaction thus follows simple second order kinetics, and in all subsequent work, this relationship is assumed to hold. The pyrazoline adducts are stable in solution and no dissociation appeared to take place under the conditions of this investigation. There was also no indication of alternative reaction paths; the addition of diazomethane to styrenes led exclusively to the pyrazoline adducts.

The second order rate constants for the reaction of diazomethane with a number of differently substituted styrenes are presented in Table II. In contrast to the addition reactions of azomethine imines and sydnones to styrenes (8) where no substituent effects were observed, our results indicate that the reaction rate is generally dependent on the nature of the substituent group; the facilitation of reaction by electron-withdrawing groups is quite evident and the Hammett equation (Figure 1) is satisfied with a value of ρ = +0.90 in dioxane and +1.31 in dimethylformamide (Table III).

In addition, there is a striking paralellism between the rates and yields of pyrazolines (see Table II). The reaction thus appears to involve nucleophilic attack by the diazomethane carbon on the methylene carbon of the styrene, which is *beta* to the *C*-phenyl activating group (Scheme A). The pyrazoline adducts have the expected structures based on this direction of orientation; that is, they are 3-substituted as shown by comparison with the products obtained by cyclization of hydrazones (4,11).

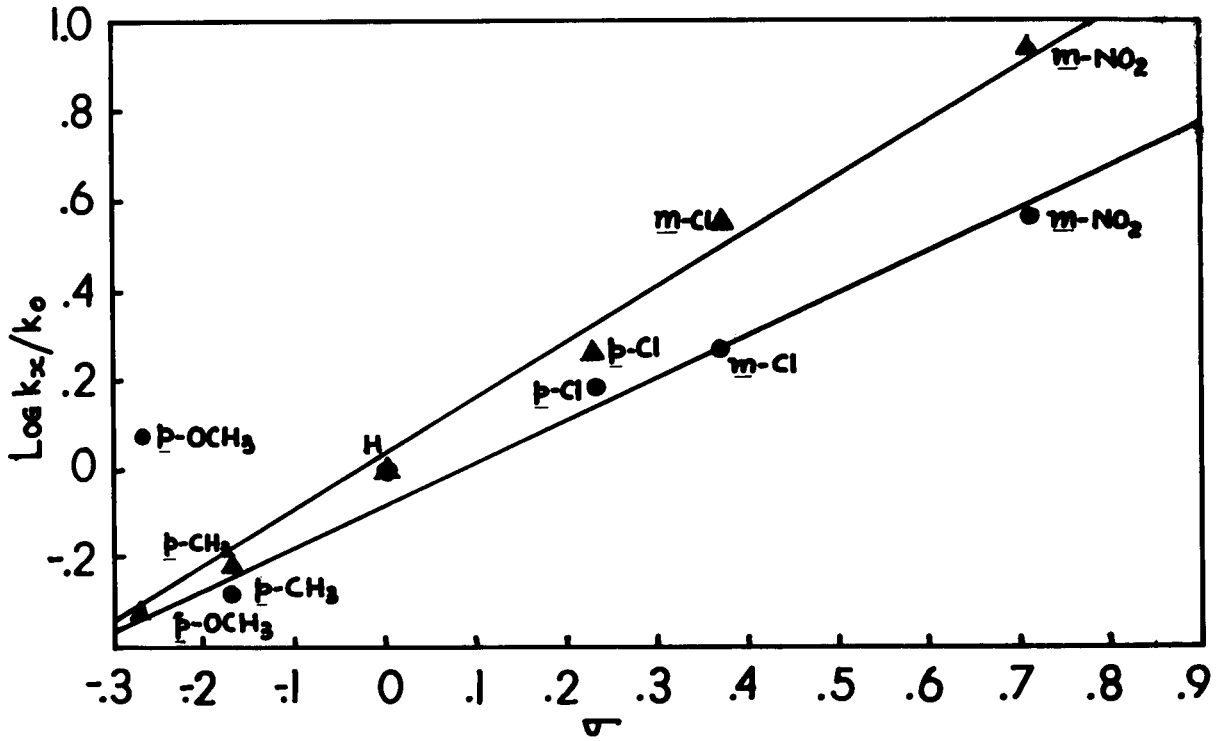
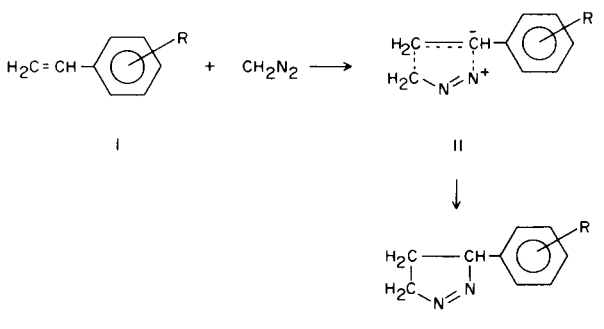


