equivalent thermal parameters of the low-temperature inclusion compounds and of photoproduct **2** are listed in Tables V-VII, respectively. Their bond lengths and angles are listed in supplementary material in Tables 5S, 6S, and 7S, respectively. The x, y, and z coordinates of the room-temperature structure of DCA-acetophenone are listed in Table 5S (d).

Acknowledgment. We thank the Israel/U.S. Binational Science Foundation, Jerusalem, for financial support. Research at Brookhaven National Laboratory was carried out under contract with the U.S. Department of Energy.

Registry No. 2, 95586-16-6; **2** (methyl ester), 95485-48-6; **3**, 95586-17-7; 5DCA·2$C_6H_5COCH_3$, 83035-58-9; 3DCA·m·$C_6H_5COCH_3$, 83047-96-5; 5DCA·2$C_6H_5COCl_3$, 95485-49-7.

Supplementary Material Available: Thermal parameters, bond angles, and bond lengths (13 pages). Ordering of information given on any current masthead page.

Communications to the Editor

Biomimetic Models for Cysteine Proteases. 2. Nucleophilic Thiolate-Containing Zwitterions Produced from Imidazole-Thiol Pairs. A Model for the Acylation Step in Papain-Mediated Hydrolyses

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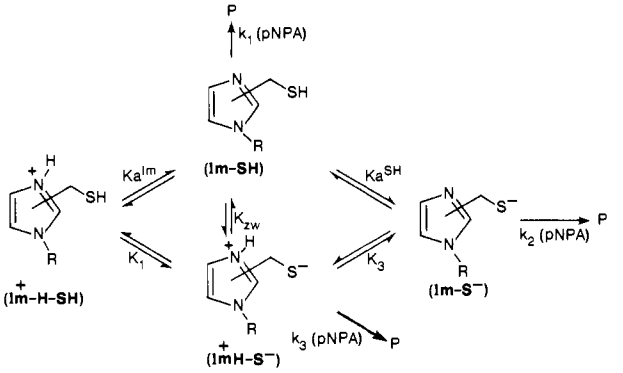
The most widely studied example of the cysteine proteases, papain, cleaves both amide and ester substrates with the formation of the intermediate Cys thiol ester.[1] The pH-rate profile for the hydrolysis of a typical ester substrate (α-*N*-benzoyl-L-arginine ethyl ester) is bell shaped and was interpreted to indicate the involvement of two groups having apparent pK_a's of ~4.3 and 8.2-8.5.[2]

The most recent evidence from spectral and potentiometric titrations and solvent isotope effects[3] indicates that Cys-25 has an unusually low pK_a of 3-4 while that of His 159 is 8.5. These and earlier kinetic studies[4] suggest that Cys-25 and His-159 exist primarily as a zwitterionic imidazolium thiolate ion pair which is catalytically viable at physicological pH.

Although small molecules incorporating both imidazole and thiol units have been studied as nucleophilic catalysts in promoting the hydrolysis of *p*-nitrophenyl acetate (*p*-NPA),[5,6] the kinetic involvement of zwitterions has never been unambiguously demonstrated. Also, there has never been demonstrated a significant cooperative effect in the catalysis of hydrolytic processes by thiol-imidazole intramolecular systems as is thought to occur in the cysteine proteases. Herein we report that **2a** and **3a**[7] (but not

Scheme I



Scheme II

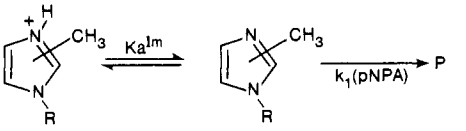


Table I. pK_a Values (Macroscopic and Microscopic) for **1-3**

	macroscopic pK_a[a,b]		microscopic pK_a[c]				
	pK_{a1}	pK_{a2}	pK_1	pK_a^{Im}	pK_3	pK_a^{SH}	K_{Zw}[d]
1a	6.54 (6.68)	9.54 (9.52)	7.72	6.57	8.36	9.51	0.07
2a	6.37 (6.41)	9.26 (9.01)	6.50	6.96	9.13	8.67	2.88
3a	6.31 (6.44)	8.88 (8.83)	6.47	6.83	8.75	8.39	2.29
1b	7.56[e]						
2b	7.94[e]						
3b	7.64[e]						

