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Nucleophilic Substitution Reactions of *trans*-3-Methoxy-4′-substituted Acrylophenones[1,2]

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Abstract: Aminations of *trans*-3-methoxy-4′-substituted acrylophenones (**1–5**) to 3-substituted amino-4′-substituted acrylophenones in water solution are characterized by (1) rates which are first order in amine and first order in acrylophenone, (2) a deuterium solvent kinetic isotope effect $k(D_2O)/k(H_2O) = 1$, (3) $\rho = 1$, (4) a Bronsted-type catalytic coefficient $\beta = 0.37$ for glycine ethyl ester, aminoethanol, and *n*-butylamine, (5) a 90-fold decrease in reactivity when a β-methyl group is substituted for a hydrogen atom, (6) formation of cis product from trans reactant for reaction of the 4′-nitro derivative with aniline, (7) formation of trans product from trans reactant for reaction of the 4′-chloro derivative with *N*-methylaniline. In light of these results, the nucleophilic addition–elimination reactions are visualized as proceeding via rate-determining nucleophilic attack of the amine at the β carbon of 4′-substituted acrylophenones.

Introduction

Nucleophilic addition–elimination reactions (eq 1) of electrophilic olefins (Y = CO, CN, NO_2, C=N–, etc.) having electronegative atoms (X = O, N, halogen) at the β carbon

$$AH + X\text{—}\overset{\beta}{C}\text{=}\overset{\alpha}{C}\text{—}Y \longrightarrow A\text{—}C\text{=}C\text{—}Y + XH \quad (1)$$

appear to be important reactions in bioorganic chemistry. Candidate examples are the methylation of 2′-deoxyuridylate to give thymidylate catalyzed by thymidylate synthetase,[3] the alkylation of biomacromolecules by plant-derived tumor inhibitors such as jatrophone,[4] and the alkylation of aspartate amino transferase by the antibacterial L-2-amino-4-methoxy-*trans*-3-butenoic acid, an irreversible k_{cat} enzyme inhibitor which is activated via ketimine formation with the pyridoxal phosphate cofactor of the enzyme.[5]

The details of mechanism of nucleophilic addition–elimination reactions of aliphatic and aromatic compounds, in particular the role of catalysis in these reactions, are of current interest.[6-12] Results show there is a general requirement for catalysis in electrophilic olefins possessing relatively poor leaving groups (X, eq 1);[9,10] this has been interpreted to entail proton transfer from zwitterionic intermediates formed from reactions of amines (AH = R_1R_2NH, eq 1) with electrophilic olefins to acceptor bases (a second amine molecule), followed by protonation of the leaving group to facilitate X–C (eq 1) bond cleavage. Here we report the kinetics results of the reactions of *trans*-3-methoxy-4′-substituted acrylophenones (**1–5**) with primary and secondary amines to give 3-substituted amino-4′-substituted acrylophenones:

$$4'\text{-}XC_6H_4COCH\text{=}CHOCH_3 + R_1R_2NH \longrightarrow 4'\text{-}XC_6H_4COCH\text{=}CHNR_1R_2 + CH_3OH$$

We were attracted to this study because of: the possibility of detecting catalysis among the reactions of **1–5** and our desire to understand the role of catalysis in such reactions; the possibility of distinguishing between a concerted nucleophilic displacement reaction and a nucleophilic addition–elimination reaction, still a disputable feature of mechanism, based on ρ; and finally the resemblance of **1–5** to electrophilic reagents of biological interest and the likelihood that the chemistry of **1–5** would contribute to an understanding of the bioorganic chemistry of similar small molecule–large molecule interactions.

Experimental Section

Apparatus. The apparatus used was previously described.[13]

Reagents and Compounds. Fisher Certified ACS grade inorganic salts and hydroxylamine were used. Aminoethanol, imidazole, *tert*-butylamine, ethyl glycinate, morpholine (Eastman Organic Chemicals), 4-methoxy-3-buten-2-one, aniline, *N*-methylaniline (Aldrich Chemicals), deuterium oxide, deuteriochloric acid (Stohler Isotope Co.) were used. *trans*-3-Methoxy-4′-substituted acrylophenones [$N(CH_3)_2$ (**1**), OCH_3 (**2**), H (**3**), Cl (**4**), NO_2 (**5**)] were previously synthesized.[13] 3-Methoxy-4′-nitrocrotonophenone (**6**) was prepared by the method of Weygand.[14]