Figure 1. Hammett plot of log k_X/k_O against Hammett σ values for the addition reaction of diazomethane to substituted styrenes in dioxane and dimethylformamide at 24.9°; k_X and k_O are second order rate constants for the substituted and unsubstituted styrenes respectively. ● Indicates values in dioxane and ▲, values in dimethylformamide. The higher ρ value in dimethylformamide (+1.31) compared to dioxane (ρ = +0.90) is the result of solvation effects in dimethylformamide.

SCHEME A



SCHEME B

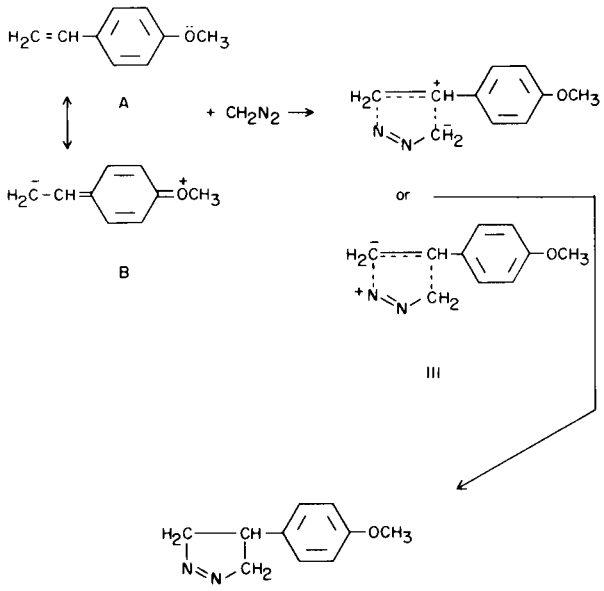


TABLE I

First and Second Order Rate Constants for the Addition of Diazomethane to Styrene at Different Styrene Concentrations in Dioxane at 24.9°

$[CH_2N_2]$ (a)	[Styrene] (a)	$k_1 \times 10^3$ (b)	$k_2 \times 10^3$ (c)
0.020	0.2070	3.91	18.90
0.039	0.3947	7.62	19.30
0.049	0.4926	9.24	18.75

(a) Units are mole liter^{-1}. (b) Units are min^{-1}. (c) Units are liter mole^{-1}min^{-1}.

Determination of rate constants in a number of different solvents of increasing dielectric constant revealed that the influence of solvent polarity is generally insignificant, and apparently a one-step concerted addition, in which the two new σ bonds are formed simultaneously, is in operation. The polar effects of substituent groups with a sizeable ρ value can best be explained in terms of negative charge stabilization in the transition state. The results support a one-step addition process involving a transition state such as II, in which the carbon-carbon and carbon-nitrogen bonds are developed unequally with resultant charge imbalance as depicted (Scheme A). Electron withdrawing groups present on the benzene ring would stabilize the negative charge and enhance the rate while electron releasing groups would have the opposite effect.

