to calculate maximum and minimum measurements of an enriched abundance, i.e., (M + 2) normalized against 100% abundance for M and corrected for the natural abundance of (M + 2) in the mixture. Thus, for each conversion we had eventually a maximum and minimum measure of the enrichment in a sample. Maximum and minimum KIE were calculated from these data and are expressed as an average with its error for each run in the tables.

Acknowledgment. We thank Dr. Frank W. Crow, Midwest Center for Mass Spectrometry (an NSF Regional Facility), Department of Chemistry, University of Nebraska, Lincoln, NE, for mass spectrometric analyses of the isotope abundances in the commercial acetone and the synthesized, labeled 2,2'-dimethoxyazobenzenes prior to their use in the rearrangements.

Registry No. 1, 787-77-9; **2**, 119-90-4; **2** (bis(trifluoroacetyl) derivative), 92241-72-0; **2**-$^{15}N_2$, 92241-73-1; **3**-$^{15}N_2$, 92241-77-5; **3**-$^{13}C_2$, 92241-86-6; *trans*-**3**-$^2H_2$, 92241-92-4; *cis*-**3**-$^2H_2$, 92241-93-5; **4**, 85167-01-7; **5**, 92241-78-6; **6**, 92241-82-2; **7**, 92241-83-3; **8**, 92269-47-1; **8** (unlabeled), 37856-18-1; **9**, 5081-36-7; **9** (acid chloride), 67579-92-4; **10**, 92241-87-7; **11**, 16292-88-9; **12**, 92241-89-9; **13**, 92241-90-2; **14**, 92241-91-3; ^{15}N, 14390-96-6; ^{13}C, 14762-74-4; D_2, 7782-39-0; $AgClO_4$, 7783-93-9; PhOCOCl, 1885-14-9; $Ag^{15}NO_3$, 92241-74-2; *o*-$HOC_6H_4{}^{15}NO_2$, 92241-75-3; *o*-$CH_3OC_6H_4{}^{15}NO_2$, 92241-76-4; *o*-$CH_3OC_6H_4{}^{15}NH_2$, 63792-03-0; $(CH_3)_2{}^{13}CO$, 3881-06-9; $O_2NC^-(CHO)_2$, 34460-99-6; *p*-HO[4-^{13}C]$C_6H_4NO_2$, 3881-07-0; *p*-HO[4-^{13}C]$C_6H_4NH_2$, 3881-08-1; [4-^{13}C]$C_6H_5NH_2$, 55147-71-2; [4-^{13}C]C_6H_5OH, 70211-36-8; *o*-CH_3O[4-^{13}C]$C_6H_4NH_3Cl$, 92241-84-4; *o*-CH_3O[4-^{13}C]$C_6H_4NH_2$, 92241-85-5; $K^{15}NO_3$, 57654-83-8; 2-[4-^{13}C]phenyl-5-nitrobenzophenone, 92241-79-7; 2-([4-^{13}C]-*o*-hydroxyphenyl)-5-nitrobenzophenone, 92241-80-0; 2-([4-^{13}C]-*o*-methoxyphenyl)-5-nitrobenzophenone, 92241-81-1; 4-chloro-2-phenylquinazoline, 6484-25-9.

Rates and Equilibria of the Reaction of 2,4,6-Triphenylthiopyrylium Ion with Piperidine and Morpholine in Me_2SO. An Unusual Proton Transfer to a Nitrogen Base

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Received April 5, 1984. Revised Manuscript Received June 21, 1984

Abstract: The complete set of kinetic and equilibrium constants of the reaction of 2,4,6-triphenylthiopyrylium ion (**1**) with piperidine and morpholine has been obtained in Me_2SO at 25 °C. The reaction involves the formation of both the corresponding 2*H*- and 4*H*-thiopyrans, which equilibrate to form only the more stable 2*H* adduct. The kinetic data are consistent with a two-step process wherein the proton transfer from the protonated 2*H*- and 4*H*-thiopyran intermediates to the amine is the rate-controlling step. The thermodynamically favored proton transfer to the neutral adducts by the solvated proton shows a rate below the diffusion limit, whereas the observed Brønsted coefficient would indicate a diffusion-controlled process. This behavior is discussed in terms of the Eigen mechanism. The factors affecting the nucleophilic addition are discussed, and a comparison is made with the previously reported reaction of **1** with primary amines.

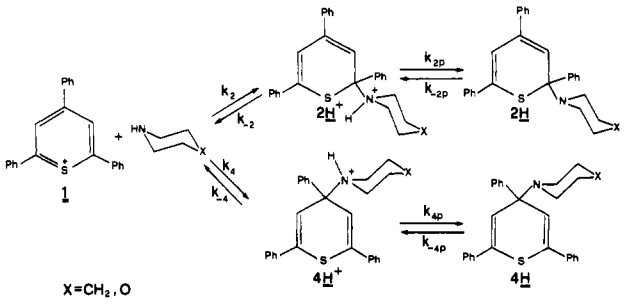
The reaction between nucleophiles and organic cations to yield the corresponding attachment products is a fundamental process in organic chemistry, but in spite of its apparent simplicity the affecting factors are not yet fully understood.[1]

The heteroaromatic cations pyridinium, pyrylium, and thiopyrylium are well suited to obtain insights into these processes. In fact, these ions can be substituted on the two reactive positions, namely the Cα and Cγ carbon atoms, with several substituents having different electronic and steric requirements; moreover, a large number of nucleophiles can react with these substrates making possible the study of the factors affecting both the reactivity and the positional selectivity.

