The signal-to-noise ratio was improved by applying a 20-Hz exponential broadening factor to the FID prior to Fourier transformation. The digital resolution was improved to ±1.4 Hz by zero filling to 16K data points prior to Fourier transformation. The reproducibility of the chemical shift data is estimated to be greater than ±1.0 ppm.

Aminolysis of 2,2,2-Trichloro-1-arylethanones in Aprotic Solvents

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The kinetics of the reaction of the title substrate with various alkylamines was studied in *n*-heptane, dichloromethane, dioxane, tetrahydrofuran, and acetonitrile. The reaction was third-order in amine when the solvent was *n*-heptane or dichloromethane. In the other solvents a second-order dependence on [RNH$_2$] was observed. The fourth-order rate constants for the reaction of *n*-butylamine with various 2,2,2-trichloro-1-arylethanones in dichloromethane yielded a ρ value of 3.0. In all solvents the observed rate constants decreased with a temperature increase. Two mechanistic possibilities were suggested, the first one in solvents of low donicity, involving a T^0 intermediate formed in a concerted process with the participation of an amine dimer; and the second one, a stepwise process in more basic solvents which takes place via a T$^{\pm}$ intermediate. Base-catalyzed collapse of the tetrahedral intermediates is the rate-determining step in both pathways.

Introduction

The 2,2,2-trichloro-1-arylethanones (1) are an interesting class of compounds which share the chemical behavior of both carboxylic acid derivatives and ketones. Like simple esters, for example, they have long been known to undergo basic hydrolysis to yield arylcarboxylic salts.[1] This observation has led to the use of these compounds as carboxylating agents in a number of scattered reports. Preparation of heterocyclic acids,[2] esters,[3] amides,[4] and sulfonamides[5] from substrates 1 have been reported. On the other hand, *O*-alkyl oximes are obtained when compounds 1 react with *O*-(pentafluorobenzyl)hydroxylamine,[6] in a behavior which is characteristic of ketones.

We have studied the alcoholysis of these substrates and shown that it proceeds via intermediate hemiketals.[7] These hemiketals are stable in neutral or acidic solutions but collapse to the corresponding esters in the presence of basic catalysts. Hydrated species are intermediates in

Table I. Third- and Fourth-Order Rate Constants for the Aminolysis of 2,2,2-Trichloro-1-phenylethanone (1a) in Various Solvents

solvent	order of the reaction in RNH$_2$	k^a	
		n-propylamine	*n*-decylamine
n-heptane	3	1.32	1.68
dichloromethane	3	0.84	1.40
1,4-dioxane	2	–	5.16
tetrahydrofuran	2	10.24	11.88
acetonitrile	2	17.50	27.70

^{a} Fourth-order rate constants in heptane and dichloromethane in M^{-3} s^{-1}, third-order rate constants in dioxane, THF, and acetonitrile in M^{-2} s^{-1}.

the basic hydrolysis of 1, but in this case the reaction occurs via two tetrahedral intermediates, a mono- and a dianionic species.[8] In all cases, however, basic catalysis is present. Since in neutral or acidic media a reversible equilibrium between the ketone and a tetrahedral intermediate is established, compounds 1 will only act as acylating agents in the presence of a basic catalyst. This fact may be exploited and these substrates utilized as selective benzoylating reagents under suitable conditions.[9] The formation of an amide by the reaction of 2,2,2-trichloro-1-phenylethanone with an amine in hexane was first reported nearly 40 years ago.[10] We have investigated in more detail the scope of this conversion, which is a smooth reaction generally proceeding in high yields.[9] We now present a detailed kinetic study of this conversion, which

