congested transition state. The ^{13}C NMR spectrum shows the following: δ 165.7 (CO), 69.2 and 67.1 (C_1 and C_{12} interchangeable), 66.3 (C_{14}), 63.0 (OCH_2), 50.6 (C_{16}); the remaining resonances are comprised between δ 29.8 and 14.0.

Anal. Calcd for $C_{21}H_{36}O_5S$: C, 62.97; H, 9.06. Found: C, 62.89; H, 8.96.

Ramberg-Bäcklund Rearrangement of 8b,b′: (1*RS*)-14-Carbethoxybicyclo[10.6.0]octadeca-1(12),14-diene (9). A solution of **8b,b′** (1.14 g, 2.97 mmol) in 14 mL of DME was added dropwise at room temperature to a stirred suspension of NaH (180 mg after being freed from oil, 7.5 mmol) in 13 mL of DME. The mixture was then ice cooled, and a solution of hexachloroethane (844 mg, 3.56 mmol) in 6 mL of DME was added. The ice bath was removed and the stirring continued for 14 h at room temperature. The reaction mixture, resulting in a white precipitate, was cautiously quenched with 20% aqueous NH_4Cl, poured into 20 mL of water, and extracted with CH_2Cl_2. After removal of the solvent, TLC analysis of the residue revealed no less than three products, which were separated by column chromatography (SiO_2, eluant 3% ethyl acetate-benzene). The first-eluted material (70 mg, 7.3%) proved to be the diene **9**, while the last-eluted fraction consisted of unreacted **8b,b′** (60 mg, 5.2%). On the basis of ^{13}C NMR, the major product (915 mg, 73.8%) appears to consist of two isomeric chloro sulfones in a ca. 1.2:1 ratio. [The relevant ^{13}C singlets are (more abundant isomer first) δ 165.0 and 166.3 (CO), 142.5, 126.8 and 143.4, 126.0 (olefinic carbons), and 89.2 and 86.6 (C_{14}). The last two resonances are particularly significant as they can only be compatible with the α-carbon carrying a chlorine as well as carbethoxy substituent.] It appears that the reaction stops at the α-chloro α-carbethoxy α′-sodio sulfone stage, which precipitates out and, in this form, is unable to undergo the Ramberg-Bäcklund reaction. Analogous results were obtained when the reaction was carried out with 3.5 equiv of NaH for 24 h; however, an effective conversion could be achieved by treatment of the recovered chloro sulfones (915 mg, 2.19 mmol) dissolved in 40 mL of DME with *t*-BuOK (240 mg, 2.6 mmol) for 2 h at room temperature. Water-dichloromethane workup and separation as described above gave 240 mg of unreacted chloro sulfone and 390 mg of diene **9** [overall yield 460 mg (64%, based on the reacted **8b,b′**)]. No further attempt was made to optimize the reaction. In the ^1H NMR spectrum the olefinic proton at δ 6.75 shows up as a triplet, further split to a quartet by long-range allylic couplings (J = 2.5 and 1.5 Hz) with the protons at δ 3.76 and 2.77. These are the diallylic protons at C_{13} and give rise to an AB quartet (J = 19.0, $\Delta\nu$ = 99 Hz). (The spacing of the olefinic H triplet corresponds to 7.5 Hz. Since, however, the H's on C_{16} to which the olefinic H is coupled are magnetically unequivalent, it is dubious that the 7.5-Hz spacing is meaningful in terms of coupling constants. Most likely this is a case of a deceptively simple ABX spectrum and arises because the AB protons are very nearly isochronous. Since, however, the AB part is not discernible, the question remains unsettled.) The remaining protons (29) occur between δ 2.6 and 1.0, the CH_3 triplet being at δ 1.29: ^{13}C NMR δ 168.8 (CO), 141.3 (C_{15}), 138.5, 137.8 and 133.5 (C_1, C_{12}, and C_{14} interchangeable), 60.4 (OCH_2), 36.0, 33.9, 32.7, 32.3, 27.8, 26.7, 26.5, 26.1, 25.5, 25.4, 25.2, 24.9, 24.7 (2 c, unassigned), 14.4 (CH_3).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.24; H, 10.69.

[1,14-(*RS,SR*)]- and [1,14-(*RR,SS*)]-14-Carbethoxybicyclo[10.6.0]octadec-1(12)-enes (10b,b′). An ethanolic solution of diene **9** (150 mg, 0.47 mmol, in 15 mL of ethanol) containing 260 mg of 10% Pd/C was hydrogenated at room temperature and at a pressure of 3 atm of H_2 for 12 h. Filtration and removal of solvent gave essentially pure **10** (95 mg, 63%) as a mixture of two diastereoisomers in a ca. 2:1 ratio. The ^1H NMR spectrum shows no olefinic absorption but shows two ethyl quartets at δ 4.16 and 4.12 (major): the remaining absorption is complex absorption from δ 3.0 to 1.2, whose only discernible feature is the major methyl triplet at δ 1.25. The ^{13}C spectrum has the following signals (major isomer first): δ 175.9 and 176.3 (CO), 138.8 and 139.3 (C_1), 133.3 and 134.9 (C_{12}), 60.2 (CH_2O, both isomers), 51.0 and 48.9 (C_{14}), 14.3 (CH_3, both isomers). The remaining resonances are comprised between δ 36.9 and 24.2.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.61; H, 11.35.

