gave significant correlations with eq 2. There is generally good agreement observed between the experimentally observed values of the unsubstituted compound, h_{obsd}, and the calculated value, h of eq 2. To determine quantitatively whether h_{obsd} is significantly different from h, "Student t tests"[17] were carried out for all of the h_{obsd} values available for sets which gave significant correlations with eq 2. The results are set forth in Table V. In 16 of the 18 sets studied, h_{obsd} does not differ significantly from h. We conclude therefore that the value for the unsubstituted compound generally lies on the correlation line for ortho-substituted nmr data. We further conclude from the previous discussion of our method of detecting steric effects that no constant steric effect is generally extant in these sets.

Mobile Keto Allyl Systems. IX.[1] Kinetics and Mechanism of Amine Exchange Reactions with β-Ketoallylamines

NORMAN H. CROMWELL,*[2] KIYOSHI MATSUMOTO, AND A. DENISE GEORGE

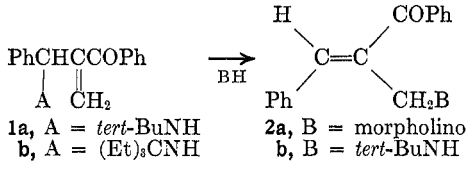
Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received May 26, 1970

Rate data for the reaction of 2-[(α-substituted amino)benzyl]acrylophenones (1) with morpholine and with *tert*-butylamine in acetonitrile and in isooctane were obtained. Overall second-order kinetics were observed. From rate and thermodynamic constants, the mechanism of the proposed "SN2′-type" reaction is discussed.

In a preceding paper of this series,[3] kinetic data concerning the aminotropic allylic rearrangements of 2-[(α-substituted amino)benzyl]-1-indenones to 3-substituted amino-2-benzal-1-indanones were interpreted by a variant of an SN2′ mechanism.

The reactions of 2-[(α-substituted amino)benzyl]-acrylophenones (1) with amines to give the corresponding α-(aminomethyl)chalcones (2) have been reported previously.[4] The need for quantitative information concerning the amine exchange reactions of **1** prompted this investigation.



1a, A = *tert*-BuNH **2a**, B = morpholino
b, A = $(Et)_3CNH$ **b**, B = *tert*-BuNH

In a preliminary experiment, it was shown that the rates of rearrangement of 2-[(α-substituted amino)benzyl]acrylophenones (1) to the corresponding α-(aminomethyl)chalcones (2) without added amine (BH) were at least 100 times as slow as the rates of the amine exchange reactions we have studied.

Similarly, the rates of reaction of compounds **2a** and of **2b** with *tert*-butylamine and with morpholine were negligible compared with rates of the amine exchange reactions of compounds **1a** and **1b**.

The kinetic results reported below in Tables I, II, IV, and V show that the reaction of **1a** with the *tert*-butylamine produced in the reaction of morpholine with **1a** may be discounted, since in acetonitrile the ratio k(morpholine)/k(*tert*-butylamine) is *ca.* 80 and in isooctane the same ratio is *ca.* 17.

Hence the rate data for the rearrangements of compounds **1** with amines would not contain any appreciable contribution from other multistep routes.

The reaction of **1a** with morpholine in acetonitrile exhibited second-order kinetics and was first order in **1a** and in the amine; the rate coefficients are given in Table I.

TABLE I
VALUES OF SECOND-ORDER RATE COEFFICIENTS k_2 FOR THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (**1a**) WITH MORPHOLINE IN ACETONITRILE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[Morpholine], mol/l.	$10k_2$,[a] l. mol^{-1} min^{-1}
10.0	0.00738	0.00649	4.9
10.0	0.00742	0.0148	4.8
10.0	0.00614	0.0221	5.1
20.0	0.00904	0.0127	9.5
20.0	0.00817	0.0221	9.4
20.0	0.00395	0.0150	9.4
30.0	0.00501	0.00252	19
30.0	0.00527	0.00988	17
30.0	0.00324	0.0137	18

[a] E = 12 kcal/mol [$k_2 = Ae\,(-E/RT)$], $\Delta S^{\pm}_{20}$ = −27 eu [$k_2 = (ekT/h)\exp(-E/RT)\exp(\Delta S^{\pm}/R)$].

The reaction of **1a** with *tert*-butylamine in acetonitrile was pseudo first order in **1a**, as required by the kinetic equation[3] (Table II).

TABLE II
VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (**1a**) WITH *tert*-BUTYLAMINE, IN ACETONITRILE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[*tert*-Butylamine], mol/l.	10^2k_2[a] l. mol^{-1} min^{-1}
20.0	0.00727	0.0942	1.2
20.0	0.00648	0.145	1.2
20.0	0.00628	0.221	1.1
30.0	0.00655	0.137	2.2
30.0	0.00797	0.177	2.2
30.0	0.0115	0.139	2.2
40.0	0.00828	0.062	4.5
40.0	0.00821	0.093	4.3
40.0	0.00882	0.124	4.3

[a] E = 12 kcal/mol, $\Delta S^{\pm}_{20}$ = −36 eu.