Kinetics. The reactions of **1–6** with various amines were monitored by recording the decrease or increase in absorbance vs. time at the analytical wavelength (nm): **1**, 370; **2**, **3**, 360; **4**, 345; **5**, 365; **6**, 360. Reactions were carried out under pseudo-first-order conditions (**1–6** = 10^{-4}–10^{-5} M) at 30 ± 0.1 °C, and ionic strength was calculated to be 0.1 M (KCl). The pH of each solution was measured before and after all runs and remained constant (±0.02 pH unit). Cuvettes (3 ml) were filled to the stopper level with appropriate solutions and allowed to come to thermal equilibrium (20–30 min). Reactions were initiated by adding a known amount of **1–6** in methanol[15] or tetrahydrofuran from a calibrated syringe to reaction solutions. Reactions were followed to at least 2 half-lives and were found to be pseudo-first-order. Pseudo-first-order rate constants, k_{obsd}, were obtained by multiplying the slopes of plots of log $(OD_\infty - OD_i)/(OD_\infty - OD_t)$ for absorbance increase and log $(OD_i - OD_\infty)/(OD_t - OD_\infty)$ for absorbance decrease vs. time by 2.303. pD was calculated by adding 0.4 to pH meter readings of pH.[16] Reactions were carried out in aqueous amine–amine hydrochloride buffers prepared by addition of calculated quantities of 1 N HCl to weighed quantities of amine.

Product Analysis.[34] Formation of *cis*-3-substituted amino-4′-substituted acrylophenones from reactions of **1–6** with various primary amines was assumed from the following experiments.

***cis*-4-Anilino-3-buten-2-one.** *trans*-4-Methoxy-3-buten-2-one (6 mmol) was added to aniline (6 mmol) suspended in water. The reaction mixture was stirred for several hours at room temperature. The

Table I. Rate Data for Reactions of Compounds (**1–6**) in Aminoethanol Buffer Solution[a]

Compd	k_2, M^{-1} min^{-1}	pH (pD) range	Range of aminoethanol concn	No. of pH's	No. of k_{obsd}
1 ($N(CH_3)_2$)	12.4 ± 0.3	8.40–9.13	0.02–0.15	4	40
1[c]	9.18 ± 0.3	8.63	0.1–1.0	1	6
2 (OCH_3)	44.5 ± 0.6	8.78–9.38	0.005–0.05	2	22
2[b]	45.4 ± 0.4	9.00–9.39	0.01–0.05	2	20
3 (H)	92.9 ± 0.8	8.39–8.78	0.008–0.05	2	20
4 (Cl)	174.4 ± 3.3	8.36–8.56	0.01–0.05	2	20
5 (NO_2)	504.5 ± 41.7	8.36–8.38	0.01–0.06	1	12
6[d]	5.65 ± 0.38	9.05–9.38	0.02–0.10	2	30

[a] Temperature, 30 °C; solvent, H_2O; μ, 0.1 M (KCl); pK_a, 9.39. [b] Solvent, D_2O; pK_a (D_2O) = 9.99. [c] μ, 1.0 M (KCl). [d] 3-Methoxy-4′-nitrocrotonophenone.

Table II. Rate Data for Reactions of *trans*-3-Methoxy-4′-dimethylaminoacrylophenone in Various Amine Buffer Solutions[a]

Amine	pK_a	k_2, M^{-1} min^{-1}	pH range	Concn range of buffer	No. of pH's	No. of k_{obsd}
Aminoethanol	9.39	12.4 ± 0.3	8.40–9.13	0.02–0.15	4	20
Imidazole	6.97	0.23	7.92	0.02–0.10	1	12
n-Butylamine[a]	10.51	38.2 ± 0.7	9.22–9.56	0.04–0.10	3	27
Hydroxylamine[b]	5.91	3.19	6.86	0.02–0.10	1	6
tert-Butylamine	10.46	0.40 ± 0.02	10.46–10.77	0.03–0.15	2	18
Glycine ethyl ester[b,c]	7.74	3.54 ± 0.31	7.74–8.17	0.04–0.10	2	14
Morpholine	8.45	19.1 ± 2.1	7.84–8.29	0.01–0.10	4	20
Morpholine[d]	8.45	19.3 ± 0.2	8.27	0.1–1.0	1	7