Registry No. **1**, 31236-94-9; **2**, 75700-50-4; **3a**, 75700-52-6; **4a**, 75700-54-8; **5a**, 75700-55-9; (±)-**5b**, 75700-56-0; (±)-**6a**, 75700-57-1; (±)-**6b**, 75764-62-4; (±)-**6b′**, 75764-63-5; **7a**, 75700-58-2; **7b**, 75700-59-3; C_s-**8a**, 75700-60-6; 1(*RS*)-**8a**, 75700-61-7; (±)-**8b**, 75700-62-8; (±)-**8b′**, 75764-64-6; (±)-**8b** α-chloro derivative, 75700-63-9; (±)-**8b′** α-chloro derivative, 75765-39-8; (±)-**9**, 75700-64-0; (±)-**10b**, 75700-65-1; (±)-**10b′**, 75764-65-7; 7-oxo-1-thiaspiro[5.11]heptadecane, 75700-66-2; 4-bromobutyl 2-oxocyclodecyl sulfide, 75700-67-3; 4-(tosyloxy)butyl 2-oxocyclododecyl sulfide, 75716-20-0; 4-hydroxybutyl 2-oxocyclododecyl sulfide, 75700-68-4; 4-hydroxybutanethiol, 14970-83-3.

Intramolecular *O,N*-Acyl Transfer via Cyclic Intermediates of Nine and Twelve Members. Models for Extensions of the Amine Capture Strategy for Peptide Synthesis

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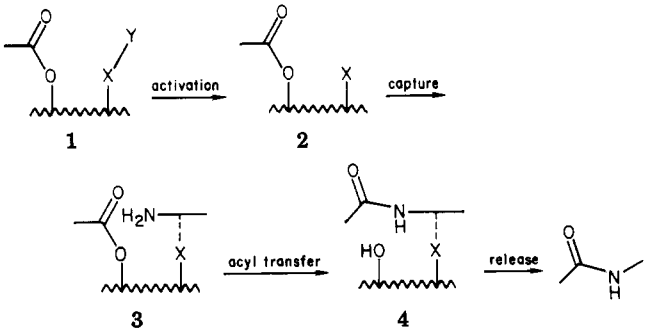
Rate constants are reported for the intramolecular *O,N*-acyl-transfer reactions of 2-amino-*N*-benzyl-*N*-[2-(acyloxy)-4-nitrobenzyl]acetamides, 2-amino-*N*-benzyl-*N*-[(4-acetoxy-5-xanthyl)methylene]acetamide, ethyl *N*-(2-acetoxybenzyl)-2-aminoacetate, methyl *N*-[(8-acetoxy-1-naphthyl)methylene]-2-aminoacetate and their alanine and valine analogues in acetonitrile, Me_2SO, and other solvents. Synthesis of these substrates is described, and a novel two-step synthesis is reported of 4-hydroxy-5-formylxanthene from 2,3-diacetoxybenzaldehyde and 2-(isopropoxymethylene)cyclohexanone in 29% yield. Facile intramolecular acyl transfer via cyclic intermediates of 9 and 12 members is described, and steric and solvent effects on rates of acyl transfer are reported for these processes and compared with those for other intra- and intermolecular acyl-transfer reactions. The significance of these results for amide formation by amine capture is discussed.

Previously, we have outlined an amine capture strategy for amide bond formation (Scheme I) and have proposed a working example, the 4-methoxy-3-(acyloxy)-2-hydroxybenzaldehydes, which react with primary amines to form Schiff bases in the capture step.[1] We have also described failures to realize rapid intramolecular *O,N*-acyl transfer in a variety of structures which were intended as

(1) D. S. Kemp, J. A. Grattan, and J. Reczek, *J. Org. Chem.*, **40**, 3465 (1975).

0022-3263/81/1946-0490$01.00/0

Scheme I



models for alternative amine capture systems.[2]

In our previous attempts to achieve rapid intramolecular acyl transfer of peptide acyl derivatives to peptide amines, we examined structures in which acyl transfer must occur through cyclic intermediates of five or six members. Even though this limitation greatly reduced the scope of the capture steps which we could entertain, we believed that acyl transfer via small, unstrained cyclic intermediates offered the best chance of realizing the intrinsic merits of the capture strategy.

In this paper we show that for peptide-derived systems this premise is unwarranted. For two aminophenyl esters we demonstrate rapid intramolecular O,N-acyl transfer which occurs through cyclic intermediates of 9 and 12 members and which exhibits very small changes in rate with modification of the structure of the α-aminoacyl substituent.[3] This result has encouraged us to seek working examples of the amine capture strategy in which the captured atom is the thiol function of an N-terminal cysteine residue, and preliminary successes with this approach will be reported elsewhere.

Given the many structural frameworks that could be chosen and the numerous examples of negligable cyclization rates for α,ω-functionalized linear molecules in which the functional group separation is between 8 and 14 atoms, we needed a design principle for selecting structural candidates. In this paper we demonstrate a successful design plan for acyl transfer via medium-sized rings. The reaction rates that are reported in the Results raise interesting mechanistic questions which cannot be completely resolved with data presently available. These questions are considered in the Discussion, where a testable model is proposed that is shown to be consistent with known facts.

The following section describes the important features of the amine capture strategy, since these serve as a background for all design considerations.

Amine Capture Strategy. The amine capture strategy is intended to be applied at the final stages of fragment-condensation (convergent) syntheses of large peptides. The function **1**, which represents an active ester of low acylating potential, is to be introduced late in the synthesis of the fragment to which it is attached by a conventional coupling between a peptide acid and an excess of single amino acid bearing the function **1**. This is the first premise on which the overall strategy rests: amide formation between large and small fragments is usually more reliable and efficient than that between pairs of large fragments (principle of excess[5]).

