Kinetics and Mechanism of the Reactions of 2,4-Dinitrophenyl Acetate with Secondary Alicyclic Amines. Different Nucleofugalities of Alicyclic Amines and Pyridines from a Tetrahedral Intermediate

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There is abundant literature on the mechanism of the aminolysis of aryl esters.[1] In most cases, by structure–reactivity correlations (Hammett and Brønsted-type plots), at least one tetrahedral intermediate ($T^{\pm}$) in the reaction path has been postulated, and the influence of the acyl[2,3] and aryloxy[2,4,5] groups of $T^{\pm}$ on the relative nucleofugalities of amines and aryloxide ions has been assessed. However, there are only few works on the influence of the amine nature on the above nucleofugalities.[2,6] In order to investigate further the latter we examine in this paper the kinetics and mechanism of the title reaction, by means of the Brønsted-type plot, and we compare it with that found in the pyridinolysis of 2,4-dinitrophenyl acetate,[5] in the aim of evaluating leaving abilities of alicyclic amines and pyridines from $T^{\pm}$.

Experimental Section

Materials. The secondary alicyclic amines used in this work were purified as previously reported.[7] 2,4-Dinitrophenyl acetate was synthesized as described elsewhere.[5]

Kinetic Measurements. The reactions were studied spectrophotometrically (Perkin Elmer Lambda 3) by following the release of 2,4-dinitrophenoxide ion at 400 nm. The reactions were initiated by the addition of 10 μL of the ester stock solution (in acetonitrile) to 3 mL of a thermally equilibrated (25 ± 0.1 °C) solution of the amine. The initial substrate concentration was 5×10^{-5} M. Acetonitrile never exceeded 0.3% in the kinetic solutions. The pH was maintained either with borate or phosphate buffer (0.01 M), except piperazinium ion, where the pH values used were within the buffering capacity of the amine. Measurements of pH were performed with a Radiometer PHM-62 pH meter provided with glass (G-2040C) and calomel (K-4040) electrodes. The reactions were carried out under pseudo-order conditions (total amine in excess) and found to follow first-order kinetics for at least 4 half-lives.

The experimental conditions of the reactions and the pseudo-first-order rate constants (k_{obsd}) obtained are shown in Table I.

Results

The kinetic law obtained for the present reactions is given by eq 1, where k_N is the rate constant for the aminolysis reaction, F_N is the free amine fraction and $[N]_{tot}$ is the total concentration of amine (free amine plus its conjugate acid). The rate constant for hydrolysis of the substrate was negligible compared to its aminolysis, under the experimental conditions employed.

$$k_{obsd} = k_N F_N [N]_{tot} \quad (1)$$

The values of k_N were obtained from the slopes of linear plots of k_{obsd} against $[N]_{tot}$ at constant F_N (constant pH). Three plots at different pH values were drawn for each amine; the k_N values found at each pH were in accord within the experimental error, and the final k_N value for

Table I. Experimental Conditions and k_{obsd} for the Aminolysis of 2,4-Dinitrophenyl Acetate in Aqueous Solution at 25.0 °C[a]

amine	$10^3[N]_{tot}$,[b] M	pH	$10^3 k_{obsd}$, s^{-1}
piperidine[c]	1.4–14.1	8.7	2.4–22.4
	1.1–11.3	9.0	3.7–35.0
	0.7–7.1	9.3	5.4–40.6
piperazine[d]	0.7–7.0	8.1	3.8–37.0
	0.5–5.3	8.4	5.2–45.7
	0.5–5.3	8.7	9.0–98.6
1-(β-hydroxyethyl)piperazine[d]	0.7–6.9	8.1	3.8–38.8
	1.4–6.9	8.4	7.2–73.2
	0.5–5.2	8.7	9.2–97.5
morpholine[e]	4.4–44.0	6.7	2.7–26.6
	4.4–44.0	7.0	5.2–48.9
	2.2–22.0	7.3	4.6–47.4
1-formylpiperazine[e]	4.4–44.1	6.7	4.2–41.0
	3.3–33.1	7.0	5.6–58.2
	2.2–22.1	7.3	6.6–63.9
piperazinium ion	6.0–60.0	5.2	1.4–15.4
	6.0–60.0	5.5	2.4–19.2
	6.0–60.0	5.8	3.8–37.2

[a] At ionic strength 0.2 M (maintained with KCl). Five runs were carried out at each pH. [b] Total concentration of amine (free base plus protonated forms). [c] In the presence of 0.01 M borate buffer. [d] In the presence of 0.02 M borate buffer. [e] In the presence of 0.01 M phosphate buffer.

