Low-Temperature Flow NMR Investigation of the Reaction of 2,4,6-Trinitroanisole with Secondary Amines

Colin A. Fyfe,* Sadrudin W. H. Damji,[1b] and Alexander Koll[1a]

Contribution from the Guelph-Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, University of Guelph, Guelph, Ontario, Canada N1G2W1.
Received November 7, 1977

Abstract: Low-temperature flow NMR has been used to investigate the reaction of 2,4,6-trinitroanisole with secondary amines in 50% Me_2SO-50% MeOH solvent. It is found that the σ complex on the substitution pathway (i.e., by attack of the amine at C_1) is formed in a very fast reaction and that it is relatively stable under these conditions. The system does not yield the expected substitution, however. Instead a side reaction involving the solvent methanol occurs yielding the 1,1-dimethoxy Meisenheimer complex.

Introduction

There has been considerable interest in the mechanism of nucleophilic aromatic substitution reactions,[2] particularly in the investigation of Meisenheimer complexes,[3] analogous to the intermediates postulated in the "two-step" mechanism proposed by Bunnett.[4] Recently there have been reports of the successful flow NMR detection of such species during the course of actual substitution reactions.[5,6] In the preceding paper we have presented the results of a flow NMR investigation which characterize such a transient intermediate formed during the nucleophilic aromatic substitution reaction of 2,4,6-trinitroanisole (TNA) (**1**) with *n*-butylamine.[6] In this paper we present the results of a study using the same techniques of the reaction of TNA with secondary amines under identical conditions of solvent and temperature where it was found that the expected substitution does not occur.

Experimental Section

All compounds used were from commercial sources or were prepared by literature techniques and had melting points in agreement with literature values and NMR spectra consistent with their proposed structures. All ^1H NMR spectra were recorded using a Varian H.A. 100 spectrometer. Flow NMR and UV-visible spectra were obtained using previously described equipment and techniques.[6-8] ^{13}C spectra were recorded using a Varian CFT 20 spectrometer (see Acknowledgments).

Results and Discussion

The reactions of TNA with both diethylamine and piperidine were studied at different amine:TNA ratios at −40, −30, and −20 °C. Low temperatures were achieved by using the solvent system 50% Me_2SO-50% MeOH (by volume) as previously. As in the investigation of the reaction of TNA with *n*-butylamine described in the previous paper, several different techniques have been employed in an attempt to unambiguously determine the structures of the species formed, and the results of these studies will be presented separately.

A. Low-Temperature Flow NMR Measurements. The results of a typical run on the TNA:diethylamine (1:2) reaction system are shown in Figure 1 (t = −30 °C). Similar spectral changes are obtained at other temperatures, taking into account changes in rates and equilibrium constants with temperature. The bottom spectrum shows the single absorption (at δ 8.95) due to the two equivalent ring hydrogens of TNA. Subsequent spectra are the results of a stopped-flow experiment and were recorded at the times indicated (beginning of scan) after stopping the flow. They show a fast equilibrium being set up between the TNA and a second species which shows an absorption at δ 8.37. Approximate values for these equilibrium constants are given in Table I. The spectra gradually change with time, a new signal appearing at δ 8.58 and the two peaks initially present gradually disappearing until a single product peak is observed.

The complete time evolution of the reaction may thus be determined from the NMR measurements by simultaneously monitoring the reactant, intermediate, and product concentrations. These are shown in Figure 2 for two typical runs. The rate of decay of the intermediate to form the final product is very temperature dependent and has been indexed by measuring the time taken for the intermediate to decay to 30% of the reaction mixture (Table I), this being a rough guide of a reasonable lower limit for the convenient, accurate measurement of the ^{13}C spectrum of a single species in a mixture (see on). Qualitatively the same spectral changes are observed for reaction mixtures of TNA:amine ratios of 1:3 and 1:4 except that the degree of conversion of TNA to the intermediate species is increased (Table I).

In the case of the reaction of piperidine with TNA there is again the very fast production of an intermediate species, which is almost quantitative at ratios of amine:TNA of 2:1 or greater, and then the subsequent, slower formation of final product. The chemical shifts of these three species are almost identical with those observed for the reaction with diethylamine except that an additional minor product is observed. There exists substantial line broadening in the peaks due to the reactant and intermediate species which could be due to the presence of anion radicals but might also be due to the first equilibrium being fast on the NMR time scale. This latter explanation is thought the more likely as the broadening is evident after relatively long times and involves a species which is thought to bear a negative charge and would be less likely to be involved in electron exchange reactions. By stopping the flow and quickly and repeatedly scanning the spectral region containing these peaks, the complete time evolution of the reaction may be found as before. Selected results are summarized in Table I.