In the steps shown in Scheme I, the masked capture site X of **1** is released by removal of the protective group Y to form **2**. The amine component is then captured at site X to form **3**, which undergoes intramolecular acyl transfer to form **4**. The resulting peptide is released from the capture site.

Peptide bond formation through intramolecular acyl transfer was demonstrated more than 20 years ago by Wieland and co-workers in cysteine and cystamine frameworks[6] and by Brenner and co-workers in a salicylamide framework.[7] Though thought provoking, these experiments left unanswered the central question of how peptide fragments might be assembled to take advantage of an intramolecular acyl-transfer process. Nevertheless, the potential advantages of intramolecular acyl transfer are striking, for peptide synthesis lacks amide-forming reagents that can be used to couple large fragments cleanly, reliably, and in high yield, and the problems with existing reagents are shared with any conceivable process in which an activated, electrophilic, acyl derivative must react intermolecularly with an amine as a nucleophile.

Under normal intermolecular amide-forming conditions the concentrations of high molecular weight peptide fragments are necessarily low, and the potentially reactive acyl and amine functions may be buried or masked by intra- or intermolecular association. Under these conditions, unimolecular reactions of the acyl derivatives (e.g., azlactone formation leading to racemization[8] or other neighboring-group reactions[9]) are often competitive with bimolecular amide formation, which may proceed slowly or incompletely. Increasing the activation of the acyl derivative to compensate for low reactant concentrations is expected to increase the rates of side reactions, and attempts to enhance the rates of aminolysis of the acyl derivative selectively have also failed to match the scope of the problem.[10] Provided the proper features can be built into the capture step **2** → **3**, the amine capture strategy has the following potential features that may offer a solution to these problems. (1) A relatively inert acyl derivative can be used in **1** since the entropic advantage of a high local concentraton of amine at the acyl site of **3** can replace the normal enthalpic requirement of an "overactivated" acyl derivative for intermolecular aminolysis.[11] (2) The amide-forming process follows first-order kinetics, and substantial product formation can occur in fewer half-times than with a second-order aminolysis, with a likely reduction in the percentage of byproducts. (3) Unimolecular side reactions at the acyl carbon must fragment **3**, and at high dilutions there is a low probability of recombinations that can form byproducts of molecular weight similar to that of the product. None of these features is significant unless the capture step **2** → **3** occurs

(2) D. S. Kemp and F. Vellaccio, *J. Org. Chem.*, **40**, 3464 (1975); D. S. Kemp and D. J. Kerkman, *Ibid.*, in press.

(3) For a preliminary report, see: D. S. Kemp, Y. A. Hsieh, D. Kerkman, S.-L. Leung, and G. Hanson, "Peptides 1978", I. Z. Siemion and G. Kupryszewski, Eds., Wroclaw University Press, Wroclaw, Poland, 1979, p 147.

(4) D. S. Kemp, D. J. Kerkman, and S.-L. Leung, *Tetrahedron Lett.*, in press.

(5) M. Bodanszky in "Prebiotic and Biochemical Evolution", A. P. Kimball and J. Oro, Eds., North-Holland Publishing Co., Amsterdam, 1971, pp 217–222.

(6) T. Wieland, E. Bokelmann, L. Bauer, H. Lang, H. Lau, and W. Schäfer, *Justus Liebigs Ann. Chem.*, **583**, 129 (1953).

(7) M. Brenner, J. P. Zimmermann, J. Wehrmüller, P. Quitt, A. Hardtmann, W. Schneider, and U. Beglinger, *Helv. Chim. Acta*, **40**, 1497 (1957).

(8) D. S. Kemp in "The Peptides", Vol. 1, E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1979, p 342.

(9) M. Bodanszky in "The Peptides", Vol. 1, E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1979, 147–149.

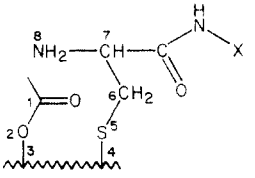
(10) D. S. Kemp, S.-W. Wang, R. C. Mollan, S. L. Hsia, and P. N. Confalone, *Tetrahedron*, **30**, 3680 (1974).

(11) M. Brenner in "Peptides 1966", H. C. Beyerman, A. van de Linde, and W. Massen van den Brink, Eds., North-Holland Publishing Co., Amsterdam, 1967, p 2.

rapidly, cleanly, efficiently, and at high dilution in a solvent that inhibits unproductive association of peptide fragments.

In our initial studies,[1,2] the captured atom was the amine nitrogen of the amine component. Although we recognized that this atom lacked the potential for rapid, clean capture at high dilution, it was chosen for our first ventures to meet the premise that acyl transfer **3** → **4** is most likely to be effective via an unstrained small ring.

As a potential capture site the thiol function of an N-terminal cysteine residue seems to us to offer the greatest potential for realizing efficient assembly of the termini of high-molecular-weight peptide fragments. However, with thiol capture, the minimum intramolecular distance that could be constructed for acyl transfer is eight atoms (cf. **5**). Before exploring the difficult chemistry of thiol capture and release, we required a proved design plan for achieving rapid *O,N*-acyl transfer via medium-size rings.