Our interest for these reactions has prompted us to report on a detailed kinetic study of the reaction of 2,4,6-triphenylthiopyrylium ion (**1**) in Me_2SO at 25 °C to yield the corresponding 2*H*- and 4*H*-thiopyrans with piperidine and morpholine, which have different nucleophilicities and identical steric requirements. The aim is to compare this reaction with the corresponding one of the butylamine and cyclohexylamine,[2] in order to study the effect of the structure of the amine on the addition reaction of such a reactive cation.

(1) (a) Ritchie, C. D. *Pure Appl. Chem.* **1978**, *50*, 1281. (b) Ritchie, C. D. *J. Am. Chem. Soc.* **1983**, *105*, 7313.
(2) Doddi, G.; Ercolani, G. *J. Org. Chem.* **1984**, *49*, 1806.

Scheme I



Results

The kinetic study of the reaction of **1** with piperidine/piperidinium and morpholine/morpholinium buffers, carried out at 410 nm, where only **1** absorbs, and at 355 nm, where both **1** and the 2*H* adduct absorb (Figure 1), showed the presence of two relaxation processes, whose separation increased on increasing the amine/ammonium ratio. Whenever the condition $\tau_1^{-1} \gg \tau_2^{-1}$ was fulfilled (τ_1 and τ_2 are the relaxation times of the first and the second process, respectively), the substrate completely disappeared when the first process was over. Similarly to the primary amine reactions,[2] monitoring the process at 355 nm, an initial decrease

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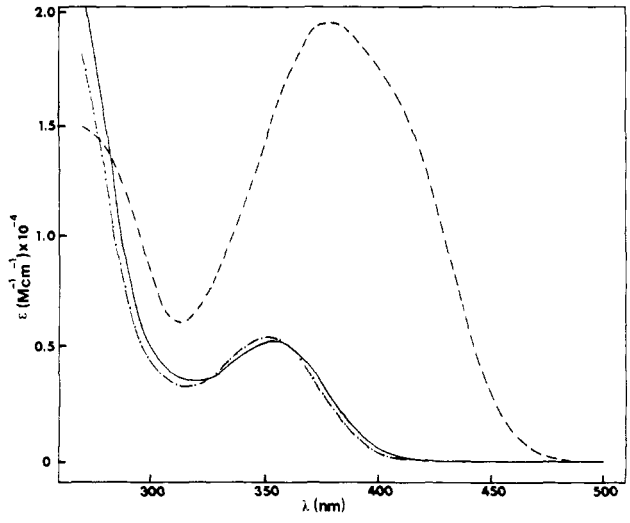


Figure 1. UV–vis spectra of 1 (---) and the corresponding 2*H* adducts with piperidine (—) and morpholine (-·-) in Me_2SO.

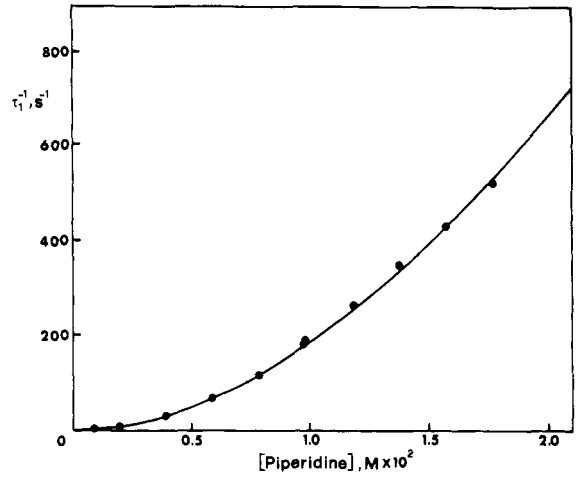


Figure 2. Plot of τ_1^{-1} vs. [piperidine] at [piperidinium] = 0.1 M.

of absorbance followed by a slower increase up to a constant value was observed. This feature, combined with the NMR evidence,[3] indicates the complete formation of the 2*H* adduct.

This pattern can be rationalized by Scheme I, in which the first process is the formation of both 4*H*- and 2*H*-thiopyrans and the second one is equilibration to the more stable 2*H* adduct. The k_p and k_{-p} terms refer to proton transfer and are defined as $k_p = k_p^s + k_p^{am}[am]$ and $k_{-p} = k_{-p}^{sH}[sH] + k_{-p}^{amH}[amH]$, in which k_p^s and k_p^{am} are the rate constants for the deprotonation of the charged adducts by solvent and amine, respectively, and k_{-p}^{sH} and k_{-p}^{amH} are the rate constants for the protonation of neutral adducts by the solvated proton and the ammonium ion, respectively.

Taking into account that the equilibrium is completely shifted toward the 2*H* adduct, the application of the steady-state approximation with respect to $4H^+$ and $2H^+$ to Scheme I, gives the following relationships:[4]

$$\tau_1^{-1} + \tau_2^{-1} = \frac{k_2[am]k_{2p}}{k_{-2} + k_{2p}} + \frac{k_4[am]k_{4p}}{k_{-4} + k_{4p}} + \frac{k_{-4}k_{-4p}}{k_{-4} + k_{4p}} \quad (1)$$

$$\tau_1^{-1}\tau_2^{-1} = \frac{k_2[am]k_{2p}}{k_{-2} + k_{2p}} \frac{k_{-4}k_{-4p}}{k_{-4} + k_{4p}} \quad (2)$$

Piperidine. Study of the Two Relaxation Processes. As mentioned above, when the reaction is carried out with buffers having [am] $\simeq 10^{-3}$–10^{-2} M and [amH] = 0.1 M, the substrate fully

(3) Cordischi, V. C.; Doddi, G.; Stegel, F. *J. Org. Chem.* **1982**, *47*, 3496.
(4) For an exhaustive treatment of the relaxation processes, see: Bernasconi, C. F. "Relaxation Kinetics"; Academic Press: New York, 1976.