At all temperatures, when the reaction mixture of either amine with TNA was quenched in dilute aqueous acid, *either* immediately after mixing *or* at the end of the reaction (as determined from the NMR results above), only a single product species was isolated. This was identified by its melting point and NMR spectrum as 2,4,6-trinitroanisole. In *no* case was the expected substitution product (the *N,N*-alkylpicramide (**4**)) found in the final reaction mixture. In the case of the reaction with piperidine no compound was observed corresponding to the minor product evident in the NMR spectra. The ^{13}C NMR experiments (see on) suggest that this is picric acid, and it is possible that it is soluble enough that small concentrations are not precipitated.

Thus, in the formation of the final product, the methoxy group of TNA has not been substituted, and both the inter-

0002-7863/79/1501-0956$01.00/0

Table I. Approximate Equilibrium Constants (L mol^{-1}) and Times Taken for the Concentration of the Intermediate to Drop to 30% of the Total Reaction Mixture for the Reaction of TNA with Diethylamine and Piperidine under the Conditions Indicated

temp, °C	[TNA],[a] mol L^{-1}	[diethylamine],[a] mol L^{-1}	K[b]	t 30%, min	[TNA], mol L^{-1}	[piperidine], mol L^{-1}	K	t 30%, min
−40	0.5	1.0	1.7	>120	0.25	0.5	43	>60
−20	0.5	1.0	0.20	[c]	0.25	0.5	21	13.2
−20	0.5	2.0	0.25	16	0.5	1.5	very large	>180
0	0.5	2.0	0.06	0.5	0.25	0.5	12	3.4
0					0.50	1.5	12	7.0
20					0.5	1.5	1.0	1.0

[a] Before mixing equal volumes of reagents. [b] Estimated errors ±20%. [c] Does not reach 30%.

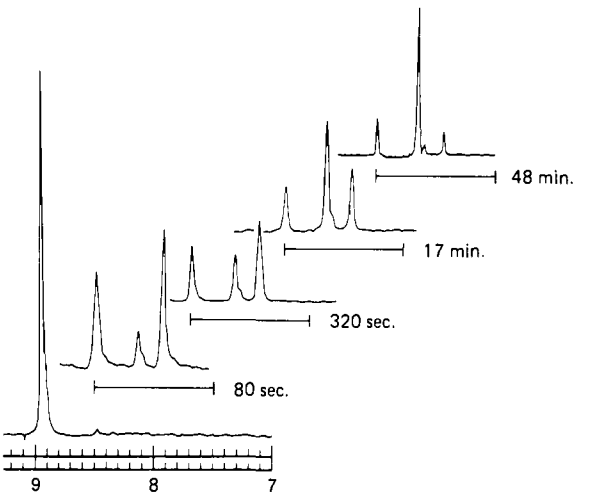


Figure 1. Spectra obtained from a stopped-flow NMR investigation of the reaction of TNA (0.25 M in 50% Me_2SO-50% MeOH) with diethylamine (0.5 M in 50% Me_2SO-50% MeOH) at −30 °C. Bottom spectrum: static spectrum of TNA before reaction. Subsequent spectra were obtained at the times after mixing indicated in the figure (time indicates the beginning of the scan).