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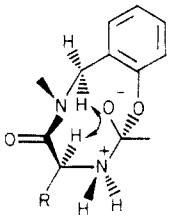
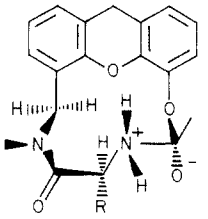
Design Plan and Acyl-Transfer Models. Structural candidates for intramolecular acyl transfer were designed to fit two criteria. First, the rate-determining transition state for acyl transfer is assumed to have tetrahedral character at both the acyl carbon and the amine nitrogen,[12] and the orientation of $^{\alpha}$C–CO and N–$^{\alpha'}$C bonds is assumed to be trans,anti about the forming C–N bond, in accord with the model that we have reported for the transition states of *p*-nitrophenyl ester aminolyses.[13] Second, the atoms that connect the ester oxygen and amide nitrogen of **3** are chosen to be part of a rigid array that does not create large van der Waals interactions or vacant spaces in the proposed transition-state model.[14]

Two structures that appear to meet these conditions are **6** and **7**. Each involves bridging by an exceptionally rigid spacer. Structure **6** which bears a nine-membered ring



6

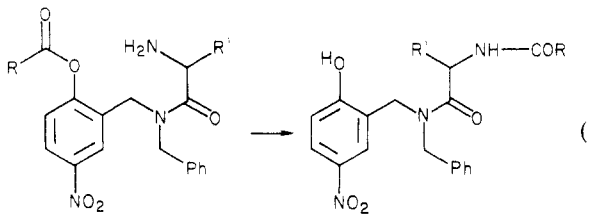


7

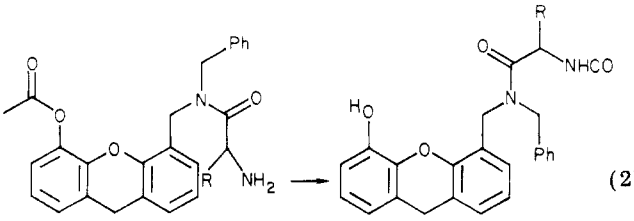
exhibits one moderately severe van der Waals interaction (arrows). The 12-membered-ring-bearing structure **7** shows no van der Waals crowding in a space-filling model. (Replacement of the xanthene oxygen by any hydrogen-bearing atom results in serious crowding.) These species provided a first test of the validity of the design plan.

It may be seen that structures **6** and **7** are the presumed intermediates in the transformations **8** → **9**, **10** → **11**.

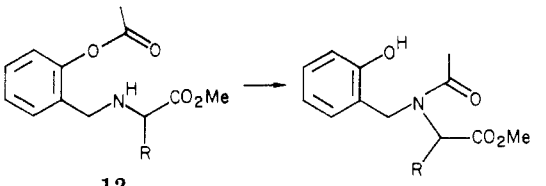
The substrates **8a–g** (Table I) were prepared by reduction of the Schiff base of 2-hydroxy-5-nitrobenz-



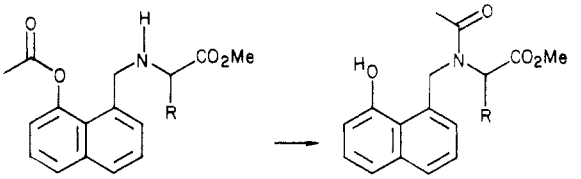
8 **9** (1)



10 **11** (2)



12 **13** (3)

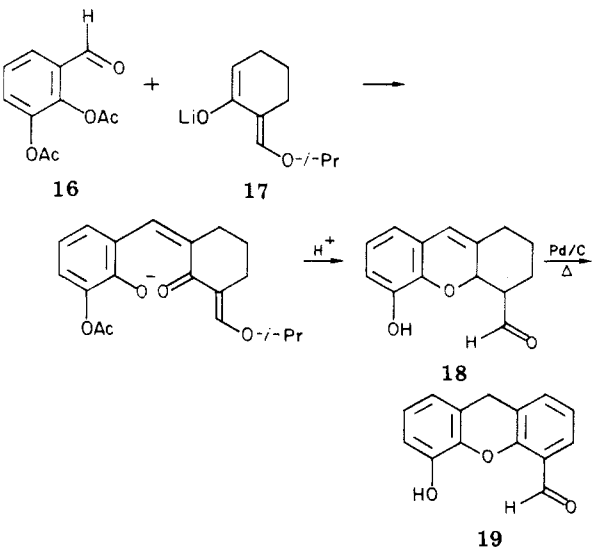


14 **15** (4)

aldehyde and benzylamine, N-acylation with a (*tert*-butoxycarbonyl)amino acid, O-acylation, and deprotection with hydrogen chloride. The resulting salt was converted to the free base **8** immediately before acyl transfer.

Similar reaction sequences were used to prepare **10a–c** from 4-formyl-5-hydroxyxanthene (**19**), **12a–c** from salicylaldehyde and **14a,b** from 8-formyl-1-naphthol.[15]

The hydroxyxanthenealdehyde **19** was prepared by dehydrogenation of its dihydro derivative **18** (eq 5), which



16 **17** **18** **19** (5)

was generated in a novel one-pot condensation of 2,3-diacetoxybenzaldehyde (**16**) with an enolate salt of 2-(iso-

(12) F. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972).
(13) D. S. Kemp, S. Hsia, and J. Pekaar, *J. Org. Chem.*, **39**, 384 (1974).
(14) Relationships between groups in an all-staggered, single-bonded array were studied by using Drieding models; van der Waals interactions and "holes" were screened with CPK space-filling models.

(15) D. S. Kemp and F. Vellaccio, *J. Org. Chem.*, **40**, 3003 (1975).