Table II. Values of pK_a of the Conjugate Acids of the Amines and Second-Order Rate Constants (k_N) Obtained in the Aminolysis of 2,4-Dinitrophenyl Acetate in Aqueous Solution at 25 °C[a]

amine	pK_a[b]	k_N, s^{-1} M^{-1}
piperidine	11.24 ± 0.04	518 ± 32
piperazine	9.94 ± 0.04	333 ± 31
1-(β-hydroxyethyl)piperazine	9.38 ± 0.03	107 ± 8
morpholine	8.78 ± 0.03	68 ± 3
1-formylpiperazine	7.98 ± 0.03	17 ± 2
piperazinium ion	5.81 ± 0.03	1.3 ± 0.1

[a] At ionic strength 0.2 M (KCl). The errors shown are standard deviations. [b] Values taken from ref 7, at the same experimental conditions of the kinetics.

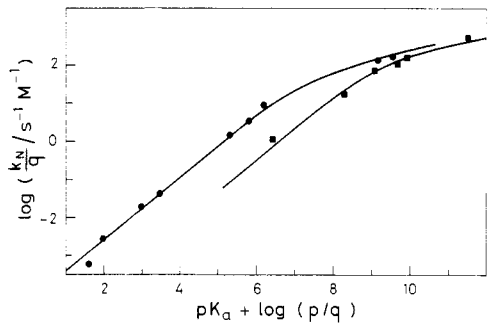


Figure 1. Brønsted-type plots (statistically corrected) obtained in the reactions of 2,4-dinitrophenyl acetate with pyridines (●, ref 5) and secondary alicyclic amines (■, this work) in water at 25 °C, ionic strength 0.2 M.

(1) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (b) Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237. (c) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622. (d) Luthra, A. K.; Ba-Saif, S.; Chrystiuk, E.; Williams, A. *Bull. Soc. Chim. Fr.* **1988**, 391. (e) Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 2051.

(2) (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (b) *Ibid.* **1977**, *99*, 6970.

(3) Castro, E. A.; Valdivia, J. L. *J. Org. Chem.* **1986**, *51*, 1668. Castro, E. A.; Becerra, M. C. *Bol. Soc. Chil. Quim.* **1988**, *33*, 67. Knowlton, R. C.; Byers, L. D. *J. Org. Chem.* **1988**, *53*, 3862.

(4) Bond, P. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 679. Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611. Yoh, S.-D.; Kang, J.-K.; Kim. S.-H. *Tetrahedron* **1988**, *44*, 2167.

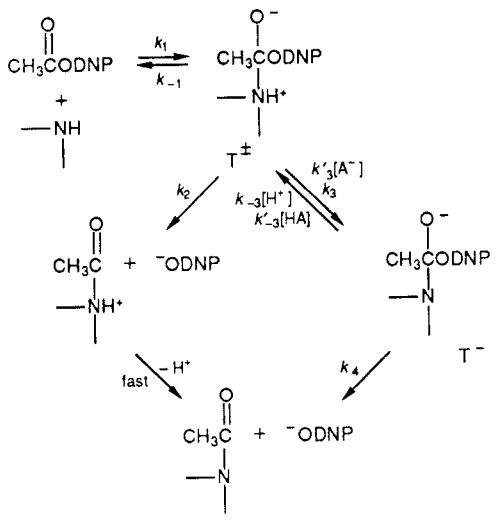
(5) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.

(6) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 499.

(7) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.

0022-3263/90/1955-1676$02.50/0

Scheme I



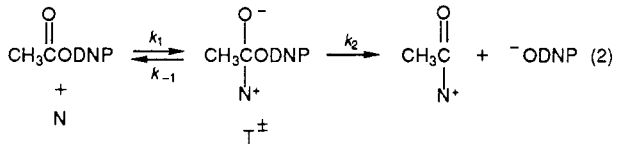
the reaction of each amine was taken as an average of the individual values.

The final k_N values found for the reactions studied and the pK_a values of the conjugate acids of the amines, under the same experimental conditions,[7] are shown in Table II.