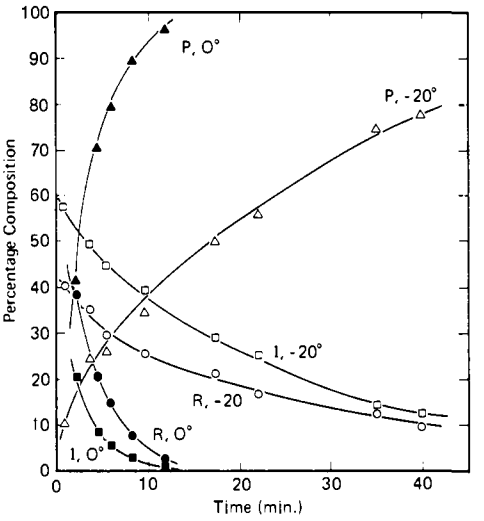
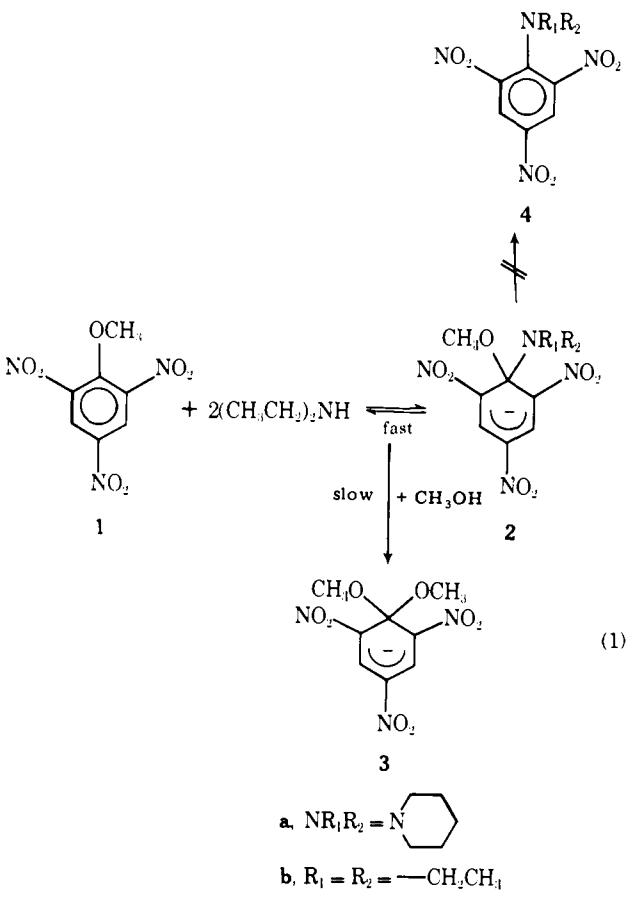


Figure 2. Composition of the reaction mixture as a function of time in terms of the percentage of reactant, intermediate, and product species present for the reaction of TNA (0.5 M in 50% Me_2SO-50% MeOH) with diethylamine (2.0 M in 50% Me_2SO-50% MeOH) at −20 (open symbols) and 0 °C (filled symbols).

mediate and the final product species which are formed must yield TNA on reaction with aqueous acid. A reaction scheme which fits these observations is given below (eq 1). As in the case of the reaction with primary amines described in the previous paper, care must be taken in the assignment of structure based on the ^{1}H NMR results alone since each species shows only a single absorption for the ring hydrogens which indicates only that the plane of symmetry of the original substrate has not been lost. Further, in the present case, there is little direct evidence in support of the assignment of structure **2** (which there was in the reaction with *n*-butylamine where an overall substitution occurred).

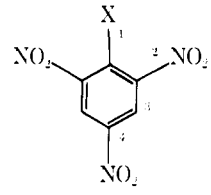
However, in this system, the intermediate species is much longer lived, and from the data in Table I suitable conditions can be chosen under which it is extremely long lived and is the major component of the reaction mixture. Thus, with a TNA:amine ratio of 1:4 and a temperature of −40 °C, it can be predicted that **2** will be the only species present in the reaction mixture and will have a *lifetime* of at least 1 h. This opens up the possibility of obtaining ^{13}C spectra by pulse FT techniques on this system, and they will yield much more diagnostic data regarding the structure of the intermediate species formed.

B. ^{13}C NMR Spectra of the Reaction Mixture and of Reference Meisenheimer Complexes. ^{13}C NMR spectra were recorded at different points during the reaction. The chemical shifts, together with those of several reference compounds, are presented in Table II. From Table II, comparison of the ^{13}C shifts of the parent substrates trinitrobenzene (**5**, X = H) and trinitroanisole (**5**, X = OCH_3) with those from known Meisenheimer complexes derived from them by nucleophilic

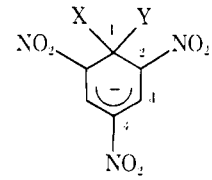


(1)

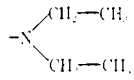
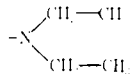
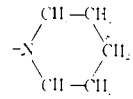
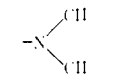
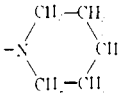
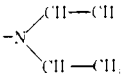
Table II. ^{13}C NMR Chemical Shifts (ppm from the Center Line of the Me_2SO-d_6 Multiplet) for the Reaction Mixtures of TNA with Secondary Amines under the Conditions Indicated, Together with Data on Known Meisenheimer Complexes and Other Reference Compounds[a]