Table I. First-Order Rate Constants and Half-Times for Intramolecular O,N-Acyl-Transfer Reactions of 8, 10, 12, and 14 at 25 °C

acyl	amine	solvent	k, s^{-1}	$t_{1/2}$
	A. Reaction 8 → 9			
acetyl	Gly (R′ = H, 8a)	CH_3CN	2.5×10^{-3}	4.5 min
	Ala (R′ = CH_3, 8b)		4.4×10^{-3}	2.6 min
	Val (R′ = *i*-Pr, 8c)		3.4×10^{-3}	3.4 min
acetyl	Gly (8a)	Me_2SO	0.28	2.4 s
	Ala (8b)		0.35	2.0 s
	Val (8c)		0.21	3.3 s
Cbz-Gly	Gly (8d)	CH_3CN	4.8×10^{-3}	2.4 min
Cbz-Ala	(8e)		3.2×10^{-3}	3.6 min
Cbz-Val	(8f)		3.4×10^{-4}	34 min
Cbz-Gly	Gly (8d)	Me_2SO	0.53	1.3 s
Cbz-Ala	(8e)		0.16	4.3 s
Cbz-Val	(8f)		1.6×10^{-2}	44 s
Cbz-Ala	Val (8g)	Me_2SO	8.4×10^{-2}	8.3 s
	B. Reaction 10 → 11			
acetyl	Gly (10a)	CH_3CN	2.2×10^{-5}	8.8 h
	Ala (10b)		2.1×10^{-5}	9.2 h
	Val (10c)		1.3×10^{-5}	15 h[a]
acetyl	Gly (10a)	DMF	2.3×10^{-4}	50 min
	Ala (10b)		2.1×10^{-4}	53 min
	Val (10c)		2.4×10^{-5}	8 h
acetyl	Gly (10a)	Me_2SO	1.4×10^{-3}	8 min
	Ala (10b)		1.15×10^{-3}	10 min
	Val (10c)		1.9×10^{-4}	61 min
	C. Reaction 12 → 13			
acetyl	Gly (12a)	$CHCl_3$	1.65×10^{-3}	7 min
		CH_3CN	1.9×10^{-2}	36 s
		DMF	1.15×10^{-3}	10 min
		Me_2SO	1.9×10^{-3}	6 min
acetyl	Ala (12b)	$CHCl_3$	8.8×10^{-5}	2.2 h
		CH_3CN	2.3×10^{-4}	50 min
		DMF	1.5×10^{-5}	12.5 h
		Me_2SO	1.7×10^{-5}	11.5 h
		H_2O (pH 10)[b]	2.85×10^{-2}	24 s
acetyl	Val (12c)	CH_3CN	4.3×10^{-5}	4.5 h
		H_2O (pH 10)[b]	3.5×10^{-3}	3.3 min
	D. Reaction 14 → 15			
acetyl	Gly (14a)	$CHCl_3$	1.3×10^{-3}	9 min
		CH_3CN	3.2×10^{-3}	3.6 min
		DMF	2.3×10^{-4}	50 min
		Me_2SO	3.2×10^{-4}	36 min
acetyl	Ala (14b)	$CHCl_3$	5.5×10^{-5}	3.5 h
		CH_3CN	5.8×10^{-5}	3.3 h

[a] Extrapolated from a value measured at 30 °C. [b] Fisher certified buffer (potassium carbonate-potassium borate).

Table II. Steric Effects on Rates of Aminolyses of Active Esters

no.	substrate	solvent	rate ratio Gly/Ala	rate ratio Ala/Val
	A. Steric Effects at the Acyl α-Carbon Atom			
1	Cbz-X-ONp + H-Gly-OEt[13]	DMF	1.6	13
2	8 → 9	CH_3CN	1.5	9.4
		Me_2SO	3.3	10.2
	B. Steric Effects at the Amine α-Carbon Atom			
1	Cbz-Gly-ONp + HXOEt[13]	DMF	4.5	2.8
2	Cbz-Phe-OTcp + HXOEt[17]	dioxane	1.6	0.9
3	8 → 9	CH_3CN	0.6	1.3
	acyl = acetyl	Me_2SO	0.8	1.6
4	10 → 11	CH_3CN	1.0	1.7
	acyl = acetyl	DMF	1.1	9.0
		Me_2SO	1.3	6.0
5	12 → 13	$CHCl_3$	18	
	acyl = acetyl	CH_3CN	83	5.4
		DMF	75	
		Me_2SO	115	
6	14 → 15	$CHCl_3$	23	
	acyl = acetyl	CH_3CN	58	

propoxymethylene)cyclohexanone (17). This condensation is probably driven by intramolecular acetyl transfer and elimination of acetic acid; it clearly shares features with the Knoevenagel and Stobbe reactions.

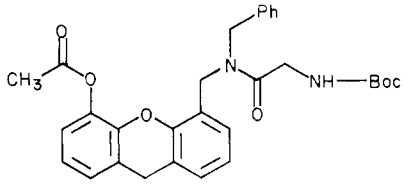
In our hands a variety of alternatives to Pd/C (DDQ, S fusion, Br_2, NiO_2, Rh/Al_2O_3, CrO_3) failed to achieve satisfactory dehydrogenation of 18.

Results

The rates of the acyl-transfer reactions of 8, 10, 12, and 14 were followed crudely by ^1H NMR shifts (0.1–0.2 M solutions) and accurately by UV absorption (ca. 10^{-4} M solutions). First-order rate constants at these widely different concentrations were found to be in good agreement of 8 and 10 establishing that the acyl-transfer processes occur intramolecularly.[16] (The behavior of 12 and 14 is discussed in the Experimental Section.) Rate constants are reported in Table I.

The data of Table I exhibit three striking features: the variations of steric effects and solvent effects among the four structural classes of substrates and the rapidity of the acyl transfers observed with 8 and 10. The latter are most easily demonstrated by comparison with intermolecular models. The amino esters 8 are analogues of *p*-nitrophenyl esters. The reaction of Cbz-Gly-ONp with 1 M H-Gly-OEt in Me_2SO at 30 °C has a half-life of 0.5 s. The reaction of 8d, which involves an intramolecular coupling of two glycine residues via a ring of nine members, has a half-life of 1.3 s at 25 °C, which is clearly of similar magnitude.