[a] Values without parentheses are averages of triplicate potentiometric titrations; ±0.05 unit. [b] Bracketed values were obtained as kinetic pK_a values obtained from computer fit to eq 1a.[11] [c] Values as defined in Scheme I and calculated by methods given in ref 12 using titrimetric macroscopic pK_a's and assuming pK_a^{Im} is that of the corresponding *S*-benzyl derivative.[13] [d] K_{Zw} = [Im$^+$H-S$^-$]/[Im-SH] = K_1/K_a^{Im}. [e] Literature values for **1b**, **2b**, and **3b** are 7.51, 8.00, and 7.85, respectively.[14]

(7) Thiols **1a**, **2a**, and **3a** were synthesized from their corresponding alcohols according to the general procedure of Schneider[8] and exhibited spectral and analytical data consistent with their structures (details to be published).

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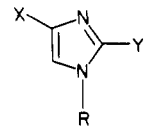

1a, X = CH_2SH; R = Y = H
1b, X = CH_3; R = Y = H
2a, X = R = H; Y = CH_2SH
2b, X = R = H; Y = CH_3
3a, X = H; R = CH_3; Y = CH_2SH
3b, X = H; R = Y = CH_3

1a) do indeed exist primarily as zwitterions at physiological pH and furthermore that such species are nucleophilic toward *p*-NPA.

Shown in the figure are second-order rate constant[9] vs. pH profiles for the reaction of *p*-NPA promoted by **1–3**. The lines through the data are computer-generated fits to eq 1 (eq 1a)[11] and 2 that respectively describe the minimum zwitterionic scheme

$$k_{cat}^{obsd} = \frac{(k_1K_a^{Im} + k_3K_a^{Im}K_{Zw})[H^+] + k_2K_a^{Im}K_a^{SH}}{[H^+]^2 + (K_a^{Im} + K_a^{Im}K_{Zw})[H^+] + K_a^{Im}K_a^{SH}} \quad (1)$$

$$k_{cat}^{obsd} = \frac{k_1K_a^{Im}}{K_a^{Im} + [H^+]} \quad (2)$$

for thiols **1a–3a** (Scheme I) and imidazoles **1b–3b** (Scheme II). Evaluation of the individual parameters in eq 1 which pertain to the activity of the zwitterion (k_3 and K_{Zw}) is not possible unless additional information is available since the observed data for **1a–3a** apparently fit a simplified but kinetically equivalent scheme having two macroscopic pK_a's, i.e., eq 1a.[11]

However, potentiometric titration of **1a–3a** (which directly yields the macroscopic pK_a's listed in Table I) allows the calculation[12] of the microscopic pK_a's in Scheme I under the reasonable assumption that K_a^{Im} is approximated by that of the corresponding *S*-benzyl derivatives.[12a,13] Also given in Table I are these derived values as well as the observed pK_a's for imidazoles **1b–3b**.[14] The most striking observations for **2a** and **3a** (but not **1a**) is that pK_1 is *lower* than pK_a^{Im} which means that the zwitterionic form (Im^+H-S^-) is the dominant neutral species between pH ~6.5 and 8.7–9.0.[15]

The thiolate of the zwitterionic species is also nucleophilically active toward *p*-NPA as is evidenced by comparison of the profiles