5



6

compd	X	Y	conditions	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
5	H		isol compd, 30 °C in Me_2SO-d_6	79.5	104.2	79.5	104.2				
6	H	^{5}-OCH_3	isol compd, 30 °C in Me_2SO-d_6	29.1	92.3	86.2	81.6	16.9			
6	H		**7** (X = H, Y = OCH_3) plus $NHEt_2$	14.4	93.4	86.1	80.7	5.0	−25.8		
5	^{5}-OCH_3		isol compd, 30 °C	103.1	105.8	85.9	113.1	26.1			
6	^{5}-OCH_3		TNA + $NHEt_2$, −40 °C	52.9	89.0	95.3	78.4	13.1	not obsd	−23.0	
6	^{5}-OCH_3		TNA + piperidine, −40 °C	53.0	89.1	93.8	78.9	13.4	9.2	−11.8	−13.0
6	^{5}-OCH_3		TNA + $NHMe_2$, −35 °C	53.1	93.2	89.5	78.9	13.8	0.6		
6	^{5}-OCH_3	^{5}-OCH_3	isol K^+ salt, 30 °C	64.1	88.8	91.4	79.1	13.0			
6	^{5}-OCH_3	^{5}-OCH_3	TNA + $NHEt_2$, 0 °C	63.9	89.1	90.8	78.9	13.0			
6	^{5}-OCH_3	^{5}-OCH_3	TNA + piperidine, 15 °C	64.1	89.0	91.1	79.1	13.1			
5			isol compd, 30 °C	103.9	105.0	86.8	99.2	13.5	−34.2	−36.1	
5			isol. compd, 30 °C	102.8	105.0	85.7	98.8	6.9	−27.2		
5	-OH										
5	$-O^-$		**6** (X = OH) plus $NHEt_2$, −40 °C	122.2	102.8	85.8	86.5				

[a] The spectra were recorded in 50% MeOH–50% Me_2SO unless otherwise noted.

attack (**6**, X = H, Y = OCH_3; **6**, X = H, Y = $-NEt_2$) and **6**, X = OCH_3, Y = OCH_3, respectively, indicates that there is a large characteristic upfield shift of the ^{13}C signals in forming the σ complex. The largest shift is that of C_1, which changes hybridization from sp^2 to sp^3, and its shift will be characteristic of the attached groups.

The top spectrum in Figure 3 is that of the reactant TNA and the signals can be assigned as indicated in Table II. In general, larger relative signals are to be expected for those carbons which have attached protons, owing to their shorter relative relaxation times and nuclear Overhauser effects. The second spectrum was recorded under conditions where (from the data of Table I) only the first intermediate species should be present. There has been a large upfield shift of all the signals, in agreement with the formation of an sp^3 hybrid carbon and the presence of a negative charge in the ring. The general pattern of signals is similar to those observed in the formation of known Meisenheimer complexes from TNA and TNB discussed above.

The spectrum is thought due to compound **2** in eq 1 where there has been attack of the nucleophile at C_1; that is, the σ complex on the substitution pathway (**6**, X = OCH_3, Y = NEt_2 in Table II). The low-field signals at δ 52.9, 89.0, 95.3, and 78.4 ppm are assigned to the ring carbons C_1, C_2, C_3, and C_4, respectively, the occurrence of four ring carbon resonances indicating that the attack must have preserved the symmetry of the substrate molecule. There is one single carbon resonance at 13.1 ppm which can be assigned to a methoxyl group. The large signals at 4.6 and −25.5 ppm are due to the excess of diethylamine in the system exchange averaged with any diethylammonium salt present and the signal at 10.2 ppm is due to the methanol solvent. There is one signal at −23.0 ppm which can be assigned to the carbon of the methyl in the attached diethylamine moiety in **2**. However, no signal is ob-

served for the carbon of the methylene group. It is thought that this may be at the same shift value as that of the carbon of the solvent methanol which gives a very large absorption. There is some further justification for this structural assignment in the results obtained for the analogous species formed from piperidine and dimethylamine (see on).