Species 20, the precursor of 10a, provides a good model for the steric and electronic environment of this active ester. In fact, 20 reacts with 1 M ethyl glycinate in Me_2SO



20

at 25 °C with a half-time of 2.4 h, which may be compared with the intramolecular half-time for 10a → 11a of 8 min in this solvent. The aminolysis of 20 in Me_2SO obeys simple bimolecular kinetics, and a useful measure of the effective local concentration of the amine function of 10 near its acyl carbonyl is the ratio of first- and second-order

(16) Reaction products were isolated in yields of 60–90% and characterized spectroscopically and in many cases by elemental analysis. In the case of 10, some oxidation to the corresponding xanthone was observed to occur concurrently with acyl transfer, but at a considerably slower rate. Linear first-order kinetic behavior was observed for all systems beyond a 3 half-lives reaction time.

Table III. Solvent Effects on Rates of Aminolysis of Active Esters

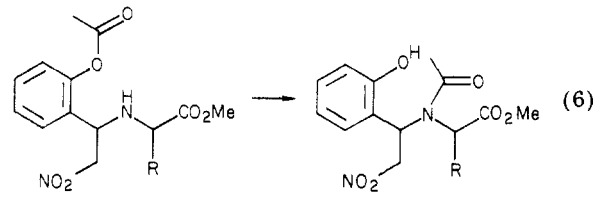
no.	substrate	rate ratio (rel to CH_3CN = 1) $CHCl_3$	DMF	Me_2SO
	A. Intramolecular Aminolyses			
1 (6-ring)	**12a** → **13a** (acetyl → Gly)	0.09	0.06	0.1
	12b → **13b** (acetyl → Ala)	0.4	0.06	0.07
2 (7-ring)	**14a** → **15a** (acetyl → Gly)	0.4	0.07	0.10
3 (9-ring)	**8a** → **9a** (acetyl → Gly)			113
	8b → **9b** (acetyl → Ala)			78
	8c → **9c** (acetyl → Val)			62
	8d → **9d** (Cbz-Gly → Gly)			111
	8e → **9e** (Cbz-Gly → Ala)			50
	8f → **9f** (Cbz-Gly → Val)			46
4 (12-ring)	**10a** → **11a** (acetyl → Gly)		11	66
	10b → **11b** (acetyl → Ala)		10	55
	10c → **11c** (acetyl → Val)		1.9	15
	B. Intermolecular Aminolysis			
	Cbz-Gly-ONp + H-Gly-OEt		43	135

rate constants for **10a** and **20**. This ratio is 18 M, which demonstrates that a properly chosen 12-membered ω-amino ester can exhibit the magnitude of proximity effects that have been conventionally associated with much shorter chain separations.

Steric and solvent effects for the intramolecular aminolysis of esters **8**, **10**, **12**, and **14** are reported in Tables II and III. These comparisons exhibit two striking patterns which should be rationalizable in terms of any general mechanism for these reactions. Amino esters **8** and **10** react via intermediates containing medium-sized rings; these substrates show remarkably small steric effects for substitution of methyl or isopropyl for hydrogen at the site α to the amine. Similar small effects are seen for aminolyses of 2,4,5-trichlorophenyl esters, studied by Pless and Boissonnas[17] (entry B2 of Table II). Much larger Gly/Ala and Ala/Val rate ratios are observed for the aminolysis of *p*-nitrophenyl esters,[13] and we have argued that these are of the magnitude expected for a rate-determining transition state with tetrahedral character at both amine nitrogen and acyl carbon.[13]

Steric effects observed for the intramolecular aminolyses of **12** (six-membered cyclic intermediate) and **14** (seven-membered intermediate) are dramatically larger and approach those which we reported for the reaction **21** → **22** for which Gly/Ala = 100 and Ala/Val = 10 in acetonitrile.[2] These systems are clearly unsuitable as foundations for the acyl-transfer step of an amine capture strategy.

As seen in Table III, the solvent effects for these intermolecular aminolyses may be grouped in two classes. Reactions of the esters **8** and **10** (cases A3 and A4) which react via medium-sized rings show a large rate increase with an increase in polarity of the dipolar aprotic solvent (CH_3CN → DMF → Me_2SO). Nearly identical behavior



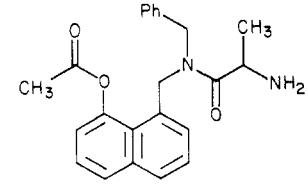
21 **22** (6)

is seen for intermolecular aminolysis of *p*-nitrophenyl esters (case B1). On the other hand the esters **12** and **14** (cases A1 and A2), which are secondary amines that react via six- or seven-membered rings, are most reactive in acetonitrile and are 10–15-fold less reactive in the more polar aprotic solvents. Similar orders of solvent activity have been observed for intermolecular aminolysis of certain cyclic acyl derivatives[18] and of active esters that are believed to react with anchimeric assistance of proton transfer from the amine.[19]

Discussion

The rapid intramolecular acyl transfer and tolerance of bulk at the amine site shown by **8** and **10** are the most important results of this study. The facility of these transfers stands in striking contrast to conventional experience for the formation of medium-sized rings from α,ω-functionalized alkanes. However, the two inhibitors of cyclization in these cases are torsional and van der Waals strains in the transition states and loss of conformational freedom at many single bonds in their formation from starting materials. For the cyclizations of **8** or **10**, the steric interactions are minimal, and the loss of conformational freedom may well approach that incurred in formation of a ring of six or seven atoms.