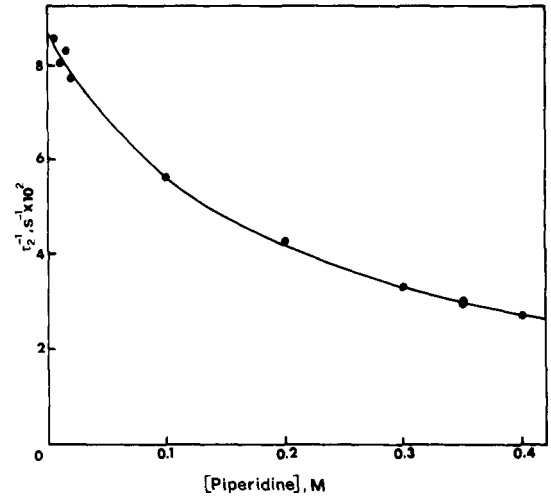


Figure 3. Plot of τ_2^{-1} vs. [piperidine] at [piperidinium] = 0.1 M.

disappears and the condition $\tau_1^{-1} \gg \tau_2^{-1}$ is fulfilled (Table S1, A, B; Figures 2 and 3).

Under these conditions an approximate expression of τ_1^{-1} holds:

$$\tau_1^{-1} = \left(\frac{k_2k_{2p}}{k_{-2} + k_{2p}} + \frac{k_4k_{4p}}{k_{-4} + k_{4p}} \right)[am] \quad (3)$$

Introducing eq 3 into eq 2 affords:

$$\tau_2^{-1} = \left(\frac{k_2k_{2p}}{k_{-2} + k_{2p}} \frac{k_{-4}k_{-4p}}{k_{-4} + k_{4p}} \right) \Big/ \left(\frac{k_2k_{2p}}{k_{-2} + k_{2p}} + \frac{k_4k_{4p}}{k_{-4} + k_{4p}} \right) \quad (4)$$

A plot (not shown) of $\tau_1^{-1}/[am]$ vs. [am] is linear at the lower amine concentrations, with an intercept that is negligible within the experimental errors, whereas at the higher ones a downward curvature is observed. This behavior indicates that at the higher amine concentrations one of the following relationships, at least, is fulfilled—$k_{-2} \simeq k_{2p}$, $k_{-4} \simeq k_{4p}$—whereas at the lower ones eq 5 holds:

$$k_{-2} \gg k_{2p} \text{ and } k_{-4} \gg k_{4p} \quad (5)$$

Moreover, since the intercept is negligible:

$$k_{2p}^{am}[am] \gg k_{2p}^{s} \text{ and } k_{4p}^{am}[am] \gg k_{4p}^{s} \quad (6)$$

and eq 3 becomes:

$$\tau_1^{-1} = \left(\frac{k_2k_{2p}^{am}}{k_{-2} + k_{2p}^{am}[am]} + \frac{k_4k_{4p}^{am}}{k_{-4} + k_{4p}^{am}[am]} \right)[am]^2 \quad (7)$$

that at the lower amine concentrations reduces to:

$$\tau_1^{-1} = \left(\frac{k_2k_{2p}^{am}}{k_{-2}} + \frac{k_4k_{4p}^{am}}{k_{-4}} \right)[am]^2 \quad (8)$$

Two sets of experiments carried out at two different amine concentrations with buffers having lower [am]/[amH] ratios than the previous ones, i.e., under conditions in which the third term of eq 1 cannot be neglected, give two parallel straight lines in the $(\tau_1^{-1} + \tau_2^{-1})$ vs. [amH] plot (Table S1 C, D; Figure 4). This feature indicates that:

$$k_{-4p}^{amH}[amH] \gg k_{-4p}^{sH}[sH] \quad (9)$$

and since at these amine concentrations both eq 5 and eq 6 hold, eq 1 becomes

$$\tau_1^{-1} + \tau_2^{-1} = \left(\frac{k_2k_{2p}^{am}}{k_{-2}} + \frac{k_4k_{4p}^{am}}{k_{-4}} \right)[am]^2 + k_{-4p}^{amH}[amH] \quad (10)$$

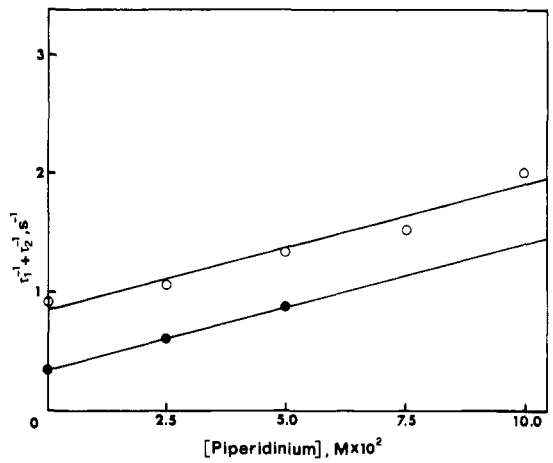


Figure 4. Plot of $(\tau_1^{-1} + \tau_2^{-1})$ vs. [piperidinium] at [piperidine] = 3.51×10^{-4} M (●) and [piperidine] = 6.15×10^{-4} M (○).

k_{-4p}^{amH} being the slope of the plots of Figure 4.