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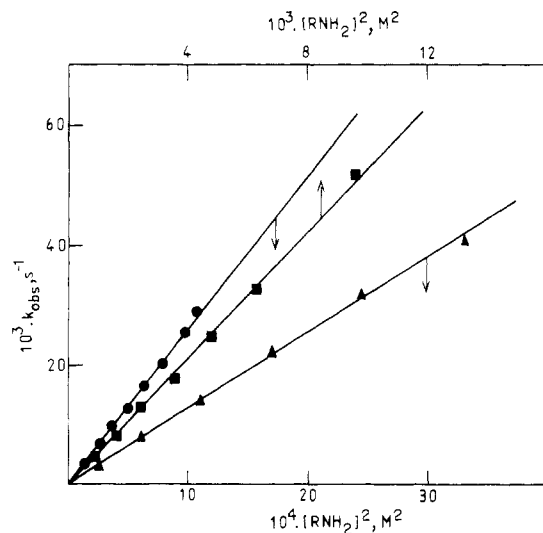
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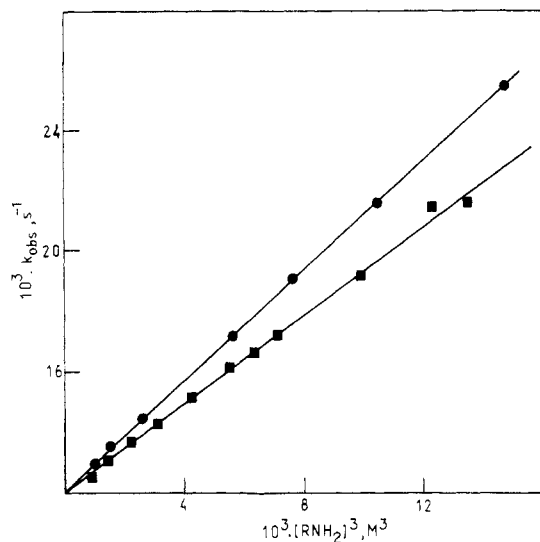
Figure 1. Variations of the observed rate constant with $[RNH_2]^3$ for the reaction of **1a** and n-decylamine at 25 °C. Reactions carried out in n-heptane (●) and dichloromethane (■).


Figure 2. Variations of the observed rate constant with $[RNH_2]^2$ for the reaction of **1a** and n-decylamine at 25 °C. Reactions carried out in dioxane (■), acetonitrile (●), and tetrahydrofuran (▲).

takes place in various solvents and with different amines.

Results

The reaction of 2,2,2-trichloro-1-arylethanones (**1**) with several aliphatic amines was studied in various aprotic solvents as a function of the temperature and the amine concentration. In all cases the only product obtained was the corresponding amide.

$$X-C_6H_4-\overset{\overset{\textstyle O}{\|}}{C}-CCl_3 + RNH_2 \longrightarrow X-C_6H_4-\overset{\overset{\textstyle O}{\|}}{C}-NHR + CHCl_3$$

1
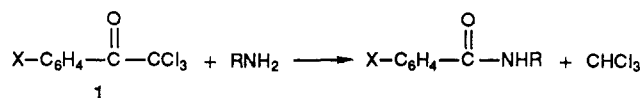
X = H(a), p-CH$_3$(b), p-Cl(c), p-Br(d), m-NO$_2$(e)

R = n-C$_m$H$_{2m+1}$ (m = 3–8, 10, and 11), (CH$_3$)$_2$CH, (CH$_3$)$_3$C, C$_6$H$_{11}$

Solvent Effects. The above reaction was investigated in n-heptane, dichloromethane, dioxane, tetrahydrofuran and acetonitrile. In all solvents the reaction exhibited a first-order dependence on the substrate concentration. In contrast, the order in amine was not the same in all sol-
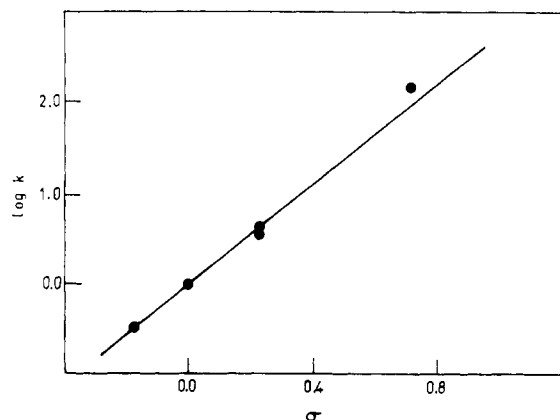
Figure 3. Hammett plot for the fourth-order rate constants obtained for the reaction of 2,2,2-trichloro-1-(X-substituted-phenyl)ethanones with n-butylamine in dichloromethane at 25 °C.