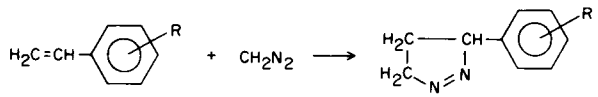
Although the addition reaction of diazomethane to substituted styrenes did not reveal any general dependence of rate on solvent polarity (Table II), a threefold increase in rate was observed in the case of nitrostyrene, when the reaction was run in a dipolar aprotic solvent such as dimethylformamide. There was also a general increase in rate in protic solvents such as water, as evidenced by synthesis. These solvent effects are in accordance with our postulates on solvation effects and the role of protic-dipolar aprotic solvents in 1,3-cycloaddition reactions (1), the rate increases apparently resulting from better solvation of the negatively charged transition state II, relative to the reactants, in the protic or dipolar aprotic solvent media as the case may be. In the reaction of nitrostyrene and diazomethane, though the polar reactant molecules are more solvated in the dipolar aprotic solvent, dimethylformamide, this is more than compensated for by the better solvation of the transition state which, due to the nitro group, has the maximum charge dissipation in this reaction series, and hence, the greatest solvation in dimethylformamide. In the case of *m*-chlorostyrene with less charge dissipation in the transition state, only a 2.5-fold increase in rate was obtained in dimethylformamide. The solvation effects in dimethylformamide were also reflected in the higher ρ value for the reaction in this solvent. Solvation in protic solvents involves hydrogen bonding and follows a reverse order, being greatest for the transition state resulting from the addition of diazomethane to styrene, with little charge distribution.

If β-addition is the general rule, then the electronic effect of substituent groups on the reaction rate would be expected to follow the order, $NO_2 > Cl > H > CH_3 > OCH_3$. However, *p*-methoxystyrene appears to be an exception. The rate constant for the addition of diazomethane to *p*-methoxystyrene is not lower than that for the methyl compound, but rather, it is double that for methylstyrene and slightly greater than that for styrene itself.

One possible explanation for this unexpected increase in rate for *p*-methoxystyrene is that the olefinic double bond in this styrene alone may be particularly more nucleophilic in character as a result of mesomeric effects of the type (A↔B) postulated by Overberger in the addition of *p*-methoxyphenyldiazomethane to *p*-methoxystyrene (6). In such a case, an α-addition could be conceived with the

TABLE II

Second Order Rate Constants for the Addition of Diazomethane to Substituted Styrenes at 24.9°.



R	$k_2 x10^3$ (liter mole^{-1}minute^{-1})					Synthesis				
	Dioxane	Ethyl Ether	Chloro-benzene	Acetone	Dimethyl-formamide	Reaction time hours	Recrystalli-zation solvent (a)	Yield, % (Aqueous dioxane((b)	Yield, % (Dry ether)	M.p.°C.
	ϵ = 2.2	4.3	5.7	20.7	37.6					
p-OCH_3	22.54	—	—	—	12.14	91	A	42	-	163-166
p-CH_3	9.95	—	—	—	15.61	96	A-P	36	-	128-132
H	18.75 16.68 (c)	10.29	22.85	12.39	25.62	168	A-P	60	28	152-153
p-Cl	27.55	—	—	—	46.52	168	A-P	76	57	157-159
m-Cl	34.53	—	—	—	90.01	95	A-P, E[d]	48	-	130-132
m-NO_2	67.62	—	71.76	—	221.88	90	A-P, E[d]	58	50	136-139°

(a) A, acetone; P, petroleum ether, b.p. 30-60°; E, ethanol. (b) Yields are for the recrystallized nitroso pyrazolines. (c) This is obtained by using undistilled styrene as supplied by Aldrich. (d) To the acetone solution was added enough petroleum ether to precipitate the dark coloured impurities and the residue left behind after evaporation of the yellow filtrate was crystallized from ethanol.

TABLE III

Hammett ρ values for the Addition of Diazomethane to Styrenes at 24.9°.