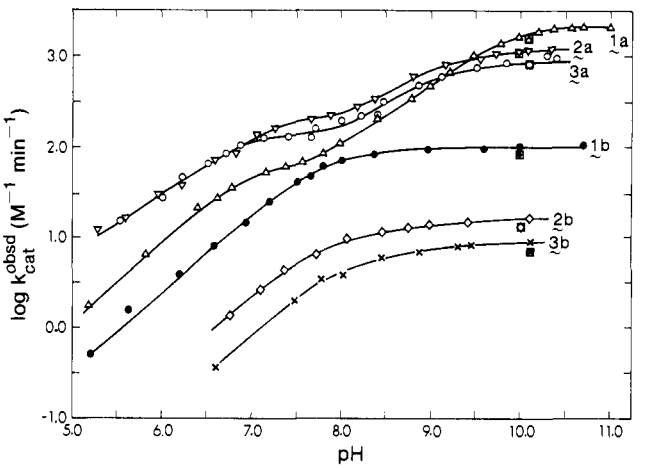

Figure 1. Plot of the second-order catalytic rate constants (k_{cat}^{obsd}) for nucleophilic attack by **1–3** on *p*-nitrophenyl acetate at 25 °C in H_2O.[9] **1a** (Δ), **1b** (●), **2a** (▽), **2b** (◇), **3a** (○), **3b** (×). Symbols in squares at pH 10 are values obtained in D_2O solvent.

Table II. Computed Rate Constants for the Attack of the Various Ionic Forms of **1–3** on *p*-NPA[a]

	k_1, M^{-1} min^{-1}	k_2, M^{-1} min^{-1}	k_3, M^{-1} min^{-1}
1a	*b*	2275	*d*
2a	*b*	1071	162
3a	*b*	1179	142
1b	92.5		
2b	7.64		
3b	13.2		

[a] Rate constants defined as in Schemes I and II. [b] Values for k_1 which represents heterocyclic N attack on *p*-NPA are assumed to be those of the corresponding imidazole. [c] Cumulative errors resulting from likely deviations in pK values force the errors in k_2 and k_3 to be 20% and 5%, respectively, but do not alter conclusions presented in text. [d] Negligible relative to k_1.

for the **1a**,**b–3a**,**b** pairs shown in Figure 1. For **1a** which shows only a small amount of Im^+H-S^- at any pH,[15] the observed plateau at ~pH 7.5 is comparable to that seen for **1b** and can best be explained in terms of nucleophilic attack on *p*-NPA by the unprotonated imidazole.[16] Apparently imidazoles **2b** and **3b** have a much reduced propensity to act as nucleophiles because of the steric encumbrance provided by the 2-substituent. Such should also be the case for the imidazole units in **2a** and **3a**, but since they show plateau regions from ~pH 7 to 8 that are 10–15-fold greater in k_{cat}^{obsd} than those seen for their comparison imidazoles, the exhalted activity of the former must be a result of attack of the thiolate portion of Im^+H-S^-. Strong confirmatory evidence for this conclusion comes from the fact that a calculated[15] plot of the total [thiolate], ([Im^+H-S^-] + [Im-S^-]) for **2a** and **3a** vs. pH shows a profile that coincides nicely with the observed k_{cat}^{obsd} vs. pH data in Figure 1. Also, UV visible spectra of **2a** and **3a** as a function of pH indicate large concentrations of thiolate ion from pH 6.5 to 8 and increasing concentrations until pH 10.5 at which point the [RS^-] is constant.

Numerical evaluation of the parameters in Scheme I was achieved by nonlinear least-squares fitting of the k_{cat}^{obsd} vs. pH data for **1a–3a** to eq 1 by using the microscopic pK_a^{Im} and pK_a^{SH} as well as the K_{Zw} values from Table I. Separation of the composite term K_a^{Im} (k_1 + k_3K_{Zw}) to evaluate k_3 is made by assuming that k_1 for **1a–3a** is approximately the same as that of the corresponding imidazoles **1b–3b**. The values are given in Table II. Zwitterionic activity for **2a** and **3a** is indicated by the magnitude of k_3 which is substantial and reduced from that calculated for Im-S^- by an amount that is expected on the basis of the reduced pK_1 vs. pK_a^{SH}.[17]

(8) Schneider, F. *Z. Physiol. Chem.* **1967**, *348*, 1034.