Table II. Fourth- and Third-Order Rate Constants for the Reaction of Various Amines with 2,2,2-Trichloro-1-phenylethanone (1a) in Dichloromethane and Acetonitrile, Respectively, at 25 °C

amine	dichloromethane k, M^{-3} s^{-1}	acetonitrile k, M^{-2} s^{-1}
n-propylamine	0.84	17.50
isopropylamine	0.011^a	0.1^b
n-butylamine	0.99	–
tert-butylamine	–	0.0064^b
n-hexylamine	1.07	–
n-octylamine	1.35	–
n-decylamine	1.40	–
n-dodecylamine	1.26	–
cyclohexylamine	–	1.35
morpholine	–	0.027

^{a} Third-order rate constant k, M^{-2} s^{-1}. ^{b} Second-order rate constant k, M^{-1} s^{-1}.

vents. The reaction of n-decylamine with trichloro-ethanone (**1a**) showed a second-order dependence in dioxane, tetrahydrofuran, and acetonitrile and a third-order dependence on [RNH$_2$] in n-hexane and dichloromethane. Similar results were observed with n-propylamine. For these two groups of solvents, straight lines were obtained when values of k_{obs} were plotted against [RNH$_2$]^3 (Figure 1) or [RNH$_2$]^2 (Figure 2).

Values for third- and fourth-order rate constants for the above reactions may be obtained from the slopes of the straight lines drawn in Figures 1 and 2 and are listed in Table I.

It is seen that, for those solvents where a third-order dependence on [RNH$_2$] is observed (n-heptane and dichloromethane), the fourth-order rate constants are nearly the same, in spite of the fact that dichloromethane is more polar than n-heptane. For the group of solvents where a second-order dependence on [RNH$_2$] is observed (dioxane, tetrahydrofuran, and acetonitrile), the third-order rate constants increase with the polarity of the medium.

This difference in the behavior of the two groups of solvents cannot be ascribed solely to their polarity. In fact, dichloromethane, which behaves very much like n-heptane, is more polar ($E_T(30) = 41.1$ kcal/mol) than either dioxane or THF ($E_T(30) = 36.0$ and 37.4 kcal/mol, respectively).[11] We shall come back to this point when discussing the mechanism of the reaction.

Nature of the Substrate. The influence of the substituent at the phenyl ring of substrates **1** was investigated

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Table III. Observed and Fourth-Order Rate Constants for the Reaction of 2,2,2-Trichloro-1-phenylethanone with n-Octylamine in Dichloromethane at Various Temperatures

	$10^3 k_{obs}$, s^{-1}				
$10[RNH_2]$, M	15 °C	20 °C	25 °C	30 °C	35 °C
1.0	2.00	1.89	–	–	–
1.2	3.41	2.93	2.31	2.88	2.23
1.4	–	–	–	4.22	–
1.6	6.93	6.04	5.59	5.33	4.65
1.8	–	–	–	7.71	–
1.9	11.58	11.03	10.31	9.77	8.39
2.3	19.86	18.52	16.81	16.00	13.89
2.7	30.05	28.31	25.46	23.83	21.56
2.9	–	–	–	28.71	–
3.0	43.01	41.46	37.50	36.07	32.09
k^a	1.54	1.43	1.35	1.21	1.13

^{a} Fourth-order rate constants k (M^{-3} s^{-1}) obtained from slopes of k_{obs} vs $[RNH_2]^3$; values correspond to $10^3 k$.

in the reaction of n-butylamine and the 2,2,2-trichloro-1-arylethanones in CH_2Cl_2 at 25 °C. The fourth-order rate constants obtained for all substrates were 0.99, 0.34, 4.25, 3.76, and 153.0 M^{-3} s^{-1} for compounds **1a**, **1b**, **1c**, **1d**, and **1e**, respectively. The corresponding Hammett plot is shown in Figure 3. A ρ value of 3.0 was obtained from this plot, with a correlation coefficient of 0.997. As expected, the reaction is facilitated by electron-withdrawing substituents, which enhance the electrophilicity of the carbonyl group.