Solvent	ρ	r(b)
Dioxane	+0.90 (a)	0.99
Dimethylformamide	+1.31	1.00

(a) The p-OCH_3 group is omitted from the calculation. (b) Correlation coefficient.

diazomethane carbon attacking the α-carbon of the styrene (Scheme B), and the nature of the charge, developed in the transition state, would depend on which one of the two σ bonds has progressed to a greater extent in III. Either situation could lead to the observed rate enhancement. This possibility was tested using solvation effects in dimethylformamide.

If an α-addition did indeed operate, the resonance between the phenyl ring and the C-C double bond would decrease as the two new σ bonds are formed, but it would not be completely inhibited. This would lead to a certain degree of electron delocalization in III. Consequently, a rate enhancement in a dipolar aprotic solvent, such as dimethylformamide, might be anticipated, arising out of specific solvation effects that involve better solvation of the polarizable anionic transition state relative to the polar reactant molecules (1). Such rate enhancements have been observed in the addition reactions of diazomethane to p-chlorobenzalaniline and p-methoxybenzalaniline, respectively, where mesomeric double bonding similar to the one

X = Cl or OCH_3

postulated in p-methoxystyrene (6), has been shown to exist (1,9,10). However, in this case no rate increase in dimethylformamide was obtained. Apparently the contribution of structure B to the resonance hybrid of p-methoxystyrene, at least in the reacting state with diazomethane, is not very large; the extent of the contribution of structure B is apparently determined by the specific reactant in question. Obviously then, the electronically anomalous orientation is the one favoured by steric factors, thus reducing the possibility of an α-attack in p-methoxystyrene.

Conclusive evidence for a β-attack in this compound was provided by synthesis; while an α-addition would result in a 4-substituted pyrazoline (Scheme B), a β-addition would lead to a 3-substituted product (Scheme A). And indeed, the product obtained by the cycloaddition of diazomethane to p-methoxystyrene proved to be identical with an authentic sample of 3-anisylpyrazoline, synthesized *via* the Mannich reaction (11). β-Addition thus appears to prevail unequivocally in the reaction of diazomethane with substituted styrenes, and the unusual rate constant for the p-methoxy compound may be explained in terms of an electron-withdrawing inductive effect predominating over the electron-releasing mesomeric effect.

The cycloaddition of diazocompounds to styrenes is the only synthetic method presently available for the preparation of 1-pyrazolines (4); and the solvation effects observed in this investigation in protic solvents can be utilized to advantage for the synthesis of a number of aryl substituted pyrazolines by carrying out the cycloaddition reaction in aqueous dioxane solutions. Furthermore, using solvation effects (1), cycloaddition of diazomethane to the very unreactive stilbenes can now be achieved leading to the 3,4-diarylpyrazolines, which cannot be readily obtained by cyclization of hydrazones (4) since the starting ketones themselves are not easily available.

EXPERIMENTAL

Materials.

All of the styrenes were used (Aldrich Chemical Co.) without further purification, except styrene itself, which was redistilled prior to use in kinetic studies, and p-methoxystyrene, which was custom synthesized by Frinton Laboratories, South Vineland, New Jersey.

Rate Measurements.

Rate constants for the addition of diazomethane to styrenes were determined at 24.9° using *pseudo*-first-order techniques described previously (9). The solvents used for the kinetic runs were all of reagent grade quality. The reaction course was followed by withdrawing 5.00 ml. aliquots at appropriate time intervals and quenching the latter in a measured volume of a 2% solution of benzoic acid in ethanol at room temperature and titrating the excess acid with standard alkali using phenolphthalein as indicator. The alkali titre values provided a direct measure of the diazomethane concentration at a given time. *Pseudo* first-order rate constants (k_1) were calculated by dividing the factor 0.693 by $t_{1/2}$, the half-life of the reaction; the latter was obtained from the plot of $\log[CH_2N_2]$ against time. The second-order rate constants (k_2) were obtained by dividing the k_1 values by the styrene concentration which was always in large excess. The reactions were followed to 70-80% completion. The data on kinetics are presented in Table II.