A semplified expression of eq 4 can be written by taking account of eq 6 and 9:

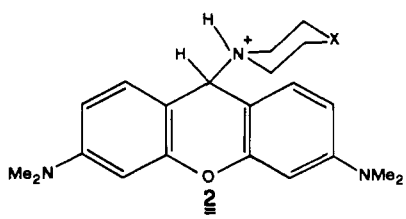
$$\tau_2^{-1} = \left(\frac{k_2 k_{2p}^{am}}{k_{-2} + k_{2p}^{am}[am]} \frac{k_{-4} k_{-4p}^{amH}[amH]}{k_{-4} + k_{4p}^{am}[am]} \right) \Bigg/ \left(\frac{k_2 k_{2p}^{am}}{k_{-2} + k_{2p}^{am}[am]} + \frac{k_4 k_{4p}^{am}}{k_{-4} + k_{4p}^{am}[am]} \right) \quad (11)$$

The k_2, k_4, k_{2p}^{am}/k_{-2}, and k_{4p}^{am}/k_{-4} terms are evaluated by the τ_1^{-1} and τ_2^{-1} data by using an iterative method (see Appendix). We were compelled to use this method because of the need to have τ_1^{-1} data at amine concentrations in which the reaction is too fast for the stopped flow method.

In Figures 2 and 3 are reported both the experimental values of τ_1^{-1} and τ_2^{-1} and the curves calculated by eq 7 and 11.

The k_{-2p}^{amH} term can be determined by the relationship $k_{-2}^{amH} = k_2 k_{2p}^{am}/k_{-2}K_{2T}$, in which K_{2T} is the equilibrium constant for the $2H$ adduct formation from **1** (see Experimental Section). By the relationship $K_{4T} = k_4 k_{4p}^{am}/k_{-4}\ k_{-4p}^{amH}$, K_{4T} can also be evaluated.

The k_{-2} and k_{-4} terms are experimentally inaccessible, but their estimation can be obtained by the relationships $k_{-2} = k_2 K_2^{am}/K_{2T}$ and $k_{-4} = k_4 K_4^{am}/K_{4T}$, where $K_2^{am} = k_{2p}^{am}/k_{-2p}^{amH}$ is the equilibrium constant for the proton transfer reaction between the $2H^+$ adduct and the amine and $K_4^{am} = k_{4p}^{am}/k_{-4p}^{amH}$ is the corresponding one for the $4H^+$ adduct. K_2^{am} and K_4^{am} could be estimated by assuming an additive effect of the thiopyranyl group on the acidity of the ammonium moiety of the charged adducts, i.e., $K_2^{but} = K_2^{pip}$ and $K_4^{but} = K_4^{pip}$ (K_2^{but} and K_4^{but} are referred to the butylamine reaction and were determined in our previous work),[2] but probably the assumption that K_2^{pip}/K_2^{but} and K_4^{pip}/K_4^{but} coincide with K^{pip}/K^{but} (1.65) reported for the deprotonation of 3,6-bis(dimethylamino)xanthylium adduct (**2**) in Me_2SO[5] is a better one. The equilibrium constants for the formation of $2H^+$ and $4H^+$ adducts, $K_2 = k_2/k_{-2}$, and $K_4 = k_4/k_{-4}$, can now be evaluated.



2

pH-Jump Experiments. When a solution of the $2H$ adduct $\simeq 10^{-5}$ M is subjected to a pH-jump by mixing it with a Me_2SO solution of *p*-toluenesulfonic acid,[6] the complete formation of **1** is observed. Considering that the equilibrium is completely shifted toward **1** owing to the protonation of the forming amine, the reaction scheme becomes:

$$2H + sH \underset{k_{2p}^{s}}{\overset{k_{-2p}^{sH}}{\rightleftharpoons}} 2H^+ \xrightarrow{k_{-2}} \mathbf{1} + \text{amine} \xrightarrow{sH} \text{ammonium}$$

As shown in Figure 5, the k_{obsd2} is linearly related to the strong acid concentration (Table S2) with 0 intercept. The rate law is consistent with $2H^+$ as a steady-state intermediate: $k_{obsd2} = k_{-2}k_{-2p}^{sH}[sH]/(k_{-2} + k_{2p}^{s})$. Since $k_{-2} \gg k_{2p}^{s}$, as inferred from relationship 5, the equation reduces to $k_{obsd2} = k_{-2p}^{sH}[sH]$, i.e., the protonation of the $2H$-thiopyran by the solvated proton is the rate-determining step. Therefore k_{-2p}^{sH} concides with the slope of k_{obsd2} plot.

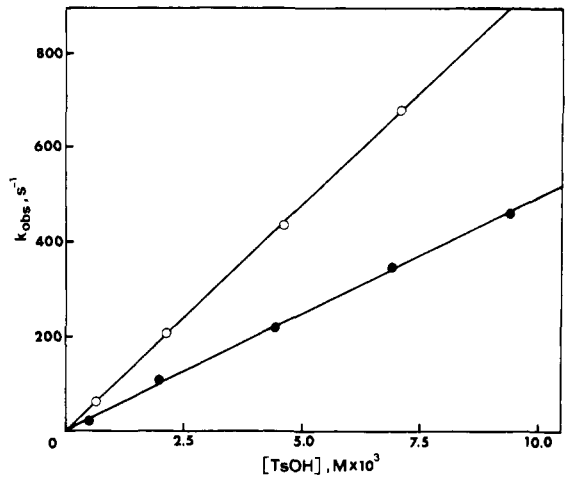


Figure 5. Plot of k_{obsd2} (●) and k_{obsd4} (○) vs. [*p*-toluenesulfonic acid].