Subsequent spectra obtained at higher temperatures show the gradual formation of product species giving the limiting bottom spectrum. The spectrum of this species is quite different from that of *N,N*-diethylpicramide (**6**, X = NEt_2 in Table II) indicating that the expected substitution has not occurred. It is also quite different from those of picric acid (**6**, X = OH) or picrate ion (**6**, X = O^-), products commonly found from side reactions in these systems. In the final spectrum there is still a large upfield shift of the signals relative to TNA, and the general profile is still that of a Meisenheimer complex. Four ring carbons are observed, so the symmetry of the molecule must have been preserved, as indicated by the ^1H NMR spectra. The single peak assigned to the methyl carbon of the diethylamino group in **2** has disappeared, as has the peak assigned to the methoxy carbon in **2**, and a new signal of about twice the intensity has appeared at 13.0 ppm, due to two equivalent methoxy groups. In fact, the spectrum is almost identical with that of compound **3** generated independently (Table II), the small differences in the shift values of the two lowest field peaks being due to the nature of the counterion. Most importantly, when **3** is added to a solution of the final product, no new peaks appear in either the ^1H or ^{13}C NMR spectra, confirming this assignment of the structure.

In the reaction with piperidine the lifetime of the first intermediate is again long enough that ^{13}C spectra can be obtained using pulse FT techniques if the correct conditions are chosen. The results are summarized in Table II. The spectrum of the first intermediate is very similar to that of the corresponding compound in the reaction of diethylamine (Table II). The spectrum is consistent with structure **2**, showing four types of ring carbon, a large upfield shift from TNA itself, one methoxyl carbon, and signals from carbons of a piperidine ring shifted downfield from those of the excess piperidine. The major product species is thought again to be the dimethoxy complex **3**. The ^{13}C peaks in the spectrum of the final solution are at positions identical with those from the final solutions of diethylamine (Table II) and signals due to free piperidine are now observed. Some picrate ion is also formed in a slow decomposition reaction contributing two minor peaks in the spectrum. These results, and those of the previous sections, can again be rationalized in terms of the reaction eq 1 proposed above. There is further support for this scheme in that the reaction of dimethylamine with TNA yields a very similar initial ^{13}C spectrum for the first intermediate (**6**, X = OCH_3, Y = NMe_2 in Table II) and again yields the dimethoxy Meisenheimer complex on warming.

C. Low-Temperature Flow UV-Visible Spectroscopic Measurements. Flow UV-visible spectroscopic measurements were carried out using the same mixing apparatus and a short path length flow cell under conditions as close to those of the NMR experiments as possible, firstly to check the general validity of the proposed reaction (eq 1) and secondly to assign the UV-visible spectra of the species involved to facilitate kinetic measurements by this technique in dilute, relatively ideal solutions. The TNA concentration was 0.02 M, amine concentrations ranged from 0.02 to 1.0 M, and the temperature range was that covered by the NMR experiments.

In the case of the reaction with diethylamine at −30 °C, the spectrum observed under flowing conditions (0.6 s after mixing) shows two maxima (λ_{1max} 430, λ_{2max} 500 nm) characteristic of a Meisenheimer complex. However, on stopping the flow, there is no longer the immediate disappearance of this spectrum as in the case of the reaction with *n*-butylamine (previous paper), but rather a gradual increase in intensity of these absorptions. Some of this might be attributed to changes in the path length of the cell in the change from flowing to nonflowing conditions, but the absolute change is thought to be outside of this error. The concentrations of the various species may be predicted at least approximately from the data in Table I, and from this it is clear that the spectral changes are due to the formation of a product which has a similar UV-visible spectrum to that of the intermediate, as is the case for the species in eq 1.

In the case of the reaction with piperidine, there is a larger degree of conversion of reactant to intermediate as would be expected from the data in Table I. The flow spectrum again shows two absorption maxima (λ_{1max} 450, λ_{2max} 500 nm) but in this case changes little with time. These observations are also in accord with eq 1, the change from intermediate to product again occurring but producing little change in the spectrum because of the larger quantity of intermediate produced in the first fast reaction and the similarity between the two spectra.