The ester of **10** is considerably less activated than that of **8**. In fact the analogues of **8** which lack the nitro group undergo no detectable acyl shift during 24 h in acetonitrile or chloroform and undergo a slow acyl migration in this period in Me_2SO[20] (half-time of ca. 3 h). The steric interaction shown in **6** may be responsible for the sluggish behavior of this system. Analogously, the substance **23**



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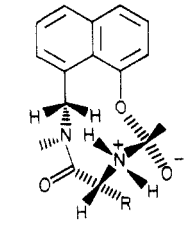


24

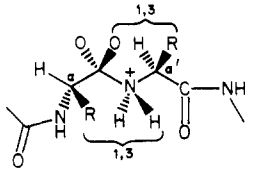
appears from models to require a transition state **24** which is more hindered than that of **7** (though less so than **6**). Intramolecular acyl transfer of **23** (via a ten-membered ring) proceeds in Me_2SO with a half-time of 90 min at 25 °C.[21] From these results it might appear that for these three systems of comparable activation and degrees of freedom in the starting materials, the reaction rate increases with ring size. However, we believe that steric interaction in the transition state is the more pertinent structural variable.

(17) J. Pless and R. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1963).

(18) M. Goodman and W. J. McGahren, *Tetrahedron*, **23**, 2037 (1967).
(19) G. T. Young in "Peptides 1972", H. Nesvadba, Ed., North-Holland Publishing Co., Amsterdam, 1973, p 20.
(20) S.-L. Leung, unpublished observations.
(21) G. Hanson, unpublished observations.

The major aim of these model studies was the testing of a design plan which can be used later in construction of cysteine capture systems, and we take the results with **8**, **10**, and **23** to mean that our criteria for structures that can achieve rapid intramolecular acyl transfer have met an important first test. In effect, a capture system that could achieve the proximity effect observed with the esters **10** would operate with an effective local amine concentration of 18 M. If even a fraction of this concentration could be observed with a structure resulting from thiol capture (cf., general structure **5**), it would represent a very satisfactory achievement of "entropic activation". Progress toward this goal will be reported elsewhere.[4]

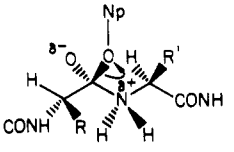
The solvent and steric effects that have been observed for intramolecular O,N-acyl transfer reactions of **8**, **10**, **12**, **14**, and **21** pose interesting mechanistic riddles. A commonly accepted picture of a transition state for this reaction is that of Menger and others in which both the acyl carbon and amine nitrogen are bulkier than in the starting materials and approach a tetrahedral geometry.[12] We have argued that for the aminolysis of *p*-nitrophenyl esters in DMF the independence of steric effects at the $^{\alpha}$C—C=O and N—$^{\alpha'}$C sites is best explained by a transition state with a trans,anti orientation of the $^{\alpha}$C—C=O and N—$^{\alpha'}$C single bonds. In such a transition state (as well as in several related structures) the new steric interactions of groups at the α and α' carbons occur at the 1,3 positions; thus the alkyl group at the α-carbon probes an increase in bulk at the amine nitrogen, and the group at the α'-carbon probes bulk at the acyl carbon (cf. **24**). In accord with this model,



24

a reduced steric effect at the α'-carbon need not be accompanied by a similar reduction at the α-carbon. (For example, compare the aminolyses of *p*-nitrophenyl esters with those of 2,4,5-trichlorophenyl esters;[17] also compare cases A1 and B1 of Table II with A2 and B3.) Unlike the steric effect at the amine α' site, that at the α-carbon of the acyl group is surprisingly constant for a variety of activated acyl derivatives and for both inter- and intramolecular aminolyses.[13] If the above model is correct, a tetrahedral nitrogen must be an invariant feature of the transition states for these reactions, and, in fact, most proposed mechanisms for aminolysis of esters invoke proton transfer from the amine nitrogen at the rate-determining transition state.[22]

Considerable evidence points to a variable structure at the acyl carbon for aminolytic transition states. Hammett ρ values for rates of aminolyses of substituted phenyl esters are observed to vary strikingly,[23] and ratios of rate constants for *p*-nitrophenoxy and phenoxy leaving groups vary from slightly over 100 for ammonolysis of phenyl acetates in water to nearly 10^5 for reaction with pyrrolidine in acetonitrile.[12,24] The very small Gly/Val rate ratios observed for aminolysis of 2,4,5-trichlorophenyl esters by amino acid esters require that the steric environment at the α' substituent must be nearly as unhindered in the transition state as in the starting material. This result is most consistent with a nearly trigonal structure at the acyl carbon and substantial charge development at the leaving group, with presumed lengthening of the bond to the leaving group. One therefore would expect a correlation of high Hammett σ values for substitution at the leaving group with low steric effects at the α'-carbon and a tolerance of steric bulk in the ortho positions of the leaving group. To our knowledge, no study in a single system of all three of these factors has been reported. However, **8** exhibits a very large rate decrease for removal of the nitro group together with a low α' steric effect, despite effective ortho substitution in the phenoxy function. Moreover, in their study of the effect of phenyl substitution on the aminolysis and hydrolysis reactions of phenyl esters, Pless and Boissonnas noted that whereas ortho substitution by halogen atoms retarded the rate of hydroxide-mediated hydrolysis of these esters, ortho substitution had a small retarding or even an accelerating effect on their aminolysis, which also showed a very small α' steric effect.[17] The hydrolysis almost certainly involves a rate-determining transition state with an unbroken bond to the leaving group and substantial tetrahedral character at the acyl carbon. It is difficult to avoid the conclusion that the aminolysis of these 2,4,5-trichlorophenyl esters involves a transition state of very different structure. The data of Tables I and II are probably best rationalized in terms of a transition state **25** which is assigned to the aminolyses