(1) For paper VIII in this series, see G. Maury and N. H. Cromwell, *J. Org. Chem.*, **34**, 596 (1969).

(2) To whom inquiries concerning this article should be addressed.

(3) G. Maury, E.-M. Wu, and N. H. Cromwell, *J. Org. Chem.*, **33**, 1907 (1968).

(4) (a) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, No. 52, 4833 (1965); (b) N. H. Cromwell and R. P. Rebman, *J. Org. Chem.*, **32**, 3830 (1967).

The reaction of 2-[α-(triethylcarbinylamino)benzyl]-acrylophenone (**1b**) with morpholine was followed kinetically in order to investigate the steric effect of the leaving amino group. The results are presented in Table III.

TABLE III

VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(TRIETHYLCARBINYLAMINO)BENZYL]ACRYLOPHENONE WITH MORPHOLINE, IN ACETONITRILE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[Morpholine], mol/l.	$10k_2$ l. mol^{-1} min^{-1}
20.0	0.00596	0.00710	5.50
20.0	0.00695	0.0142	5.47
20.0	0.00596	0.0213	5.47

In the nonpolar solvent isooctane, the rate data for the reaction of **1a** with morpholine and with *tert*-butylamine were obtained, and are shown in Tables IV and V.

TABLE IV

VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE WITH MORPHOLINE, IN ISOOCTANE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[Morpholine], mol/l.	10^2k_2[a] l. mol^{-1} min^{-1}
20.0	0.00612	0.193	1.5
20.0	0.00834	0.116	1.5
20.0	0.00766	0.0774	1.4
30.0	0.00181	0.0132	3.0
30.0	0.00115	0.0129	3.2
30.0	0.00383	0.0110	3.1
40.0	0.00947	0.0986	6.1
40.0	0.0101	0.0407	5.8
40.0	0.00789	0.163	6.0

[a] E = 13 kcal/mol, $\Delta S^{\ddagger}_{20}$ = −32 eu.

TABLE V

VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (**1a**) WITH *tert*-BUTYLAMINE, IN ISOOCTANE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[*tert*-Butyl-amine], mol/l.	10^2k_2 l. mol^{-1} min^{-1}
30.0	0.00851	0.166	2.0
30.0	0.00937	0.154	1.9
30.0	0.0108	0.295	1.9

Discussion

Nucleophilic substitution reactions in which the strength of the new CN bond is of major kinetic importance frequently exhibit an order of reactivity which parallels the order of basicity of the nucleophile toward a proton.[5a] For example, the order of reactivity, di-*n*-butylamine > cyclohexylamine, for the direct substitution reactions of arylsulphonylhalogenoethylenes[5b] is in agreement with the relative basicities of the amines.[6] However, the observed order of reactivity of morpholine and of *tert*-butylamine toward 2-[α-(*tert*-butylamino)benzyl]acrylophenone, k(morpholine)/k(*tert*-butylamine) ~ 80, opposes the relative basicities of these amines in aqueous solution[6] and is indicative of a considerable sensitivity of the reaction toward the steric requirements of the nucleophile. A similar but smaller sensitivity for the size of the leaving group is apparent in the reactions of **1a** and of **1b** with morpholine, where the rate ratio k(**1a**)/k(**1b**) ~ 2.

Stork and White established a cis orientation of the incoming and leaving groups in a SN2′ reaction.[7] The steric effects observed in the reactions of **1a** and of **1b** with amines may result from a similar cis orientation of the nucleophile and the departing amine in a rate limiting transition state.

Solvent effects on the rates of the reactions of 2-[α-(*tert*-butylamino)benzyl]acrylophenone with morpholine and with *tert*-butylamine were k(acetonitrile)/k(isooctane) ~ 60 and ~ 12, respectively. The observed rate enhancement by a factor of 60 for the reaction of morpholine in acetonitrile and the less negative value for the entropy of activation in acetonitrile (−27 eu) compared with the entropy of activation in isooctane (−32 eu) are of an order of magnitude which may be accommodated by a dipolar transition state.[8] A dipolar transition state may result if the carbonyl group were to act as a sink for a considerable amount of the developing negative charge. The smaller solvent effect on the rate of the reaction with *tert*-butylamine may be attributed to steric hindrance of solvation.