The k_{obsd4} term was determined by performing the pH-jump immediately after the solution of **1** and amine was prepared, before any significant equilibration between the two adducts had occurred. Only one relaxation process was detected, indicating that the decompositions of the two adducts to yield **1** occur at similar rates. As already reported,[2] k_{obsd4} can be obtained by the following equation:

$$\exp(-k_{obsd4}t) = \frac{\Delta OD - \Delta OD_2^{\circ} \exp(-k_{-2p}^{sH}[sH]t)}{\Delta OD_4^{\circ}} \quad (12)$$

Where ΔOD_2° and ΔOD_4° are the amplitudes related to the decomposition of the $2H$ and $4H$ adducts and are given by the following relationships:

$$\Delta OD_2^{\circ} = \Delta OD^{\circ} \left[\frac{k_2 k_{2p}^{am}}{k_{-2}} \Bigg/ \left(\frac{k_2 k_{2p}^{am}}{k_{-2}} + \frac{k_4 k_{4p}^{am}}{k_{-4}} \right) \right] \quad (13)$$

$$\Delta OD_4^{\circ} = \Delta OD^{\circ} \left[\frac{k_4 k_{4p}^{am}}{k_{-4}} \Bigg/ \left(\frac{k_2 k_{2p}^{am}}{k_{-2}} + \frac{k_4 k_{4p}^{am}}{k_{-4}} \right) \right] \quad (14)$$

ΔOD° being the amplitude of the entire process.

As shown in Figure 5 and Table S2, also k_{obsd4} shows a linear dependence on the concentration of the acid, and therefore k_{-4p}^{sH} can be obtained by the corresponding slope.

The k_{2p}^{s} and k_{4p}^{s} terms can now be evaluated by the relationships $k_{2p}^{s}/k_{-2p}^{sH} = K_{2a} = K_a K_2^{am}$ and $k_{4p}^{s}/k_{-4p}^{sH} = K_{4a} = K_a K_4^{am}$, where K_{2a} and K_{4a} are the acid dissociation constants of $2H$ and $4H$ adducts, respectively, and K_a is the acid dissociation constant of the conjugated acid of the amine.

(5) Ritchie, C. D. *J. Am. Chem. Soc.* **1983**, *105*, 3573.

(6) *p*-Toluenesulfonic acid is completely ionized in Me_2SO over the concentration range from 10^{-4} to 10^{-2} M: Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 1721.

Table I. Kinetic and Equilibrium Constants for the Reaction of **1** with Piperidine, Morpholine, Butylamine, and Cyclohexylamine in Me_2SO at 25 °C[a]

	piperidine (K_a = 2.2 × 10^{-11} M)[b]	morpholine (K_a = 1.1$_5$ × 10^{-9} M)	butylamine[c] (K_a = 1.3 × 10^{-11} M)	cyclohexylamine[c] (K_a = 1.3 × 10^{-11} M)
k_2,[d] s^{-1} M^{-1}	4.1 × 10^4	9.0 × 10^3[f]	3.7 × 10^3	7.0 × 10^2
k_{-2}, s^{-1}	1.7 × 10^4[e]	1.7 × 10^5[g]	5.4 × 10^2	>7 × 10^2
K_2, M^{-1}	2.5[e]	5.2 × 10^{-2}[g]	7.0	
k_{2p}^{am}, s^{-1} M^{-1}	7.2 × 10^4[e]	5.8 × 10^4[g]		
k_{-2p}^{amH}, s^{-1} M^{-1}	1.9 × 10^{-2}	1.0 × 10^{-2}		
K_2^{am}	3.8 × 10^6[e]	5.8 × 10^6[g]	2.3 × 10^6	
k_{2p}^{s}, s^{-1}	4.1[e]	3.4 × 10^2[g]		
k_{-2p}^{sH}, s^{-1} M^{-1}	4.9 × 10^4	5.2 × 10^4		
K_{2a}, M	8.4 × 10^{-5}[e]	6.6 × 10^{-3}[g]	3.0 × 10^{-5}	
K_{2T}, M^{-1}	9.5 × 10^6	3.0 × 10^5	1.6 × 10^7	4.8 × 10^6
k_4, s^{-1} M^{-1}	1.1 × 10^5	2.5 × 10^4[f]	1.4 × 10^4	2.7 × 10^3
k_{-4}, s^{-1}	2.9 × 10^4[e]	7.0 × 10^5[g]	6.5 × 10^2	>7 × 10^2
K_4, M^{-1}	4.0[e]	3.6 × 10^{-2}[g]	22	
k_{4p}^{am}, s^{-1} M^{-1}	5.0 × 10^5[e]	5.0 × 10^5[g]		
k_{-4p}^{amH}, s^{-1} M^{-1}	10	6.9		
K_4^{am}	4.8 × 10^4[e]	7.2 × 10^4[g]	2.9 × 10^4	
k_{4p}^{s}, s^{-1}	0.1[e]	6.8[g]		
k_{-4p}^{sH}, s^{-1} M^{-1}	9.5 × 10^4	8.1 × 10^4		
K_{4a}, M	1.1 × 10^{-6}[e]	8.3 × 10^{-5}[g]	4 × 10^{-7}	
K_{4T}, M^{-1}	1.9 × 10^5	2.6 × 10^3	6 × 10^5	2.5 × 10^4

[a] μ = 0.1 M. [b] From ref 25. [c] From ref 2. [d] Uncorrected for the statistical factor. [e] Estimated by the assumption K_i^{pip}/K_i^{but} = 1.65, as described in the text. [f] Estimated by the assumption $(k_2/k_4)_{mor} = (k_2/k_4)_{pip}$. [g] Estimated by the assumption K_i^{mor}/K_i^{but} = 2.50, as described in the text.