(9) Kinetic data were obtained at 37 °C in degassed aqueous 0.1 M buffered solutions[10] (μ = 0.3) containing 4.33 × 10^{-5} M *p*-NPA and a 10–100-fold excess of the thiol (as its HCl salt) by observing the rate of formation of the *p*-nitrophenylate anion at 400 nm. Pseudo-first-order rate constants (k_{obsd}) were obtained by fitting the absorbance vs. time data to a standard exponential model by a nonlinear least-squares treatment. True second-order rate constants (k_{cat}^{obsd}) were obtained from the slopes of the plots of k_{obsd} vs. [added thiol] at each pH, the slopes being evaluated by a linear least-squares treatment. Buffer catalysis was not observed between 0.05 and 0.3 M. D_2O solvent isotope effects were evaluated at pD 10.0 in 0.1 M aqueous potassium carbonate.

(10) Street, J. P.; Brown, R. S. *J. Am. Chem. Soc.*, in press.

(11) This can be verified by assuming in Scheme I that K_{Zw} = [ImH^+-S^-]/[Im-SH] = 0 in which case eq 1 reduces to the kinetically equivalent form eq 1a.

$$k_{cat}^{obsd} = \frac{k_1K_a^{Im}[H^+] + k_2K_a^{Im}K_a^{SH}}{[H^+]^2 + K_a^{Im}[H^+] + K_a^{Im}K_a^{SH}} \quad (1a)$$

(12) For methods of calculation, see: (a) Edsall, J. T.; Blanchard, M. H. *J. Am. Chem. Soc.* **1933**, *55*, 2337–2353. (b) Edsall, J. T.; Martin, R. B.; Hollingworth, B. R. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 505–517. (c) Benesch, R. E.; Benesch, R. *J. Am. Chem. Soc.* **1955**, *77*, 5877–5881.

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(14) Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Solution"; Butterworths: London, 1965.

(15) This conclusion is based on the calculated pH-dependent concentrations of the various species in Scheme I, using the microscopic pK_a's in Table I.

(16) Nucleophilic catalysis by imidazole is evidenced by the fact that a deuterium solvent isotope effect of unity is observed. See also: Bender, M. L.; Turnquist, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1652–1655. Bender, M. L. *Chem. Rev.* **1960**, *60*, 53.

The above account indicates that in imidazole thiol model systems where individual pK_a^{Im} and pK_a^{SH} values approach each other a substantial proportion of zwitterionic material is present at physiological pH and that these species are capable of nucleophilic attack on *p*-NPA.[18] This provides some precedence for the similar situation proposed to occur in papain.[3,4]

Acknowledgment. We gratefully acknowledge the financial support of the University of Alberta and the Natural Sciences and Engineering Research Council of Canada.

(17) Hupe and Jencks (Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451-464) have shown that rate constants for acyl transfer from *p*-NPA to thiol anions show a small sensitivity to thiol basicity ($\beta_{nuc} = 0.27$) for rate-limiting attack of basic thiols.

(18) Species **2a** and **3a** are indeed catalysts. We have observed that repeated monitoring of the UV/vis spectra of the reaction of 1×10^{-4} M *p*-NPA and equimolar **2a** or **3a** at pH 7.9 leads to a reduction in [thiolate] at the same rate *p*-nitrophenoxide builds up. The analysis of the kinetic data for this adheres to second-order kinetics. The hydrolysis of the *S*-acyl intermediate, even though subject to intramolecular general base catalysis by the imidazole, is quite slow ($\sim 5 \times 10^{-5}$ s^{-1}). Brown, R. S.; Skorey, K.; Street, J. P. *J. Am. Chem. Soc.*, submitted.

Total Synthesis of (±)-Reserpine

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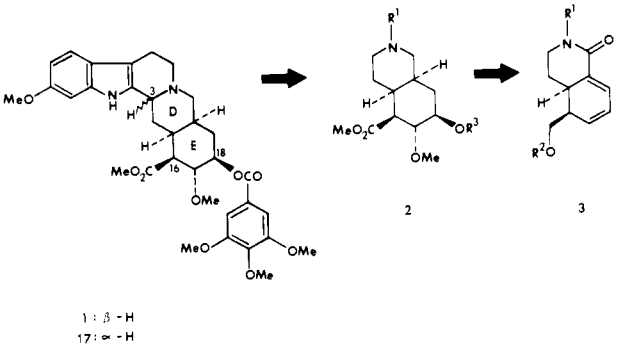
Received January 31, 1985