Two main reaction pathways may be envisaged as rationale of the present observations. The reaction may be synchronous, with a small amount of bond cleavage as represented by path a, in Scheme I. Alternatively, the mechanism may involve the addition of the amine to the α,β-unsaturated ketone to give an intermediate, followed by the elimination of a molecule of amine in a second step. Initial addition of the amine may give structure **8**. If the collapse of **8**, resulting in the departure of the leaving group, were to occur more rapidly than proton transfer to the carbonyl group, then **8** would represent a metastable intermediate. If proton transfer were the more rapid process or if the amine added in a concerted manner to the starting substituted aminobenzylacrylophenone, the 1,4 adduct **5** or **6** would result as the intermediate. Although the adduct **5** or **6** was not detected in any of the reactions, such negative evidence does not preclude its existence.

In summary, all of the data obtained are consistent with a variant of an SN2′ mechanism in which the β-carbonyl function supports a major portion of the developing negative charge in a dipolar transition state.

Experimental Section[9]

2-[α-(*N*-Triethylcarbinylamino)benzyl]acrylophenone (1b).—From 6.02 g (0.02 mol) of α-(bromomethyl)chalcone[4] was obtained 5.0 g of **1b**: yield, 78%; mp 71° (recrystallized from *n*-hexane); $\nu_{C=O}$ (CCl_4) 1681 cm^{-1}; nmr peaks *ca.* 445 (m, 10 H, aromatic), 380 (t, 1 H, J = 1.5 Hz, vinyl), 334 (t, 1 H, J = 1.5, vinyl), 301

(5) (a) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Organic Chemistry monographs, Vol. 6, A. T. Blomquist, Ed., Academic Press, London, 1965, Chapter 4. (b) S. Ghersetti, *et al.*, *J. Chem. Soc.*, 2227 (1965).

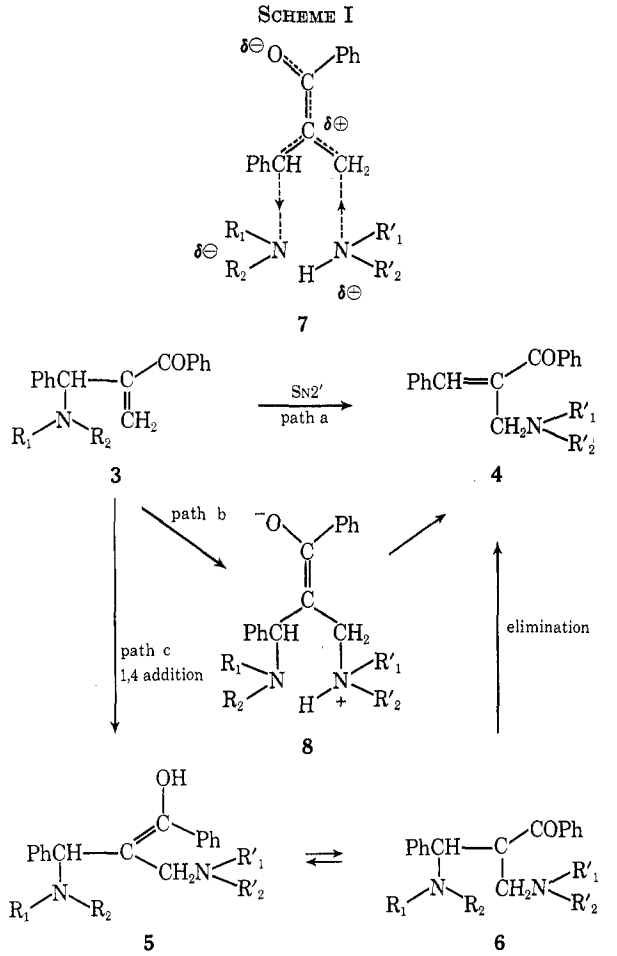
(6) J. J. Christenson, *et al.*, *J. Chem. Soc. A*, 1212 (1969).

(7) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(8) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 379.

(9) Melting points were read with a calibrated thermometer. Infrared spectra were measured with a Perkin-Elmer Model 21 instrument. Nmr spectra were determined with a Varian A-60 spectrometer. Ultraviolet absorption spectra were obtained with a Cary Model 14 spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Inc.

SCHEME I



(s, 1 H, benzyl), 82 (q, 6 H, J = 7 Hz, methylene), 41.5 Hz (t, 9 H, J = 7 Hz, methyl).

Anal. Calcd for $C_{28}H_{29}NO$: C, 82.33; H, 8.71; N, 4.11. Found: C, 82.22; H, 8.75; N, 4.12.

Synthetic and Kinetic Procedures.—The reactants were prepared by methods previously reported[4,10] and recrystallized from Spectrograde *n*-hexane or isooctane.

The morpholine and *tert*-butylamine were distilled over BaO and then redistilled twice. Spectro grade acetonitrile and isooctane were used as solvents.