In Table I are collected the kinetic and equilibrium constants evaluated or estimated for the piperidine reaction, together with the corresponding data for the morpholine reaction. For a comparison in this table are reported also the data for the butylamine and cyclohexylamine reaction.[2]

Morpholine. The morpholine reaction behaves similarly to the piperidine one. At variance with this reaction the proton transfer step is rate controlling also at the higher accessible amine concentrations, as indicated from both the linear dependence of τ_1^{-1}/[am] vs. [am] (with a negligible intercept within the experimental errors) and the independence of τ_2^{-1} on the amine concentration, (Table S3A). Under these conditions eq 11 is reduced to:

$$\tau_2^{-1} = \left(\frac{k_2 k_{2p}^{am}}{k_{-2}} k_{-4p}^{amH}[amH]\right) \Big/ \left(\frac{k_2 k_{2p}^{am}}{k_{-2}} + \frac{k_4 k_{4p}^{am}}{k_{-4}}\right) \quad (15)$$

According to eq 8 the slope of the plot of τ_1^{-1}/[am] vs. [am] coincides with $([k_2 k_{2p}^{am}/k_{-2}] + [k_4 k_{4p}^{am}/k_{-4}])$. Introducing into eq 15 this term and k_{-4p}^{amH} as obtained as previously reported for the piperidine reaction (Table S3 B, C), $k_2 k_{2p}^{am}/k_{-2}$ and hence $k_4 k_{4p}^{am}/k_{-4}$ can be evaluated.

The k_2 and k_4 terms were evaluated by experiments carried out in the presence of acetate buffers, in order to make the deprotonation step fast with respect to the nucleophilic attack. Plots of τ_1^{-1} vs. [am] are linear with slopes that are independent of the concentrations of the acetate ion (Table S4). Under these conditions the slopes coincide with $(k_2 + k_4)$. With the assumption that the k_2/k_4 ratio coincides with that observed for the piperidine reaction, k_2 and k_4 can now be evaluated.[7]

The equilibrium constants K_2^{mor} and K_4^{mor} were obtained as previously indicated for piperidine, by the ratio K^{mor}/K^{but} = 2.5.[5]

The remaining kinetic and equilibrium constants reported in Table I are obtained as previously indicated for the piperidine reaction (Table S5).

Discussion

Nucleophilic Attack Step. The order of reactivity for the attack on the α and γ positions, piperidine > morpholine $\gtrsim$ butylamine > cyclohexylamine (Table I), is closely related to the one observed in many attachment reactions of amines to organic cations,[5,8] activated alkenes and benzenes,[9] and in nucleophilic aromatic substitutions of heteroaromatic cations or neutral activated compounds.[10] The higher reactivity of secondary amines with respect to the less hindered primary ones indicates that severe steric strain to the approach of the nucleophile is not involved.[11] However, the lower reactivity of cyclohexylamine with respect to butylamine indicates that this effect is not quite negligible.

Two-point Brønsted plots of log K_i (i = 2, 4) vs. pK_a of the conjugated acid of the amines yield β_{eqi}. Both β_{eq2} (0.98) and β_{eq4} (1.2) indicate that the difference of carbon basicity between piperidine and morpholine is comparable to their difference of proton basicity.

The β_{nuc2}^{n} (0.4) and β_{nuc4}^{n} (0.32), obtained by the slopes of log k_i vs. log K_i plots, indicate that in the transition state leading to $2H^+$ and $4H^+$ adducts, about 30–40% of the positive charge is localized on the attacking amino group and hence the forming C–N bond is less than half complete.

A comparison of k_4/k_2 ratio (2.8) with that observed for the less reactive primary amines (3.8)[2] and for the more reactive methoxide ion in methanol (1.4)[12] shows that the decrease of selectivity with the increase of reactivity ($\simeq$100×) is quite negligible, as observed for nucleophilic reactions of organic cations.[1a]

A comparison of the k_{-i} terms of the primary and secondary amines (Table I) indicates that in consequence of the greater steric strain of the secondary amine moieties, the latter are better leaving groups that the former. Moreover the nucleofugicity of morpholine is enhanced by the electronic effects responsible of its lower basicity.

The most important feature that distinguishes the secondary amine reaction from that of primary amines is the different rate-controlling step. In the latter reaction the rate-determining

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step is the nucleophilic attack to yield the $2H^+$ and $4H^+$ adducts, whereas in the former the rate-controlling step is the deprotonation of the charged adducts to yield the neutral ones, even though with piperidine the rates of the two steps become comparable at the higher amine concentrations. This different behavior depends both on the increase of k_{-i} and mainly on a decrease of the k_{ip}^{am} terms for the secondary amine reaction (Table I). In fact, since for the primary amine reaction $k_{ip}^{am}[am] > 10k_{-i}$,[2] we can estimate that $k_{ip}^{am} > 10^6$ M^{-1} s^{-1}, i.e., more than 10× that observed for the secondary amines, in spite of the comparable K_i^{am}.

In the following section we account for the factors that can affect such proton transfer processes.

Rate-Limiting Proton Transfer. A very significant result is the finding that the strongly favored deprotonation of the charged adducts by amines (K_i^{am}) and the protonation of neutral adducts by the solvated proton ($1/K_{ia}$) are activated rather than encounter controlled (k_{ip}^{am}, k_{-ip}^{sH}).

It is well-known that proton transfer between nitrogen atoms in water is diffusion controlled, provided that the reaction is thermodynamically favored by 2 or more pK_a units.[13] Moreover, Bianchin and Delpuech reported a rate constant for proton transfer between NH_4^+ and NH_3 in Me_2SO (1.17×10^9 M^{-1} s^{-1}) that coincides with that observed in aqueous solution (1.21×10^9 M^{-1} s^{-1}).[14] This result shows that a fast proton transfer can also occur in an aprotic solvent. However, recent reports on thermodynamically favored proton transfer between bases and charged amine adducts of 1,3,5-trinitrobenzene,[9e,f,15] 3,6-bis(dimethylamino)xanthylium ion,[5] and activated alkenes,[9a,b] and acid such as 1-*cis*-2-*cis*-6-trimethylpiperidinium ion,[16] in Me_2SO or 50% aqueous Me_2SO solutions, indicate that the rates of these processes are below the diffusion limit. This behavior was attributed to steric interactions hindering the approach of the base to the crowded adduct, and actually an increasing of bulkiness of base can depress the rates of these processes without any relationship with its basicity.[9a]