Nature of the Amine. The reactivity of various amines toward the trichloro ketone **1a** was compared in dichloromethane and acetonitrile. The calculated rate constants derived from these experiments are given in Table II.

In a series of normal aliphatic amines it is apparent that the reactivity of the attacking nucleophile is practically independent of the size of the alkyl chain. The ketonic substrate is, however, strongly sensitive to steric effects. Isopropylamine reacted much slower than normal propylamine in dichloromethane, and the reaction with *tert*-butylamine in the same solvent was too slow to be followed. The same trends were observed in acetonitrile. Steric bulk decreased not only the reaction rates but also the reaction orders in amine. Plots of long k_{obs} vs log $[RNH_2]$ gave slopes of 3.0 ± 0.1 for the reactions with normal amines in dichloromethane and slopes of 2.0 ± 0.1 for the same aminolyses in acetonitrile. For the more hindered isopropylamine, however, the slopes were 2.1 and 1.3 in dichloromethane and acetonitrile, respectively. The same plot for the reaction of **1a** with *tert*-butylamine in acetonitrile yielded a first-order dependence of k_{obs} on the amine concentration.

In order to test the effectiveness of different amines as base catalysts in these reactions, aminolyses of substrate **1a** in the presence of a fixed concentration of n-octylamine and increasing concentrations of hindered *tert*-butylamine were carried out in dichloromethane and in acetonitrile. In both solvents the isolated product was n-octylbenzamide and the reaction showed a first-order dependence on [*t*-BuNH$_2$]. The extrapolation to zero *tert*-butylamine concentration of the straight lines obtained as the plots of k_{obs} vs [*t*-BuNH$_2$] gave rate constant values very close to those obtained for the reactions of n-octylamine with **1a** in the same solvent and concentration.

Effect of the Temperature. The reaction of the ethanone **1a** and n-octylamine at various temperatures and amine concentrations was followed in dichloromethane and acetonitrile. The observed rate constants are given in Tables III and IV. The corresponding calculated third-

Table IV. Observed and Third-Order Rate Constants for the Reaction of 2,2,2-Trichloro-1-phenylethanone with n-Octylamine in Acetonitrile at Various Temperatures

	$10^3 k_{obs}$, s^{-1}				
$10^2[RNH_2]$, M	15 °C	20 °C	25 °C	30 °C	35 °C
1.0	3.27	2.54	2.49	2.33	2.06
1.6	7.99	7.12	7.06	6.01	5.59
2.0	12.94	11.58	10.56	10.12	9.48
2.6	21.82	20.03	19.01	18.04	16.81
3.0	28.72	26.18	24.98	24.19	23.52
3.6	38.60	36.89	35.50	34.11	30.98
k^a	30.26	29.08	27.97	27.24	25.15

^{a} Third-order rate constants k (M^{-2} s^{-1}) obtained from the slopes of k_{obs} vs $[RNH_2]^2$; values correspond to $10^3 k$.