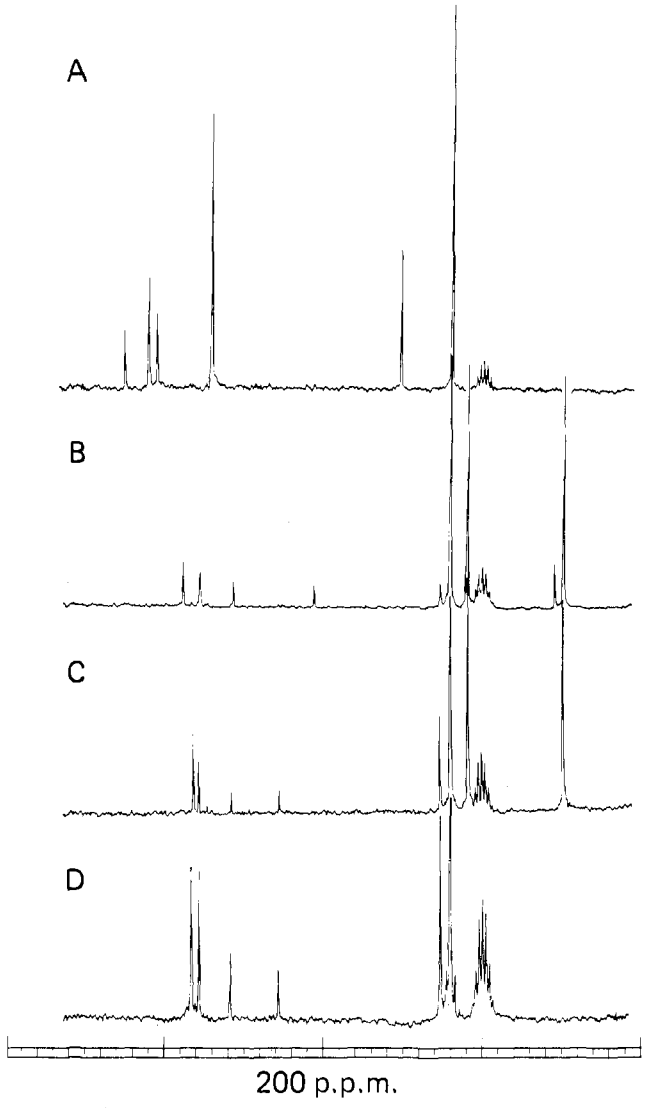


Figure 3. ^{13}C NMR spectra recorded at low temperatures during the reaction of TNA (0.5 M in 50% Me_2SO-d_6–50% MeOH) with added diethylamine to make the solution 2.0 M in diethylamine. Top spectrum: ^{13}C spectrum of TNA at −40 °C before reaction. Second spectrum: ^{13}C spectrum after the addition of diethylamine at −40 °C (accumulation time = 60 min). Third spectrum: ^{13}C spectrum of reaction mixture warmed to 0 °C (accumulation time = 60 min). Bottom spectrum: ^{13}C spectrum of the isolated dimethoxy Meisenheimer complex (**3**) redissolved in 50% Me_2SO–50% MeOH.

Conclusions

Thus, in the attack of secondary amines on TNA, it is thought that the σ complexes on the substitution pathway are formed in a very rapid equilibrium and are much longer lived than that from the primary amine discussed in the previous paper. However, the expected conversion to the substituted picramide product **4** does not occur. There is, instead, a reaction to produce the dimethoxy Meisenheimer complex **3**. The difference between this and the reaction of the primary amine where substitution does occur is possibly due to steric interactions. Thus, in the case of secondary amines, steric interactions between the dialkylamino group and the two ortho nitro groups in the *product* picramide will raise the energy of this species and the transition state for its formation from the intermediate and allow for the slow formation of the dimethoxy complex. Such considerations may well also explain the exceptional stabilities reported for the $OR-NR_1R_2$ complexes from dinitro- and trinitronaphthyl ethers,[9,10] and from hindered picryl ethers with very hindered amines.[11] A complete description of this system was possible only using ^{13}C NMR and flow NMR at low temperatures, although it is important to note that ^1H NMR investigations alone may well be "ambiguous" for reactions involving symmetrical species where only single signals are observed.

Acknowledgments. The authors would like to acknowledge the financial support of the National Research Council of Canada in a personal research grant (to C.A.F.). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The authors would also like to acknowledge very helpful discussions with Drs. J. F. Bunnett and C. F. Bernasconi. Part of this work was done while one of us (C.A.F.) was a Visiting Foreign Scientist at the IBM Research Laboratory, San Jose, Calif., and he would like to acknowledge these facilities and the technical assistance of T. Horikawa and E. Nazal.