The importance of the steric effects is also shown by the reaction of **2** with morpholine in Me_2SO, in which the steric hindrance on the ammonium nitrogen should be lower than the $4H^+$-thiopyran, having a rate 3× higher than k_{4p}^{mor}, in spite of a three order of magnitude lower acidity.[5] Similar conclusions are drawn from the comparison between k_{2p}^{am} and k_{4p}^{am} showing that the more acidic $2H^+$ adduct (≃100×) is deprotonated by the amine more slowly than the $4H^+$ isomer. Moreover our finding $k_{2p}^{mor} \simeq k_{2p}^{pip}$ and $k_{4p}^{mor} \simeq k_{4p}^{pip}$ clearly shows that if the steric situation between the acid and the base is unchanged, the rate of the proton transfer is not affected.

Steric effects seem to be operating also in the protonation of the $2H$ and $4H$ adducts by the solvated proton. A Brønsted plot of log k_{-ip}^{sH} vs. log K_{ia} is linear with $\beta \simeq 0$, whereas the thermodynamically unfavored reverse reaction has $\alpha \simeq 1$. Brønsted slope is commonly interpreted as indicating the degree of proton transfer in the transition state.[17] It follows that in the transition state the proton is released to a very small extent to the neutral adducts. This behavior resembles that shown by diffusion-controlled reactions of "normal" acids,[18] whereas the k_{-ip}^{sH} terms are largely below the diffusion limit.

A plausible explanation involves restructuring of the solvation shell of the proton. Since the structure of this reagent in Me_2SO is $[Me_2SO\cdots H\cdots Me_2SO]^+$,[19] the proton cannot be transferred along a Grotthus chain, and a molecule of the solvent must be replaced by the sterically crowded adduct in order for the proton transfer to take place. The Eigen scheme for this proton transfer process is

$$\underset{a}{\text{Add} + [Me_2SO\cdots H\cdots Me_2SO]^+} \rightleftarrows \underset{b}{\text{Add, } [Me_2SO\cdots H\cdots Me_2SO]^+} \rightleftarrows \underset{c}{\text{Add}\cdots{}^+\text{H-}Me_2SO, Me_2SO} \rightleftarrows \underset{d}{\text{Add-H}^+\cdots Me_2SO}$$

Our findings indicate that the rate-controlling step is the conversion of the encounter complex b into the hydrogen-bonded complex c.

Kreevoy reported on a slow protonation of substituted tribenzylamines by the solvated proton in Me_2SO that shows $\beta = 0.59$.[20] Tribenzylamines should be less hindered than the $2H$- and $4H$-thiopyrans, and the b–c process is expected to be favored, making the proton transfer process c–d concurring to the overall rate.

Even though Brønsted coefficients suggesting diffusion-controlled processes are reported for proton transfer reactions of carbon acids whose rates are below the diffusion limit,[21] this is a remarkable finding for a nitrogen base.

Experimental Section

Materials. 2,4,6-Triphenylthiopyrylium perchlorate was available from our previous work.[2]

Me_2SO was dried as previously described.[2] The amines were refluxed over sodium for 2 h and distilled under argon.

Piperidinium and morpholinium perchlorates were prepared by the respective amines and aqueous perchloric acid (70%) and, after removal of the water, recrystallized twice from benzene–acetone 3:1 and 2:1, respectively. (**Warning**: Organic perchlorates are potentially explosive.)

Tetramethylammonium acetate was prepared by neutralization of a 25% aqueous solution of tetramethylammonium hydroxide (FLUKA) with acetic acid and by crystallization from acetone after removal of the water. All the salts were dried by warming at 80 °C under vacuum.

Spectra. The UV–vis spectra of the substrate and the corresponding $2H$ adducts with piperidine and morpholine (Figure 1) were recorded on a Cary 219 spectrophotometer.

Rate Measurements. All kinetic experiments were carried out on a Durrum 110 stopped-flow spectrophotometer at 25 °C under pseudo-first-order conditions. The ionic strength was maintained at 0.1 M with $KClO_4$. The reaction solutions were freshly prepared and handled under argon. The two relaxation processes were monitored at 410 nm, where only **1** absorbs ([**1**] ≃ 10^{-5} M), and at 355 nm, where both **1** and the corresponding $2H$ adduct absorb.[22]

Equilibrium Measurements. The pK_a of morpholine (8.9) in Me_2SO at μ = 0.1 M was determined spectrophotometrically as previously described.[2]

The equilibrium constant K_{2T}, referred to the equilibrium **1** + 2amine ⇄ $2H$ + ammonium (see Scheme I), was determined spectrophotometrically as previously described[2] (for the morpholine reaction a 1-cm quartz cell was used).

Appendix

Assuming at first that during the first process the formation of the $2H$ adduct is negligible with respect to the $4H$ isomer,[23] eq 7 reduces to:

$$\tau_1^{-1} \simeq \frac{k_4 k_{4p}^{am}[am]^2}{k_{-4} + k_{4p}^{am}[am]} \tag{16}$$

that rearranged gives:

$$\frac{[am]}{\tau_1^{-1}} \simeq \frac{k_{-4}}{k_4 k_{4p}^{am}[am]} + \frac{1}{k_4} \tag{17}$$

The plot of $[am]/\tau_1^{-1}$ vs. $1/[am]$ is linear with intercept $\simeq 1/k_4$ and slope $\simeq k_{-4}/k_4 k_{4p}^{am}$, and hence k_4 and k_{4p}^{am}/k_{-4} can be

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estimated. Rearranging eq 11 affords:

$$\frac{\tau_2^{-1}[k_4k_{4p}^{am}[am]^2/(k_{-4} + k_{4p}^{am}[am])]}{[k_{-4}k_{-4p}^{amH}[amH]/(k_{-4} + k_{4p}^{am}[am])] - \tau_2^{-1}} = \frac{k_2k_{2p}^{am}[am]^2}{k_{-2} + k_{2p}^{am}[am]} \quad (18)$$

The left-hand term of eq 18 that for the sake of simplicity we indicate as k_2*, can be evaluated by introducing the approximate value of k_4 and k_{4p}^{am}/k_{-4} just obtained.