Scheme I
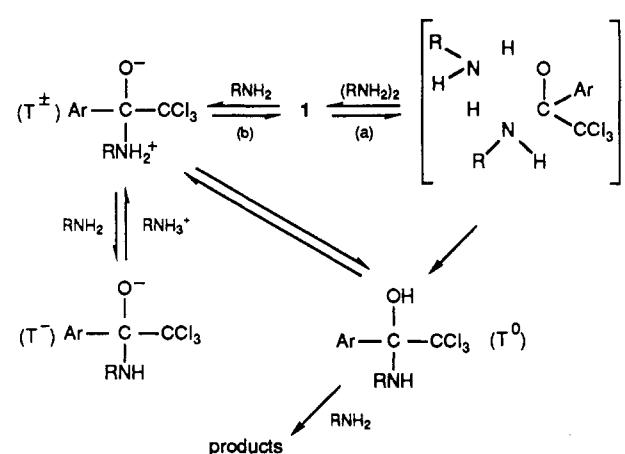
and fourth-order rate constants are also included in these tables. It is seen that all rate constants decrease with the temperature increase, in an unusual anti-Arrhenius behavior.

An anti-Arrhenius behavior has been observed previously for reactions involving amines in nonpolar media.[12,13] Although there was no agreement as to the mechanistic model suggested by these observations, the authors have agreed on the existence of preceding equilibria which would contribute to the overall observed rate constant. Such exothermic equilibria would counterbalance the positive activation energy of the rate-determining step, resulting in overall negative E_a values.

Discussion

Several mechanistic possibilities may be put forward to conciliate the above data. Some of them are depicted in Scheme I.

Route a involves an initial concerted step, involving two associated molecules of amine, and leading directly to a tetrahedral T^0 intermediate. This intermediate would then go to products with the assistance of a third molecule of amine, acting as a general base.

In route b a tetrahedral $T^\pm$ intermediate is formed by the initial attack of one molecule of the amine. Abstraction of a proton from $T^\pm$ by a second molecule of amine leads to T^-, which would then decompose to products. Alternatively, $T^\pm$ might equilibrate with T^0 prior to a base-catalyzed decomposition through T^-.

Routes a and b are two alternative rationalizations for reactions with amines in aprotic solvents: a concerted and a stepway mechanism. Other mechanistic variations could be imagined, but they would contribute little to the discussions and controversies which have been motivated by these two possibilities.[12-16]

It is tempting to envisage the change in the order of the reaction in amine as arising from a change of mechanism, when going from nonpolar, poor donor solvents (*n*-heptane and dichloromethane) to more polar and better donor solvents, like dioxane, tetrahydrofuran, and acetonitrile. A tetrahedral zwitterionic $T^{\pm}$ intermediate would be favored in more polar media, and route b might well describe the process in the latter solvents, with a second-order dependence on the amine concentration. However, polarity is not the only factor to be considered. As mentioned above, dichloromethane is a more polar solvent than either dioxane or THF, but it still behaves like heptane, with a third-order dependence on the amine concentration. The higher order in [RNH$_2$] in heptane and dichloromethane probably reflects a higher degree of amine association in these solvents, which is a consequence of their reduced donicity. Poor donor solvents can hardly disrupt hydrogen-bonding association between amine molecules. In the more basic ethers and acetonitrile, where solvation should operate through hydrogen bonds between the NH group and solvent molecules, the nucleophilic amine molecules are less associated. The change in the reaction order should then parallel the trends in the donor numbers of the employed solvents.[17] Indeed, in heptane and dichloromethane (DN $\approx$ 0), amine association is higher and reactions are third-order in [RNH$_2$]; as the donor number increases in acetonitrile (DN = 14.1 kcal/mol), dioxane (14.8 kcal/mol), and tetrahydrofuran (20.0 kcal/mol), both amine association and the reaction order in [RNH$_2$] decrease. It follows that, in those solvents where amine association is higher, the reactivity of the attacking associated nucleophile should be practically independent of the solvent polarity. In the second group of solvents, where amine association is broken up by solvent molecules, the reactivity of the solvated nucleophile should depend on the nature of the solvent. The rate constants listed in Table I bear out this rationalization.

We may thus tentatively suggest route a for the process where a third-order dependence on [RNH$_2$] is observed and route b for the second group of better solvating solvents. We shall analyze now all the evidences we have, and show that they are compatible with these suggestions.