Both the pK_a and k_N values were statistically corrected before plotting the Brønsted-type equation, with $q = 1$ (except piperazine with $q = 2$) and $p = 2$ (except piperazinium ion with $p = 4$).[7,8] The statistically corrected Brønsted-type plot obtained in this work is shown in Figure 1, together with the one found in the pyridinolysis of the same substrate ($p = q = 1$ for all the pyridines) under the same experimental conditions.

Dicussion

The Brønsted-type curves shown in Figure 1 were calculated through a semiempirical equation based on the existence of a tetrahedral intermediate ($T^{\pm}$ in eq 2, where N represents an amine and DNP is 2,4-dinitrophenyl) in

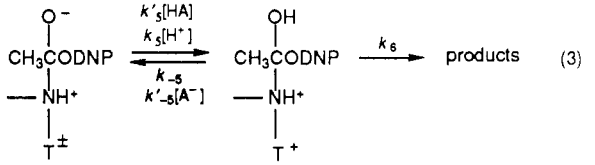


(2)

the reaction path and a change in the rate-determining step from k_2 to k_1 in eq 2 as the basicity of the amine increases.[2,4,5,7] Both curves fitted the experimental data with the slopes $\beta_1 = 0.20$ and $\beta_2 = 0.85$, for the formation and breakdown of $T^{\pm}$, respectively, which are similar to the values found in the aminolysis of other reactive carbonyl compounds.[2,4,5,7,9] The values used for log $k_N°$ and $pK_a°$ (the other adjustable parameters) were 1.55 and 7.3, respectively, for the reactions of the pyridines,[5] and 1.85 and 9.1, respectively, for the reactions of the alicyclic amines. The parameters $k_N°$ and $pK_a°$ refer to an (hypothetical) amine, for which $k_{-1} = k_2$ in eq 2.

We show below that, under the experimental conditions shown in Table I, reactions of the alicyclic amines can be totally described by eq 2, i.e., there are no other significant reactions (such as acid–base catalysis) involved, and therefore the Brønsted-type curve observed (Figure 1) must be due to the change in the rate-limiting step mentioned above.

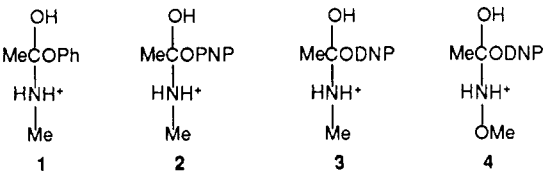
A general mechanism for the reaction studied in this work is depicted in Scheme I. Paths such as that described by eq 3, where HA and A^- represent a general acid and its conjugate base, were omitted from Scheme I since they are not important, under the experimental conditions employed, as we will show now.



(3)

The hydroxylic pK_a (pK_a^{OH}) of T^+ in eq 3 can be estimated following the procedure of Jencks and co-workers.[10,11] Starting with $pK_a = 9.98$ for the hydroxyl group of $MeNH_2^+CH_2OH$ and correction for a methyl group gives $pK_a^{OH} = 10.3$ for $MeNH_2^+CH(Me)OH$.[10] α-Phenyl substitution for H lowers the pK_a 0.2 unit,[11] which results in $pK_a^{OH} = 10.1$ for $MeNH_2^+C(Ph)(Me)OH$.

Since substituent effects through a tetrahedral carbon are mainly inductive,[10,11] taking $\rho_I = -8.4$ for the pK_a correlation of α-substituted alcohols,[10,11] one gets $pK_a^{OH} = 10.1 - 8.4(0.39 - 0.10) = 7.7$ for **1**, using $\sigma_I = 0.39$ and 0.10 for phenoxy and phenyl groups, respectively.[12] The



1 **2** **3** **4**

pK_a^{OH} of **2** (PNP is *p*-nitrophenyl) can be estimated as 6.8 by taking $\rho = 1.1$ for the ionization of trifluoroacetophenone hydrates,[11,13] and $\sigma_p = 0.78$ for the nitro group.[14] Assuming additivity of substituents and using $\sigma_o = 0.57$ for the second nitro group,[15,16] one obtains $pK_a^{OH} = 6.2$ for **3**. Using $\sigma_I = 0.10$ and 0.18 for methylamine and methoxyamine,[10] one gets $pK_a^{OH} = 5.5$ for **4**.