Applying the same mathematical treatment of eq 16 to eq 18 affords:

$$\frac{[am]}{k_2^*} = \frac{k_{-2}}{k_2k_{2p}^{am}[am]} + \frac{1}{k_2} \quad (19)$$

From the plot of $[am]/k_2$* vs. $1/[am]$, approximate values of k_2 and k_{2p}^{am}/k_{-2} can be obtained.

With the introduction of these terms into eq 7, better values of $[k_4k_{4p}^{am}[am]^2/(k_{-4} + k_{4p}^{am}[am])]$ are obtained, and so on, until constant values of k_2, k_4, k_{2p}^{am}/k_{-2}, and k_{4p}^{am}/k_{-4} are obtained.

Actually this iterative procedure was carried out with a personal computer by using a non-linear least-squares method.[24]

Registry No. **1**·CO_4^-, 2930-37-2; **2**·$HClO_4$, 92314-76-6; **2H** (X = CH_2), 92314-68-6; **2H** (X = O), 87691-76-7; **2H**·$HClO_4$ (X = CH_2), 92314-69-7; **2H**·$HClO_4$ (X = O), 92314-70-0; **4H** (X = CH_2), 92314-71-1; **4H** (X = O), 92314-73-3; **4H**·$HClO_4$ (X = CH_2), 92314-72-2; **4H**·$HClO_4$ (X = O), 92314-74-4; $Me_4N^+OH^-$, 75-59-2; $CH_3C(O)O^-$ Me_4N^+, 1058-12-1; piperidine, 110-89-4; piperidinium perchlorate, 57367-18-7; morpholine, 110-91-8; morpholinium perchlorate, 35175-75-8.

Supplementary Material Available: Tables S1–S5 summarizing all the kinetic measurements (6 pages). Ordering information is given on any current masthead page.

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Kinetics of the 1,2-Migration of Carbon-Centered Groups in 2-Substituted 2,2-Dimethylethyl Radicals[1]

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Abstract: The rearrangements $RCMe_2CH_2\cdot \rightarrow RCH_2\dot{C}Me_2$ (k_r) (R = Ph, $Me_3CC{\equiv}C$, $Me_3CC{=}O$, and $N{\equiv}C$) have been studied over a range of temperatures by product analyses with use of the common competing reaction $RCMe_2CH_2\cdot + CCl_4 \rightarrow RCMe_2CH_2Cl + CCl_3\cdot$ (k_{Cl}). For R = $H_2C{=}CH$ the rearrangement was so fast that only the rearranged chloride, RCH_2CMe_2Cl, was produced. All these rearrangements occur via a 3-membered cyclic intermediate radical (or transition state). Various considerations led to the following Arrhenius equation for chlorine abstraction: $\log (k_{Cl}/M^{-1}\ s^{-1}) = (8.14 \pm 0.42) - (5.52 \pm 0.63)/\theta$, where $\theta = 2.3RT$ kcal/mol, and this equation is used to calculate Arrhenius parameters for migration of all but the $H_2C{=}CH$ group. Comparison of these parameters with those already available from kinetic EPR measurements leads to a choice of preferred Arrhenius parameters for all five rearrangements. The cyano group had an unexpectedly low mobility while the pivaloyl group underwent a surprisingly rapid 1,2-shift. Migratory aptitudes increase along the series R = $N{\equiv}C < Me_3CC{\equiv}C < Ph < Me_3CC{=}O < H_2C{=}CH$, with k_r at 25 °C = 0.9, 93, 762, 1.7×10^5, and 1.0×10^7 s^{-1}, respectively. The preferred pre-exponential factors all lie in the range $10^{10.9}$–$10^{12.0}$ s^{-1}, while the activation energies vary from 16.4 kcal/mol for R = $N{\equiv}C$ to 5.7 kcal/mol for R = $H_2C{=}CH$. These results are discussed in relation to the results of thermochemical kinetic calculations and to earlier work on the 1,2-migration of unsaturated groups in radicals.

In free radical chemistry the 1,2-migration of an unsaturated group has excited interest[3] ever since the discovery by Urry and Kharasch[4] in 1944 of the neophyl rearrangement, i.e., **1a** → **2a**.

$$\underset{\mathbf{1}}{RCMe_2CH_2\cdot} \xrightarrow{k_r} \underset{\mathbf{2}}{Me_2\dot{C}CH_2R} \quad (1)$$

a, R = C_6H_5; **b**, R = $Me_3CC{\equiv}C$;
c, R = $CH_2{=}CH$; **d**, R = $Me_3CC{=}O$; **e**, R = $C{\equiv}N$

In the early 1970's kinetic EPR spectroscopic methods were developed for measuring the rates of unimolecular radical reactions.[5-9] This advance was important because once the Arrhenius parameters for a radical rearrangement have been determined the rearrangement can serve as a "clock" to measure rate constants for appropriate radical–molecule reactions.[10] We have used the EPR technique to measure Arrhenius parameters for the neophyl rearrangement[11] and for some related reactions;[11] for a homopropargylic rearrangement,[12] **1b** → **2b**; and for a homoallylic rearrangement,[13-16] **1c** → **2c**. To the best of our knowledge there

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0002-7863/84/1506-7087$01.50/0 Published by the American Chemical Society