[a] Temperature, 30 °C; solvent, H_2O; μ, 0.1 M (KCl). [b] The method proposed by Swinbourne[20] was applied to obtain $(OD)_\infty$. [c] A decrease in pH with time was observed, which is due to the hydrolysis of glycine ethyl ester to glycine. [d] μ, 1.0 M, KCl.

crystals which formed were filtered and recrystallized from CH_3OH–H_2O, mp 97–100 °C. This compound appeared as a single spot on TLC [silica gel, benzene–methanol (8:1)]: NMR δ ($CDCl_3$) 2.1 (s, 3, CH_3CO), 7.0 (m, 5, aromatic), 5.3 (d, J = 7.5 Hz, 1, COCH=), 7.3 (d, J = 7.5 Hz, 1, N—CH=), 11.4 (broad, 1, NH). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88. Found: C, 74.43; H, 6.89.

***cis*-3-Anilino-4′-nitroacrylophenone.** *trans*-3-Methoxy-4′-nitroacrylophenone (6 mmol) was allowed to react with aniline (6 mmol) in water as described above. The yellow crystals which were formed were collected and recrystallized from methanol: mp 173–174 °C; NMR δ ($CDCl_3$) 6.2 (d, J = 7.5 Hz, 1, COCH=), 7.9 (d, J = 7.5 Hz, 1, N—CH=), 8.3 (q, 4, $NO_2C_6H_4$), 7.4 (m, 5, NC_6H_5), 12.4 (m, 1, NH). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.06; H, 4.51; N, 10.44. Found: C, 66.97; H, 4.54; N, 10.25. The uv spectra of aqueous reaction mixtures containing **5** and aniline at the completion of kinetics runs are identical with that of *cis*-3-anilino-4′-nitroacrylophenone.

Isomerization of 4-Anilino-3-buten-2-one. A solution of *cis*-4-anilino-3-buten-2-one (1 g) in 20 ml of benzene was heated to reflux for 2 days. After evaporation of solvent, the crystalline residue was recrystallized from CH_3OH–H_2O. The product was identified as a mixture of cis–trans isomers by NMR ($CDCl_3$): vinylic protons of the cis isomer at δ 5.3 (d) had J = 7.6 Hz; vinylic protons of the trans isomer at δ 5.72 (d) had J = 12 Hz. The spectrum also showed that the trans isomer undergoes spontaneous conversion to the cis isomer in $CDCl_3$. The doublet at δ 5.72 gradually diminished in intensity as the doublet at δ 5.33 concurrently increased in intensity with time. After 2 h, the doublet at δ 5.72 had completely disappeared.

Formation of *trans*-3-substituted amino-4′-substituted acrylophenones from the reactions of *trans*-3-methoxy-4′-substituted acrylophenones with secondary amines was assumed from the following experiment.

***trans*-3-*N*-Methylanilino-4′-chloroacrylophenone.** *trans*-3-Methoxy-4′-chloroacrylophenone (6 mmol) in methanol was allowed to react with *N*-methylaniline (6 mmol) suspended in water for 4 h at room temperature with stirring. The yellow crystals which formed were filtered and recrystallized from methanol: mp 119–120 °C; NMR δ ($CDCl_3$) 3.3 (s, 3, NCH_3), 6 (d, J = 12.5 Hz, 1, COCH=), 8.1 (d, J = 12.5 Hz, 1, NCH=), 7.6 (m, 4, ClC_6H_4), 7.2 (m, 5, N-C_6H_5). Anal. Calcd for $C_{16}H_{14}NOCl$: C, 70.72; H, 5.19; N, 5.16; Cl, 13.05. Found: C, 70.55; H, 5.05; N, 4.99; Cl, 12.92. The uv spectrum of the aqueous methanolic reaction mixture containing **4** and *N*-methylaniline was identical with that of *trans*-3-*N*-methylanilino-4′-chloroacrylophenone.