References and Notes

(1) (a) Department of Chemistry, University of Wroclaw, Wroclaw, Poland. (b) Pearson College, Victoria, B.C., Canada.
(2) C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 33 (1973).
(3) (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Q. Rev., Chem. Soc.*, **22**, 123 (1968); (c) M. R. Crampton, *Adv. Phys. Org. Chem.*, **7**, 211 (1969); (d) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970); (e) C. A. Fyfe in "The Chemistry of the Hydroxyl Group", S. Patai, Ed., Interscience, New York, N.Y., 1971.
(4) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 275 (1951).
(5) C. A. Fyfe, A. Koll, S. W. H. Damji, C. D. Malkiewich, and P. A. Forte, *Can. J. Chem.*, **55**, 1468 (1977).
(6) C. A. Fyfe, A. Koll, and S. W. H. Damji, *J. Am. Chem. Soc.*, preceding paper in this issue.
(7) S. W. H. Damji, Ph.D. Thesis, University of Guelph, 1976.
(8) C. A. Fyfe, M. Cocivera, S. W. H. Damji, T. A. Hostetter, D. Sproat, and J. O'Brien, *J. Magn. Reson.*, **23**, 377 (1976).
(9) S. Sekiguchi, K. Shinoyaki, T. Hirose, K. Matsui, and K. Sekine, *Bull. Chem. Soc. Jpn.*, **49**, 2264 (1974).
(10) S. Sekiguchi, T. Itagaki, T. Hirose, K. Matsui, and K. Sekine, *Tetrahedron*, **29**, 3527 (1973).
(11) L. B. Clapp, H. Lacey, G. G. Beckwith, R. M. Srivastara, and N. Muhammed, *J. Org. Chem.*, **33**, 4262 (1968).

Pyruvamides. 3. Involvement of the Amide Group in Carbinolamine Formation, *gem*-Diamine Formation, and Transimination[1]

William Lopatin, Paul R. Young, Jr., and Terence C. Owen*

Contribution from the Department of Chemistry, University of South Florida, Tampa, Florida 33620. *Received August 3, 1978*

Abstract: Previous work on the addition of nitrogen nucleophiles to the ketone groups of pyruvamides had led to the suggestion that the amide group might be involved as an intramolecular catalyst. The main purpose of the present work was to confirm or to negate this possibility. Rate constants for carbinolamine formation from semicarbazide with pyruvanilide and four ring-substituted pyruvanilides at pH 7 yielded a linear σ correlation with a ρ of 0.28, which is consistent with a normal mechanism involving rate-determining trapping of a zwitterionic intermediate by water. *N*-Methylpyruvanilide reacted one-third as quickly as pyruvanilide did. *gem*-Diamine formation from semicarbazide and pyruvamide imines proceeds to a good equilibrium extent and can be observed directly. Isomerization of the initial semicarbazide-protonated *gem*-diamine to the more stable amine-protonated diamine is responsible for the unusually favorable equilibrium position. An imine for which intramolecular amide group involvement is structurally precluded yielded a pH-rate profile markedly different from that given by a simple pyruvamide imine, but the difference is probably due to factors other than this preclusion. Transimination of pyruvamide and pyruvanilide imines with amines in nonpolar aprotic solvents is slow and is strongly accelerated by small amounts of acid. The rate of the spontaneous reaction is attributable to the amide group behaving simply as an intermolecular proton donor or acid catalyst. *p*-Chloropyruvanilide methylimine reacted four times as rapidly as pyruvanilide methylimine and an *N*,*N*-disubstituted imine reacted 100 times more slowly than did the corresponding pyruvamide imine, as would be expected on this basis. A σ correlation for substituents in the amine was linear with $\rho = -0.79$. Reactions in pyridine-water mixtures were no faster than in dry pyridine. We conclude that in no case was the amide group involved as an intramolecular catalyst despite the most favorable geometry of these systems, a finding which bodes ill for the likelihood of intramolecular catalysis by amide groups in biochemical systems generally.

The reaction of pyruvamides with semicarbazide to give carbinolamines, necessary intermediates in the formation of semicarbazones, is rather fast.[2] Of itself this is not unduly surprising. The electron-withdrawing carboxamide group is attached directly to the site of nucleophilic attack, and the effects of such groups in promoting both the rates and the equilibria of formation of carbonyl addition compounds are well documented and entirely reasonable.[3-5] There seemed to be indications, however, that the effects might be larger than would be expected in terms of electronic factors alone. Methyl

0002-7863/79/1501-0960$01.00/0