Alternatively, the pK_a of **3** can be determined either from the pK_a^{OH} of $MeNH_2^+CH(Me)OH$ and $\sigma_I = 0.53$ for the 2,4-dinitrophenyl group,[17] or from the pK_a^{OH} of **1**, and $\sigma_I = 0.53$ and 0.39 for 2,4-dinitrophenoxy and phenoxy groups, respectively.[12,17] The values thus obtained are 5.9 and 6.5, respectively, which satisfactorily agree with the pK_a^{OH} value of **3** found above.

The sensitivity of the pK_a^{OH} of T^+ (eq 3) to the basicity of the amine (β) can be inferred from the pK_a^{OH} values of **3** and **4** and the pK_a values of methylamine and methoxyamine (10.6 and 4.6, respectively[18]), assuming that

(8) Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1959; p 159.
(9) Palling,. D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869.
(10) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.
(11) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637.
(12) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222.
(13) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399.
(14) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981.
(15) This value was obtained from $\sigma_o = 0.78\,(2.78 - 2.43)/(2.91 - 2.43)$, where 0.78 is σ_p for the nitro group and 2.91, 2.78, and 2.43 are σ^* values for *p*-nitrophenoxy, *o*-nitrophenoxy, and phenoxy groups, respectively.[14] The σ_o value thus determined agrees well with $\sigma_o = 0.55$ obtained from the ionization of phenylpropiolic acids.[16]
(16) Shorter, J. *Correlation Analysis in Organic Chemistry: An Introduction to Linear Free-Energy Relationships*; Oxford: London, 1973; p 44.
(17) Guthrie, J. P.; Pike, D. C. *Can. J. Chem.* **1987**, *65*, 1951.
(18) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971.

alicyclic amines behave similarly to primary amines as far as their influence on the pK_a^{OH} of T^+ is concerned. These values give $\beta = 0.12$, which together with the above data eq 4 obtains, where $pK_a(N)$ is the pK_a of the conjugate acid of either a primary or an alicyclic amine.

$$pK_a^{OH}(T^+) = 4.9 + 0.12pK_a(N) \quad (4)$$

With the pK_a^{OH} value of T^+ we can now determine the values of k_5, k'_5, k_{-5}, and k'_{-5} of eq 3. Let us start with the case of piperazinium as the amine moiety of T^+ (in this case T^+ is a dication).

For the above amine (pK_a of conjugate acid = 5.8), $pK_a^{OH}(T^+) = 5.6$, according to eq 4; since the k_5 step of eq 3 is thermodynamically favorable, $k_5 \approx 10^{10}$ s^{-1} M^{-1} and $k_{-5} \approx 10^{10} \times 10^{-5.6} \approx 2 \times 10^4$ s^{-1},[19] which gives $k_5[H^+] \approx 3 \times 10^4$ s^{-1} at the experimental pH values (ca. 5.5 in this case). If HA and A^- in eq 3 are piperazinium dication and piperazinium ion, respectively (external buffer was not used in this case), neither k_5 nor k'_{-5} steps would be thermodynamically favorable, and we can assume $k'_5 \approx k'_{-5} \approx 10^9$ s^{-1} M^{-1}.[19] At the highest concentrations used for HA and A^-, $k'_5[HA] \approx k'_{-5}[A^-] \approx 3 \times 10^7$ s^{-1}. This value should be lower than k_6, which in turn should be somewhat smaller than the estimated value of k_2 of Scheme I ($k_2 \approx 3 \times 10^9$ s^{-1}, see below) in view that the "push" exerted by OH from T^+ to expel 2,4-dinitrophenoxide ion should be weaker than that of O^- from $T^\pm$. If $k_6 > k'_{-5}[A]$, the k'_5 step should be rate limiting, but since $k'_5[HA]$ is smaller than k_2, the path described by eq 3 is not important compared to the k_2 step.[20]

In the cases of the other amines as moieties of T^+, the path through T^+ (eq 3) is even less favorable than in the case of piperazinium ion, as shown by calculations similar to those described above.[21]

Let us now turn to Scheme I. In order to know whether the path through T^- (k_3, k'_3) is significant compared to the k_2 step, we must first estimate the pK_a of $T^\pm$.

The pK_a of $MeCH(O^-)R^1R^2NH^+$ is 2.2 higher than that of the parent aminium ion.[7] Introduction of the 2,4-dinitrophenoxy group ($\sigma_I = 0.53$[17]) and using $\rho_I = -7.3$ for the ionization of α-substituted morpholinium ions,[7,10] one gets eq 5, where $pK_a(T^\pm)$ and $pK_a(N)$ are the pK_a's of $T^\pm$ of

$$pK_a(T^\pm) = -1.7 + pK_a(N) \quad (5)$$

Scheme I and the parent aminium ion, respectively.