The diazomethane solutions were freshly prepared prior to use. There was no nitrogen evolution from the reaction mixture during the course of a kinetic run which lasted only 6-7 hours even for the slowest reaction; this indicated that no decomposition of either diazomethane or the pyrazoline adduct occurred.

For rate determinations in solvents other than dioxane, the diazomethane was prepared in the solvent in question. In the case of solvents such as acetone and dimethylformamide, blank experiments indicated no reaction between the solvent and diazomethane.

In the runs using dioxane, a correction was made for the volume occupied by the styrene in the aliquots, as this solvent (being

slightly acidic) adds appreciably to the blank alkali titre value. If this correction is not made, a slight upward drift in the k_2 values with decreasing reactant concentration, for a given reaction, becomes apparent (9, Table I).

The Hammett ρ values were calculated from least squares plots of log k_X/k_O vs. σ, using an IBM 1130 computer at the Christian Brothers College Computer Center. The program was adapted from Golden's Fortran IV-Programming and Computing (12). Presented in Table III are the ρ values in dioxane and dimethylformamide, respectively. The data for the *p*-methoxy group in dioxane were omitted from the ρ calculation, because of their anomalous nature. The higher ρ value in dimethylformamide results from solvation effects in this solvent.

The correlation coefficients (r) (Table III) were also calculated in the usual manner (13), employing the IBM 1130.

Synthesis of Pyrazoline Adducts.

A procedure very similar to the one previously described in the synthesis of 1,2,3-triazolines (14,15) was used. The styrene (0.015 mole) was dissolved in a freshly prepared solution of diazomethane (0.05 mole) in aqueous dioxane (75 ml.) and the reaction mixture was allowed to stand at room temperature for 4-7 days as required, depending on the reactivity of the styrene. At the end of this period, the mixture was filtered, cooled, and diluted with water. It was then made acidic with dilute hydrochloric acid (150-200 ml.; 3 parts concentrated acid and 20 parts water) and extracted twice with ether to remove any acid-insoluble organic matter. Thereafter, the aqueous solution was cooled to 0° and treated with a slight excess of sodium nitrite; the 1-pyrazoline adducts were converted to the *N*-nitroso derivatives of the isomeric 2-pyrazolines and separated out almost immediately as straw yellow-coloured, voluminous precipitates. The products, after crystallization from appropriate solvents, exhibited m.p.'s identical with those reported for the *N*-nitroso derivatives of 3-substituted-2-pyrazolines, resulting from cyclization of hydrazones (11). The syntheses of the various pyrazolines are listed in Table II, along with other pertinent data.

All of the aryl-1-pyrazolines are reported as the nitroso derivatives of the isomeric 2-pyrazolines, since preliminary attempts at isolating the free 1-pyrazolines have not been quite successful. The 3-aryl-1-pyrazolines were very sensitive to exposure to air and gave rise to high-melting orange-yellow products which failed to yield the *N*-nitroso derivative and appeared to be pyrazoline polymers (probably dimers). Further work on the isolation and characterization of the 1-pyrazolines is in progress.

An authentic sample of 3-anisyl-2-pyrazoline was prepared from diethylaminoethyl *p*-anisyl ketone hydrochloride by heating the latter with potassium hydroxide and hydrazine hydrate according to published procedures (11). Treatment of the pyrazoline in methanolic solution with hydrochloric acid and sodium nitrite yielded the *N*-nitroso derivative, light yellow crystals from acetone, m.p. 163-166° (lit. (11) m.p. 169°). Upon addition of concentrated hydrochloric acid to the methanolic solution, a colourless hydrochloride salt separated out with ease; after crystallization from acetone-methanol mixture, it sintered from 180° and melted at 198-200°. The mixture m.p.'s of these derivatives with those of the adduct from the cycloaddition were undepressed.

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