Reactions of **1–5** in dilute potassium hydroxide solution gave quantitative yields of para-substituted benzoylacetaldehydes, as determined from comparison of product uv spectra with those of authentic benzoylacetaldehydes. These products slowly decompose in alkaline solution to give para-substituted acetophenones and formate ions.[17]

No intermediates were detected spectrophotometrically during reaction of **6** with aqueous 0.02 M aminoethanol (f base = 0.1); an absorbance increase at λ_{max} 370 nm was accompanied by an absorbance decrease at λ_{max} 275 nm (shoulder ca. 300 nm) which resulted in an isosbestic point at 333 nm. For this reaction the rates of absorbance increase and decrease were equal. Reaction of **6** with 0.2 M ammonium chloride solution (f base = 0.5) gave a product whose spectrum (λ_{max} 273, 358) was identical with that of 3-amino-4′-nitrocrotonophenone prepared by the method of Holtzclaw et al.[18]

Results

In aqueous solution **1–5** react with primary amines to give the corresponding *cis*-3-substituted amino-4′-substituted acrylophenones (eq 1); with secondary amines **1–5** give the corresponding *trans*-3-substituted amino-4′-substituted acrylophenones (eq 1). Under pseudo-first-order conditions the rate law for these reactions is given by

$$v/\mathbf{1\text{–}5} = k_{obsd} = k_2 f[\text{amine}]_{total} + k_{OH}[OH^-] \qquad (2)$$

where f is the fraction of free amine present in the reactant buffer solution. Plots of k_{obsd} vs. the concentration of total amine at constant pH gave as slope $k_2 f$ and intercept $k_{OH}[OH^-]$. The second-order rate constant k_2 was obtained by dividing the apparent second-order rate constant $k_2 f$ by f ($=K_a/(K_a + a_H)$). The value of k_2 so obtained was constant for a given amine and substrate for several pH values, i.e., for several constant buffer ratios (Tables I, II).

Values of k_{OH} for reactions of **1–5** with hydroxide ion were obtained from the slopes of plots of k_{obsd} vs. the stoichiometric hydroxide ion concentration for reactions run in dilute potassium hydroxide solution (Table III).

Table III. Rate Data for the Hydration of **1–5** in Alkaline Solution[a]

Compd	k_{OH}, M^{-1} min^{-1}	Range of OH^-	No. of k_{obsd}
1 ($N(CH_3)_2$)	5.07 ± 0.11	0.01–0.10	12
2 (OCH_3)	18.03 ± 0.39	0.01–0.06	8
3 (H)	18.9 ± 0.78	0.005–0.04	10
4 (Cl)	31.3 ± 1.41	0.005–0.02	8
5 (NO_2)	121.2 ± 2.32	0.005–0.04	10

[a] Temperature, 30 °C; solvent, H_2O; μ, 1.0 M (KCl).

The deuterium solvent kinetic isotope effect, $k_2(D_2O)/k_2(H_2O)$, is 1.02 for reactions of *cis*-3-methoxy-4′-methoxyacrylophenone (**2**) with aminoethanol (Table I).

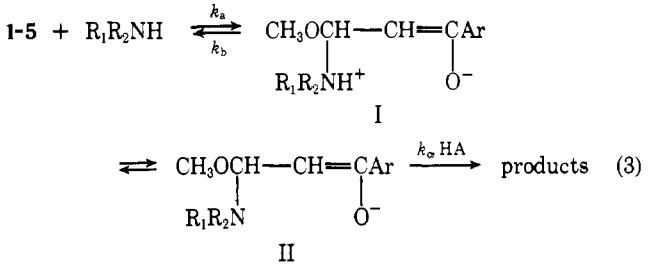
Plots of log k_2 (aminoethanol) vs. Hammett σ constants, σ range = −0.83–0.778, and log k_{OH} vs. σ gave $\rho = 1.02 \pm 0.04$ ($r = 0.998$) and $\rho = 0.82 \pm 0.008$ ($r = 0.985$), respectively. The reactant aminoethanol was chosen as a representative amine for the Hammett-type plot because it gave conveniently measurable rates for the series **1–5.**

The Bronsted-type equation log $k_2 = (0.37 \pm 0.03)\, pK_a - 2.32$ ($r = 0.997$) was obtained for reactions of **1** with glycine ethyl ester, aminoethanol, and *n*-butylamine.

Methyl substitution for a hydrogen atom reduced the rate of nucleophilic attack of aminoethanol on **5** by 90-fold (Table I).