With the pK_a of $T^\pm$ we can now estimate k_3 (H^+ transfer to water) and k'_3 (H^+ transfer to either the amine or the basic component of the buffer). We will take as an example the transfer from the $T^\pm$ formed with 1-formylpiperazine.

In the above case $pK_a(T^\pm) = 6.3$, according to eq 5. Since phosphate buffer ($pK_a \approx 7$) was used in this reaction, the proton transfers to the amine and HPO_4^{2-} are thermodynamically favorable, therefore $k'_3 \approx 10^{10}$ s^{-1} M^{-1} for both processes,[19] which multiplied by the corresponding concentrations (Table I) gives ca. 4×10^7 and 5×10^7 s^{-1} for the proton transfers to the amine and HPO_4^{2-}, respectively. The transfer to water (k_3) is not favorable thermodynamically, and since proton addition to T^- (Scheme I) by H_3O^+ is favorable, $k_3 \approx 10^{10} \times 10^{-6.3} \approx 5 \times 10^3$ s^{-1}. At the pH conditions (Table I), $k_{-3}[H^+] \approx 10^3$ s^{-1} and $k'_{-3}[HA] \approx 4 \times 10^7$ ($10^{-7}/10^{-6.3}$) $\approx 8 \times 10^6$ s^{-1} for the aminium ion, and 5×10^7 ($10^{-7}/10^{-6.3}$) $\approx 1 \times 10^7$ s^{-1} for $H_2PO_4^-$.

The value of k_4 should be larger than that of k_2 since expulsion of the leaving group is aided by the "push" provided by the amine moiety of T^- (this "push" cannot be exerted from $T^\pm$), therefore $k_4 > 3 \times 10^9$ s^{-1} (see below). Since $k_4 \gg k_{-3}[H^+] + k'_{-3}[HA]$ for the reactions of 1-formylpiperazine, the rate-determining step of the process $T^\pm \rightleftarrows T^- \rightarrow$ products is the first: $k_3 + k'_3[A^-]$, but since $k_2 \approx 3 \times 10^9$ s^{-1} (see below) $\gg k_3 + k'_3[A^-]$, the path through T^- of Scheme I is not significant compared to the k_2 step, under the experimental conditions of the reaction.

Estimations analogous to the ones described for the reaction of 1-formylpiperazine can be made for the reactions of the other amines. In all cases, under the experimental conditions of the reactions, $k_3 + k'_3[A^-]$ is rate-determining on the right hand side of Scheme I, and also k_2 is larger than the former rate, the path through T^- being negligible compared to that of k_2.

The above results are in agreement with those found in the aminolysis (primary and secondary amines) of *p*-nitrophenyl and 2,4-dinitrophenyl acetates, and 1-acetoxy-4-methoxypyridinium perchlorate, at 1 M ionic strength. In these reactions second-order amine kinetics were not found (except in the reaction of one primary amine with the former substrate) when breakdown of $T^\pm$ is rate-limiting.[2c] Also, in the hydrazinolysis of the above substrates[22] and in the aminolysis of *p*-nitrophenyl benzoate[23] no base catalysis was found when breakdown of $T^\pm$ is the rate-determining step. These results mean that for the mentioned reactions the direct breakdown of $T^\pm$ to products is faster than its deprotonation by a second amine molecule or a general base, in accord with our results.

Therefore, the mechanism of the reactions studied in this work can be completely described by eq 2, and the curved Brønsted-type plots obtained in this study and in the pyridinolysis of the same substrate[5] (Figure 1) can be explained by a change in the rate-determining step, from k_2 to k_1 of eq 2 as the amine becomes more basic.