A constant temperature water bath was employed with a contact thermometer, which had an accuracy of ±0.03°. Optical densities were determined on a Cary Model 14 ultraviolet spectrophotometer.

The stabilities of the starting aminoacrylophenones and resulting aminochalcones were checked under the conditions used during the kinetic studies and found to be satisfactory.

The reaction rate was followed by measuring the rate of appearance of the band at 282 mμ due to the cinnamoyl chromophore of the aminochalcone. A correction was made in each case for the interference by slight absorption in this region due to the reactant. The concentrations of the reactant and product were deduced from the corrected optical density at λ_{max} (282 mμ).

(10) E. Doomes and N. H. Cromwell, *J. Org. Chem.*, **34**, 310 (1969).

The rate constants were calculated using the following expression, $k_2 = 1/(b-a)\ln[a(b-x)/b(a-x)]$, where a and b are the initial concentrations of the starting ketone and amine, respectively; x is the concentration of the product. Rate constants were obtained by the least-squares method.

Reaction of 2b with Morpholine in Methanol, Benzene, and Acetonitrile.—A 0.30-g sample of **2b** was dissolved in 20 ml of methanol and 1.01 g (10 equiv) of morpholine added and the mixture stirred for 8 days. After evaporation of solvent under vacuum, a sample of the oily residue was dissolved in carbon tetrachloride containing TMS. Nmr analysis showed the presence of only **2a**. The pale yellow crystals were obtained from *n*-hexane, 0.29 g (90%). The experiment described above was repeated in benzene and in acetonitrile. A 100% conversion to **2a** was observed in acetonitrile and a 75% conversion in benzene using nmr analyses. Periodic analysis during the course of the reaction in benzene-d_6 and in acetonitrile-d_3 showed the presence of only **2a** and **2b**.

Attempts to Prepare Other 2-[(α-Substituted amino)benzyl]-acrylophenones. Reaction of α-(Bromomethyl)chalcone with Diisopropylamine.—The mixture of 1.50 g (0.005 mol) of α-(bromomethyl)chalcone and 10.0 g (0.01 mol) of diisopropylamine in 120 ml of benzene was stirred for 24 hr and allowed to stand at room temperature for 15 days. Periodic nmr analysis showed the presence of α-(*N*-diisopropylamino)methylchalcone (main) and of only a small amount of the corresponding acrylophenone. The precipitated amine hydrobromide was removed by filtration. Evaporation of solvent gave an oil. Attempts at crystallization failed.

This oily material turned in color from yellow to purple on standing for a day: nmr peaks 420–490 (m, 11 H, vinyl and aromatic), 224 (d, 2 H, J = 1.2 Hz, methylene), 108.5 (quintuplet, 2 H, J = 6.5 Hz, methine), 48 and 65 Hz (two d, 12 H, J = 6.5 Hz, methyl). In this case only weak signals due to the aminoacrylophenone were detected, *i.e.*, 322 (t, J = 15 Hz, vinyl), 351 (s, vinyl), 328 Hz (s, methine). These signals did not disappear after 24 hr in chloroform-*d* at room temperature. The same reaction was carried out in acetonitrile. Only the aminomethylchalcone was obtained.

Reaction of α-(Bromomethyl)chalcone with Methyl Isopropylamine.—A 6.02-g sample (0.02 mol) of α-(bromomethyl)chalcone was dissolved in 500 ml of *n*-pentane. To this solution 2.93 g (0.04 mol) of methyl isopropylamine was added with stirring. After 1 hr almost all of the α-(bromomethyl)chalcone had disappeared (tlc). The precipitated amine hydrobromide was removed and evaporation of solvent gave oily products. Nmr showed the presence of 2-[α-(methylisopropylamino)benzyl]-acrylophenone and 2-(α-methylisopropylaminobenzyl)chalcone in *ca.* 1:1 proportion. In this case, the signals due to the aminoacrylophenone disappeared in chloroform-*d* after 24 hr at room temperature: nmr peaks for the aminochalcone 430–480 (m, 11 H, aromatic and vinyl), 219.5 (s, 2 H, methylene), 172 (quintuplet, 1 H, J = 6.5 Hz, methine), 131 (s, 3 H, *N*-methyl), 58 Hz (d, 6 H, J = 6.5 Hz, methyl). The same reaction was carried out in acetonitrile and only the aminomethylchalcone was obtained.

Registry No.—**1a**, 7204-42-4; **1b**, 26885-66-5; morpholine, 110-91-8; *tert*-butylamine, 75-64-9.

Acknowledgments.—This investigation was supported in part by the National Cancer Institute of the U. S. Public Health Service, Grant No. CA-02931, and in part by the Research Council of the University of Nebraska.