Jencks' predictions that most additions of amines to the carbonyl group should not be subject to concerted general base catalysis, but should take place in a stepwise fashion, arise from his "libido" rule.[16] This applies strictly to processes taking place in aqueous solutions. In nonpolar solvents, the high free energy requirements met in a concerted process may be compensated by the greater instability of a transition state leading to an ionic species. If one is allowed, like Jencks,[18] to take an anthropomorphic view of things, one might say that nonpolar solvents, such as *n*-heptane and dichloromethane, constitute an ideal background for the initial "ménage-à-trois" depicted in route a. As argued by Nudelmann and Palleros,[12] an amine preassociation followed by an attack of the dimeric nucleophile at the carbonyl group is to be preferred to a high-entropy three-body transition state. The same authors suggested that the anti-Arrhenius behavior observed in our case could well be explained in terms of an exo-

thermic preassociation of the attacking dimer.[12] The criticism raised by Banjoko and Ezeani,[13] which might also apply to our reaction, as to the arbitrary choice of an amine dimer in the first step and of the monomer in the second may be answered by a consideration of the cyclic transition states involved. Although those authors were right in seeing no reason why the amine association should stop at the dimer stage, and why the monomer should not be as good a nucleophile as the dimer, formation of the geometrically most favorable six-membered transition states in both steps requires that only two molecules of the amine intervene in the formation of T^0 and just one in the base-catalyzed collapse of this intermediate.

The cross experiments performed in CH$_2$Cl$_2$ by reacting substrate 1a with increasing concentrations of *tert*-butylamine in the presence of a constant amount of *n*-octylamine showed that the first amine acts as a base and not as nucleophile in the process. The first-order dependence on [*t*-BuNH$_2$] is to be expected if one considers the exclusive intervention of the hindered amine in the rate-determining base-catalyzed decomposition of the T^0 intermediate in route a.

Route a should be finally compatible with the ρ value of 3.0 obtained for the reaction of *n*-butylamine with various trichloroethanones in dichloromethane. If the rate-determining step is the base-catalyzed collapse of the intermediate aminal (T^0), electron-withdrawing substituents on the phenyl ring should favor the process by making this aminal more acidic. This implies a positive value for this step. An estimate of this value may be obtained from our studies of the basic decomposition of related 1-aryl-2,2,2-trichloroethanols via a $(E1cB)_R$ mechanism.[19] A Hammett plot for the ionization of these ethanols yielded a ρ value of 0.72. It is true that the value of 3.0 found in this work is still too high for such a process. One should, however, bear in mind that the fourth-order rate constants are really composites of the rate-determining and preequilibrium constants. The contributions of the latter to the observed rate constants are far from negligible. In fact, our ρ value probably reflects a large contribution from the preequilibrium between T^0 and reagents. An estimate of this contribution may be gathered from studies of the hydration and ketalization of substrates 1. We obtained a ρ value of 2.3 for the equilibrium of hydration of these substrates in water[20] and a value of 2.6 for the hemiketal/ketone equilibrium of the same compounds in methanol.[7] Accordingly, the value of 3.0 reported in the present work agrees with the postulated route a. It mirrors a large contribution from the preequilibrium between T^0 and reagents and a smaller acceleration by electron-withdrawing substituents of the rate-determining base-catalyzed collapse of the intermediate aminal.

The stepwise aminolysis represented in route b is a classical pathway for processes taking place in polar, protic media.[21] In our case, however, the aminolysis takes place in aprotic, reasonably good donor solvents. These solvents not only decrease the order of the reaction in RNH$_2$ by reducing amine association, they also enhance the reactivity of the attacking nucleophile by hydrogen bonding to the NH group. As the temperature is increased, so is the amine nucleophilicity reduced, because of a decrease of hydrogen bonding between the donor solvent and the amine. This is probably the reason for the anti-Arrhenius

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behavior which is also observed here in these solvents.