Discussion

Aminations of *trans*-3-methoxy-4′-substituted acrylophenones (**1–5**) to give 3-substituted amino-4′-substituted acrylophenones are characterized by: (1) rates which are first order in both amine and **1–5;** (2) a deuterium solvent kinetic isotope effect $k_2(H_2O)/k_2(D_2O) = 0.98$; (3) $\rho = 1.02$ for reactions of **1–5** with aminoethanol; (4) a Bronsted-type catalytic constant $\beta = 0.37$ for reactions of **3** with ethyl glycinate, aminoethanol, and *n*-butylamine; (5) a 90-fold decrease in reactivity when a β-methyl group is substituted for a hydrogen atom. In our view these data are best interpreted with the addition–elimination mechanism (eq 3), or its minor variants,



(3)

which was convincingly established for aromatic nucleophilic substitution reactions of dinitroaryl ethers with amines,[10] reactions of electrophilic olefins with amines,[9] and aminolysis of methyl formate.[21] For the first two reaction types cited, the rate-determining step (k_a, k_c) appears to depend on the nature of the leaving group. Thus for diaryl ethers possessing good leaving groups, e.g., *p*-nitrophenol, amine attack via k_a is rate determining; for diaryl ethers or 2,4-dinitrophenyl methyl ether possessing poor leaving groups, amine attack is quick and decomposition of the anion II via k_c is rate determining.[22] These conclusions appear to be applicable to the reactions of electrophilic olefins with amines. However, for aminolysis of methyl formate the rate-determining step is controlled by pH of the solution containing reactants and the pK of the zwitterion analogous to I (vide infra).

For aminations of **1–5** the data appear to be in accord with the mechanism of eq 3, k_a rate determining. From the experimental rate law (eq 2) and the mechanism of eq 3, k_2 (Table I) = k_a (eq 3). The negligible deuterium solvent kinetic isotope effect is that expected for a reaction not involving proton transfer and is in agreement with the postulated mechanism. In the case of addition of piperidine to 2,4-dinitrophenyl phenyl ether, followed by elimination of phenol, $k_a(H_2O)/k_a(D_2O) = 1.03$ in aqueous dioxane at 0 °C.[22] The value of ρ (1.02) for reactions of **1–5** with aminoethanol indicates increased electron density in the benzoyl portion of **1–5** in the transition state and likely anionic character at the carbonyl oxygen atom. This result supports the mechanism of eq 3 and implies that the transition state resembles the zwitterion I. We are more comfortable with this interpretation than one of bimolecular nucleophilic substitution; for the latter we would expect a small ρ, although how small we are not prepared to say.[23] For reactions of **1–5** with hydroxide ions, ρ is 0.82: this suggests that the transition state is reached earlier along the reaction coordinate than is the case for reactions with amines and electron density about the benzoyl group is correspondingly less. For analogous addition–elimination reactions of esters (**1–5** are vinylogous methyl benzoates) with oxyanions and amines, Jencks and Gilchrist[24] concluded on the basis of Bronsted β values that bond formation (and bond breaking) are more extensive in the transition state for aminolysis than hydrolysis, i.e., the transition state for aminolysis resembles products (I, eq 3), while that for reaction with oxyanions resembles starting material (**1–5**). Further extending the vinylogous ester analogy, we note that ρ is 1.08 for nucleophilic reactions of ammonia with *p*-chlorophenyl para-substituted benzoates in aqueous acetonitrile.[25]

The reactivity of amine nucleophiles with **1–5** may be conveniently discussed using the Bronsted type relationship established for aminoethanol, ethyl glycinate, and *n*-butylamine. For these amines basicity appears to be a good index of nucleophilicity ($r = 0.997$): steric effects, solvation effects, etc. are expectedly similar for the amine groups acting as nucleophiles. Positive deviations from this arbitrarily established relationship are shown by hydroxylamine (+0.37 log unit) which is typically superreactive (α effect)[21,26–28] in addition–elimination reactions at sp^2 carbon and morpholine (+0.47 log unit) for which steric effects and desolvation effects are likely more favorable than for primary amines.[29,30] Negative deviations from the Bronsted-type relationship are shown by imidazole (−0.38 log unit) and *tert*-butylamine (−1.15 log units). This depressed reactivity is attributed to base-type differences in the case of imidazole and to steric hindrance to nucleophilic attack (eq 3, k_a) in the case of *tert*-butylamine. Here we offer a comparison which may be made to support the mechanism. The value of β is 0.37 ± 0.03 for **1–5:** the value of β is 0.42 ± 0.01 for addition of amino acids to acrylonitrile and similar electrophilic olefins, a reaction for which rate-determining amine attack was reasonably postulated.[31]