The fact that the pK_a value at the curvature center (pK_a°) is larger for the reactions of the substrate with alicyclic amines compared to those with pyridines, means that the ratio k_{-1}/k_2 (eq 2) for isobasic amines is also larger for the former reactions.[2-5]

The rate for expulsion of aryloxide anion from the zwitterionic tetrahedral intermediate formed in the aminolysis of aryl acetates (k_2), in water at 25 °C, has been found to obey eq 6, where $pK_a(lg)$ refers to the conjugate acid of the above leaving group.[2,7]

$$\log k_2 = 11.5 - 0.5pK_a(lg) \quad (6)$$

According to this equation, $k_2 \approx 3 \times 10^9$ s^{-1} for the expulsion of 2,4-dinitrophenoxide ion ($pK_a(lg) = 4$) from $T^\pm$ of eq 2. This rate constant is independent on the amine nature or basicity, since a "push" by the amine moiety of $T^\pm$ is not possible.[2] Therefore, considering that k_{-1}/k_2 is larger for alicyclic amines than for pyridines, one concludes that the nucleofugality of an alicyclic amine from $T^\pm$(k_{-1}) should be greater than that of an isobasic pyridine.

There are very few examples in the literature of comparisons between nucleofugalities of different types of amines. Gresser and Jencks found that the rate of expulsion of isobasic amines from the zwitterionic tetrahedral intermediates formed in the aminolysis of *p*-nitrophenyl phenyl carbonate was in the order: quinuclidines > pyr-

(19) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(20) Even if k_6 were smaller than 3×10^7 s^{-1}, and therefore the first step of eq 3 were at equilibrium, the observed rate would be $\leq 10^7$ s^{-1}, since $K'_5 \approx 1$. This rate is $\ll k_2$ and therefore the above conclusion is valid even if $k_6 < 3 \times 10^7$ s^{-1}.

(21) In the cases of the amines other than piperazinium ion, it must be taken into account that HA and A^- can be both the buffer components and also the protonated and free forms of the amines, respectively.

(22) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.

(23) Campbell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378.

idines > imidazoles.[2b] It has been also noted that aliphatic amines are expelled much faster than imidazoles of the same pK_a from phtalimidium addition compounds.[6]

The poor nucleofugality of pyridines compared to secondary alicyclic amines found in this work is consistent with a resonance stabilization by electron donation from the pyridine to the carbonyl group of the acetylpyridinium product and to the dinitrophenoxy oxygen in the transition state for the second step of eq 2.[2b]

The rate for amine expulsion from the zwitterionic tetrahedral intermediate formed in the pyridinolysis of aryl acetates (k_{-1}) is given by eq 7, where $pK_a(N)$ is the pK_a of

$$\log k_{-1} = 13.0 + 0.4pK_a(lg) - 0.7pK_a(N) \quad (7)$$

the protonated amine.[2,7] This equation was tested for pyridines only and together with eq 6 can predict reasonably well the $pK_a°$ values found in the pyridinolysis of aryl acetates.[7,24] According to our results, eq 7 cannot be applied to alicyclic amines, as was erroneously done,[7] nor to quinuclidines or imidazoles (see above),[2b] and since no information is available at the moment on nucleofugalities of other amines, this equation should only be valid for pyridines.

It is very likely that only the constant term of eq 7 should vary with the amine nature, in view that the sensitivity of the microscopic rate constants concerning $T^{\pm}$ to the basicity of the nucleophile and leaving group (β_N and β_{lg}) seems to be independent of the amine nature.[2a]

According to the $pK_a°$ value obtained in this work (9.1) and the discussion above, the leaving abilities of secondary alicyclic amines from $T^{\pm}$ in the aminolysis of aryl acetates is given by eq 8.[25] Comparison of eq 7 and 8 shows that

$$\log k_{-1} = 14.3 + 0.4pK_a(lg) - 0.7pK_a(N) \quad (8)$$

secondary alicyclic amines leave $T^{\pm}$ ca. 20-fold faster than pyridines of the same basicity, which is similar to the ratio of nucleofugalities of quinuclidines and isobasic pyridines from the $T^{\pm}$ formed in the aminolysis of *p*-nitrophenyl phenyl carbonate, as found by Gresser and Jencks.[2b,26]

The $pK_a°$ values found in the reactions of phenyl and *p*-nitrophenyl thiolacetates with secondary alicyclic amines are >11.5 and 10.5, respectively.[7] The $pK_a°$ values calculated by means of eqs 6 and 8 for the aminolysis of the *O*-aryl acetates with leaving aryl oxide anions isobasic with thiophenoxide and *p*-nitrothiophenoxide anions (pK_a 6.5 and 4.6, respectively) are 12.4 and 9.9, respectively. Therefore, the ratio k_{-1}/k_2 from the thio-$T^{\pm}$ is only a little larger than that from the isobasic oxy-$T^{\pm}$, and since it is known that the nucleofugalities of ArS^- are lower than those of isobasic ArO^-,[27] it is doubtful whether k_{-1} from the thio-$T^{\pm}$ should be larger than that from the isobasic oxy analogue, as stated.[7] Obviously, more data are needed to quantify the leaving abilities of ArS^- groups before evaluation of the "push" (to expel the amine) provided by ArS and isobasic ArO from the corresponding tetrahedral intermediates.