A point to be raised is the decrease of the reaction order, both in dichloromethane and acetonitrile, as the amine becomes more sterically hindered. This observation also agrees with the postulated schemes. Steric bulk prevents amine association or effective solvation. It also reduces the nucleophilicity of the attacking amine. On the other hand, a bulkier tetrahedral intermediate (T^0 or T^-) collapses faster to products because of steric acceleration. All these effects may cause the initial amine attack on the carbonyl to become slower than the decomposition of the tetrahedral intermediate and therefore to become the rate-determining step. By thus shifting the rate-determining step, sterically hindered amines decrease the rate of aminolysis and the reaction order in RNH_2, in agreement with the postulated schemes.

The fact that the cross aminolysis (*n*-octylamine/*tert*-butylamine) of 1a in acetonitrile showed a first-order dependence on [*t*-BuNH$_2$], when the *n*-octylamine concentration was kept constant, reinforces the above arguments. The presence of the more reactive octylamine ensures a fast equilibrium between $T^\pm$ and reagents. The more hindered *tert*-butylamine can only intervene as a base catalyst in the formation of T^- from $T^\pm$ or, alternatively, in the decomposition of T^0. In both cases, a first-order dependence on [*t*-BuNH$_2$] is to be expected, if the rate-determining step is the collapse of the tetrahedral intermediates.

In conclusion, we propose essentially two mechanisms to accommodate our data. In the first one, in solvents like *n*-heptane and dichloromethane, where a third-order dependence on [RNH_2] is observed, the reaction proceeds through a neutral T^0 intermediate, which decomposes to products in a base-catalyzed rate-determining step (route a). In the second, stepwise mechanism (route b), the reaction proceeds through a zwitterionic $T^\pm$ intermediate, which is converted by a second molecule of the amine into a T^- intermediate. Collapse of this intermediate is rate-determining. This process takes place in solvents like THF, dioxane, and acetonitrile, where a second-order dependence on [RNH_2] is observed, and amine association

is disrupted by solvation through hydrogen bonds with the donor solvent.

The anti-Arrhenius behavior observed in both groups of solvents is explained as arising from contributions from fast exothermic preequilibria to the observed rate constants. In the first mechanism (route a) we agree with Nudelmann and Palleros[12] in regarding the amine association as the source of this contribution. In the second mechanism (route b), a similar argument holds, and the associated amine molecules are replaced by molecules of the better donor solvents.

Experimental Section

Synthesis of Fused Polyazapolycyclic Compounds through Condensation of Diaminoalkanes with Carbonyl Compounds

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1,3-Diaminopropane and 1,3-diamino-2,2-dimethylpropane react with glyoxal to give crystalline 2,2'-bis-(hexahydropyrimidine) derivatives 1 and 2. Subsequent treatment with formaldehyde and acetaldehyde gives trans- and to a lesser extent cis-fused 1:1 addition products, e.g. 4a,8b-*trans*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (8) and 4a,8b-*cis*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (14), or tetracyclic cis-fused 1:2 addition products, e.g. 8b,8c-*cis*-2,2,6,6-tetramethylperhydro-3a,4a,7a,8a-tetraazacyclopentano-[*def*]fluorene (18), depending upon the ratio of the reactants and upon reaction conditions. Similar condensation with acetone required mild acid catalysis and gave only the 1:1 addition products. The bis(hexahydropyrimidine) nature of the initial products was confirmed by conversion to their tetranitroso derivatives and by X-ray crystallographic analysis of the tetranitro derivative, 2,2'-bis(1,3-dinitrohexahydropyrimidine) (5), of compound 1.

Introduction

The condensation of linear and cyclic tetraamines with glyoxal provides a direct route to monomeric, tricyclic,[1,2]

and tetracyclic[3–5] nitrogen heterocycles. Similar tricycles have also been reportedly prepared from linear tetraamines

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(1) Fuchs, B.; Ellenzweig, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 326.

(2) Jazwinski, J.; Kolinski, R. A. *Tetrahedron Lett.* **1981**, *22*, 1711.