Owing to its importance as a medicinal agent that is widely prescribed for the treatment of hypertension and mental disorders, reserpine (**1**), which was originally isolated from the Indian snake root, *Rauwolfia serpentina* Benth.,[2] has been the subject of extensive chemical and pharmacological investigations.[3,4] These remarkable physiological properties coupled with its structural complexity have made reserpine an attractive target for a number of synthetic efforts,[5,6] three of which have culminated in its total synthesis.[6] The principal synthetic challenge posed by the pentacyclic nucleus of reserpine is the stereoselective elaboration of the D/E ring system, which is a *cis*-hydroisoquinoline richly endowed with stereochemistry and functionality. Consequently, several years ago we initiated an investigation, which was directed toward the design and development of a general strategy for the construction of substituted hydroisoquinolines[7] that featured as a key step the intramolecular Diels-Alder reactions[8] of azatrienes. The application of that methodology to an efficient, total synthesis of reserpine constitutes the substance of the present report.

The overall strategy for the synthesis of reserpine (**1**) required the initial preparation of a hydroisoquinoline derivative such as **3** that would be suitably functionalized for eventual modification



1 : β - H
17 : α - H

to provide the fully intact D/E ring system present in **2**. Subsequent coupling of this key structural subunit with the 6-methoxytryptophyl synthon would then afford a *seco*-dihydroreserpine analogue, which could then be cyclized to reserpine.

The first phase of the total synthesis (Scheme I) thus entailed the construction of an intermediate related to **3** via the intramolecular Diels-Alder reaction of a suitable trienic precursor. To this end, propargyl alcohol was protected (CH_3OCH_2Br, $PhNEt_2$, CH_2Cl_2, -78 °C → room temperature, 5 h; 95%) as its methoxymethyl ether derivative **4**.[9] Subjection of **4** to sequential two-carbon chain extension (*n*-BuLi; $\overline{CH_2OCH_2}$, THF, -78 °C → room temperature, 20 h; 81%) and catalytic hydrogenation (H_2/45 psi, $Pd/CaCO_3/PbO$, EtOAc, room temperature, 15 min; 96%) provided the homoallylic alcohol **5**, which was converted to the olefinic amine **6** by tosylation (*p*-TsCl, Py, CH_2Cl_2, 0 °C, 12 h; 90%) and aminolysis ($PhCH_2NH_2$, catalytic NaI, Me_2SO, room temperature, 20 h; 85%). The amine **6** was then coupled with 2-pyrone-6-carbonyl chloride[10] (Et_3N, CH_2Cl_2, -30 → 5 °C, 1.5 h) to give the trienic amide **7** in 89% yield. Subsequent thermolysis of **7** in refluxing xylene (24 h) proceeded smoothly to afford the cycloadduct **8** in 93% yield.

With the lactam **8** in hand, the next subgoal of the synthetic effort involved the stereoselective refunctionalization of the E ring. In the event, regioselective epoxidation of the more nucleophilic carbon-carbon double bond (*m*-CPBA, CH_2Cl_2, 0 °C, 6 h) proceeded with a high degree of stereoselectivity from the less encumbered α face to provide the epoxide **9** in 88% yield. Acid-catalyzed opening of the epoxide moiety [BuCH(Et)-COOH/BuCH(Et)COOLi, DME, reflux, 12 h; 90%] occurred exclusively at the allylic terminus at C(18) to afford the alcohol **10**, which was smoothly converted to the corresponding methyl ether **11** in 98% yield upon treatment with methyl iodide in the presence of silver(I) oxide. Transformation of **11** into **12**, which incorporates all of the requisite stereocenters present in the D/E ring of reserpine, was smoothly effected by catalytic hydrogenation [H_2/1800 psi, 20% $Pd(OH)_2/C$,[11] MeOH, 24 h, room tempera-

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(9) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by distillation, recrystallization, or preparative HPLC and gave satisfactory combustion analysis (C, H, N) and/or identification by high-resolution mass spectrometry. All yields are based upon isolated, purified materials that were homogeneous as determined by capillary GLC or HPLC.

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