(24) The $pK_a°$ value for a given Brønsted-type correlation can be calculated as the $pK_a(N)$ value for which $k_{-1} = k_2$, i.e. eq 6 = eq 7.

(25) The constant term of eq 8 was obtained from: $11.5 - 0.5pK_a(lg) = X + 0.4pK_a(lg) - 0.7pK_a(N)$, where $pK_a(lg) = 4$ and $pK_a(N) = 9.1$.

(26) From ref 2b, p 6978, k_N/k_O (k_{-1}/k_2 in our work) = 4 for 4-(dimethylamino)pyridine/*p*-nitrophenoxide ion from $T^{\pm}$, in the pyridinolysis of *p*-nitrophenyl phenyl carbonate. Since $\beta_N = -0.7$ for k_{-1} in the aryl phenyl carbonate system,[2a] it follows that $k_{-1}/k_2 = 400$ for a pyridine of pK_a 7/*p*-nitrophenoxide ion. Since $k_N/k_O = k_{-1}/k_2 = 7800$ for a quinuclidine of pK_a 7/*p*-nitrophenoxide ion,[2b] it means that a quinuclidine of pK_a 7 leaves $7800/400 \approx 20$-fold faster from $T^{\pm}$ than an isobasic pyridine. For isobasic amines of pK_a 9.8, the ratio of k_1 values is ≈ 28.[2b]

(27) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476. Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186.

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Registry No. 2,4-Dinitrophenyl acetate, 4232-27-3; piperidine, 110-89-4; piperazine, 110-85-0; 1-(β-hydroxyethyl)piperazine, 103-76-4; morpholine, 110-91-8; 1-formylpiperazine, 7755-92-2; piperazinium ion, 22044-09-3.

A Practical Synthesis of the [(2*R*)-3-(Morpholinocarbonyl)-2-(1-naphthylmethyl)propionyl]-L-histidine Moiety (P_4–P_2) in Renin Inhibitors

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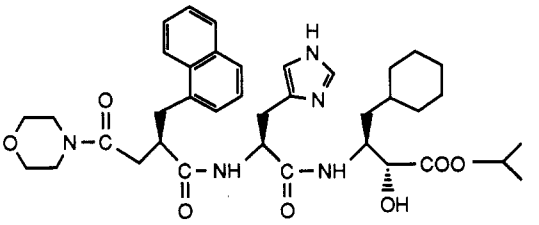
A large number of renin inhibitors have been investigated as therapeutic agents of hypertension.[1,2] The peptide inhibitors derived from renin substrate angiotensinogen have been considered to be unsuitable as drugs for oral administration due to proteolytic degradation by chymotrypsin, especially at the Phe–His amide bond (P_3–P_2)[3] of the inhibitors.[4] Recently, we have reported a novel class of low molecular weight renin inhibitor such as **1** which was stabilized against proteases by incorporating (−)-3-(morpholinocarbonyl)-2-(1-naphthylmethyl)-propionic acid [(−)-**2**] with a retro-inverso amide bond as the P_4–P_3 moiety.[1] In addition, the analysis of inhibitor–renin interaction[5] showed that the β-carbonyl group of (−)-**2** was at a suitable position to accept a hydrogen bond from the side chain OH of Ser-230 in human renin, the naphthyl group of P_3 was accommodated in the hydrophobic subsite S_3 of renin, and the imidazole of P_2 His was hydrogen bonded to the side chain OH of Ser-233.



1

Thus, we considered a large amount of optically pure compound would be required for further evaluation of renin inhibitors as an antihypertensive drug. In this paper, we describe a convenient and practical method for synthesizing *N*-[(2*R*)-3-(morpholinocarbonyl)-2-(1-naphthylmethyl)propionyl]-L-histidine methyl ester (**3**), which is useful as a common precursor (P_4–P_2 moiety) for the syntheses of renin inhibitors such as **1**.[1,6] In addition, the absolute configuration of (−)-**2** was established from NMR spectra.

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