Substitution of a β-methyl group for a hydrogen atom of **5** decreased reactivity toward aminoethanol by 90-fold. This large reactivity difference between **5** and **6** is attributed to increased ground-state stabilization of the methyl-substituted olefin and steric hindrance to approach of amine at the β carbon as the transition state is approached. In connection with this result, there is an eightfold decrease in the rate of addition of methanol to methyl vinyl ketone when a β-methyl group is introduced into that compound: there is no detectable reaction of methanol with mesityl oxide under the same reaction conditions.[32] That the reactivity difference between **5** and **6** is not greater may be rationalized on the basis of the greater electrophilicity of the β carbon of **5** and **6** vs. that for derivatives of methyl vinyl ketone. The reactivity difference between **5** and **6** coupled with the results of nucleophilic addition of methanol to methyl vinyl ketone derivatives may be taken as support for the addition–elimination mechanism (eq 3).

A somewhat disconcerting result of this study was the failure of **1–5** to employ catalysis in their reactions with amines. This result may signal a mechanism different from that of eq 3, although at this time we do not believe so. Kinetics studies of nucleophilic addition–elimination reactions of the types mentioned in the beginning of this discussion provide hard evidence for formation of tetrahedral intermediates and for involvement of general acid catalysis in the breakdown of these intermediates. Detection of general acid catalysis by aminium ions in the breakdown of intermediates to products appears to depend on the nature of the solvent used for the reactions and as well on the nature of the leaving group: protic solvents in the case of electrophilic olefins mentioned above can preempt aminium ions as catalysts as judged by changes in rate laws. In hydrazinolysis of methyl formate water catalysis is quite competitive with hydrazinium ion catalysis in decomposition of anionic tetrahedral intermediates to formyl hydrazide. With this background information in hand we anticipated at the beginning of this study that aminolysis of **1–5** could provide kinetics evidence of general acid catalysis during breakdown of vinylogous tetrahedral intermediates to products, although we were prepared to discover that for **1–5** solvent played the role of proton donor. The results of the heavy water experiments disabused us of that prediction. Although the lack of catalysis is disappointing in terms of one of the goals of this study, the result is not necessarily unusual. In fact, to the degree that **1–5** resemble vinylogous esters in their reactions with amines, failure to detect catalysis of breakdown of intermediates is predictable a priori.[21] Thus results of aminolysis of methyl formate convincingly establish amine attack as rate determining at high pH and decomposition of tetrahedral anion as rate determining at low pH. Analogously, for **1–5** in more acidic solution, I (eq 3) expels amine (pK = 8–11) faster than methanol (pK = 15) so that breakdown of II (eq 3) is rate determining; in more alkaline solution, II expels methanol faster than amine ($pK \sim 30$) so that amine attack is rate determining. If the mechanism of eq 3 is accepted, then the latter situation obtains for reactions of **1–5** with amines of this study under our experimental conditions: the pH of solutions and the pK's of I's and the relative values of the rate constants conspire so that k_a is rate determining. The experimental results obtained with **1–5** support this interpretation of the reaction course, although we have no information bearing on the existence of I or II or on changes in rate-determining step.

Briefly considering the question of stereochemistry of products obtained from reactions of *trans*-**1–5** with amines we note here that reactions of **5** and of 4-methoxy-3-buten-2-one with aniline give the thermodynamically more stable cis product while reaction of **4** with *N*-methylaniline gives the thermodynamically more stable trans product. These results are in agreement with findings of Dudek et al.[33] concerning isomer distribution among various β-amino-α,β-unsaturated ketones in solution: cis isomers are favored whenever the potential for hydrogen bonding between amino and carbonyl groups exists. For **1–5** vinylogous tetrahedral intermediates with appreciable stability could undergo rotations about σ bonds so as to give stabilized ion-reinforced hydrogen-bonded intermediates (II, R_2 = H) which could break down while maintaining the hydrogen bond to give cis product. For reactions of **1–5** with secondary amine hydrogen bonding is unavailable to II and the reaction course is influenced by steric interactions; minimization of these interactions leads to trans products. Certainly other possibilities exist which include isomerization of first-formed products to the final products; *trans*-4-anilino-3-buten-2-one readily undergoes conversion to the cis isomer in $CDCl_3$ at room temperature.

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