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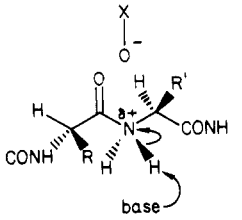

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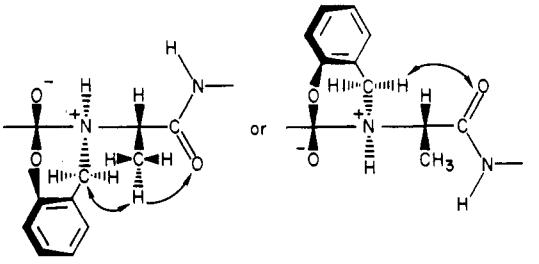

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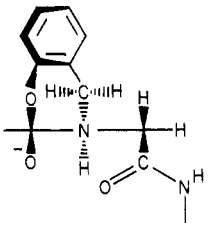


28

of *p*-nitrophenyl esters and the secondary amines **12**, **14**, and **21** and a transition state **26** which is assigned to the trichlorophenyl ester aminolyses and the reactions of **8** and **10**. The extremely large steric effects that are observed with **12**, **14**, and **21** can then be rationalized as resulting from 1,3-interactions between benzylic hydrogens and the substituents at the α'-carbon. Only in the case of glycine is this transition state free of crowding (compare **27** with

(22) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960); G. Fodor and J. Kiss, *Ibid.*, **72**, 3495 (1950); T. H. Fife and B. R. DeMark, *Ibid.*, **98**, 6978, (1976).

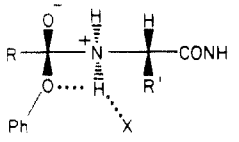
(23) T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms", Vol 1, W. A. Benjamin, New York, 1966, p 20.

(24) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960).

28). The structural factors that cause each starting material to be associated with a particular transition state are not obvious, and this question hopefully can be resolved by further studies.

Aminolysis reactions of phenyl esters that are conducted in dipolar aprotic solvents differ from those that are run in water in several important respects, not the least of which is the product structure. In water, phenols are completely ionized under the reaction conditions, and phenoxide ions are likely leaving groups. In dipolar aprotic solvents all but the most highly substituted phenoxide ions are strong bases,[25] and proton transfer to the leaving group may be an important stabilizing feature of the reaction. Many aminolyses of phenyl esters in dipolar aprotic solvents involve catalysis by solvent or by other additives. Su and Watson have noted that in chlorobenzene the reaction follows third-order kinetics overall and is first order in additive; they also note that the catalytic efficiency of an additive is related to its capacity to accept hydrogen bonds (e.g., phosphine or arsine oxides) and not to its basicity.[26]

One plausible role for a hydrogen bond acceptor is assistance of proton transfer from amine nitrogen to the oxygen of the phenoxide leaving group. A trans,anti disposition of C—C=O and N—C single bonds in the transition state requires that an assisted proton transfer must occur to an oxygen orbital that is contiguous to the amine nitrogen, as in **29**. This geometry is available to all the esters that are observed to react more rapidly in the strongly hydrogen-bonding solvents, DMF and Me_2SO. Interestingly, for these esters the sovlent catalysis is most marked for the Gly cases and least for the Val (Table III, cases A3 and A4), which is in accord with structure **29** for which solvent molecules are proximate to the α' substituent.



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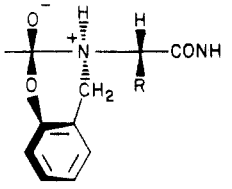

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A trans,anti disposition of C—C=O and N—O single bonds in transition states formed from **12** or **14** results in a geometry shown in **30**, in which the leaving group OPh and the ammonium proton are on opposite sides of the structure. In this case, assistance of a concerted proton transfer is impossible, in accord with the experimental finding that the reactions of these esters are not catalyzed by strongly hydrogen bonding solvents. A variety of predictions follow from this model, and some of these appear to be testable. Studies of this sort are in progress and will be reported subsequently.

Experimental Section

Melting points were taken in a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 567 grating infrared spectrometer. Varian T-60, Perkin-Elmer R-22, and Hitachi Perkin-Elmer R-248 spectrometers were used for measuring ^1H NMR spectra. Mass spectra were determined on a Varian MAT-44 spectrometer; high-resolution mass spectra were obtained through the courtesy of Professor K. Biemann and Dr. C. E. Costello. Ultraviolet spectra were measured with a Zeiss PMQ-II spectrophotometer, which was equipped with a temperature-controlled cell block and used for kinetic runs with half-times of minutes or longer. Kinetics of faster reactions were followed by using a Durrum-Gibson stopped-flow spectrophotometer. High-performance LC analyses were carried out on a μ-Porasil column by using a Waters liquid chromatograph equipped with a Model 440 UV absorbance detector. Microanalyses were performed by Galbraith Laboratories.

4-Formyl-5-hydroxy-$\Delta^{9,9a}$-1,2-dihydro-3*H*-xanthene (18). To a solution of 4.4 g (26.2 mmol) of 2-(isopropoxymethylene)-cyclohexanone[27] in 400 mL of dry THF at −78 °C under nitrogen was added by cannula over 5 min to 1 equiv of lithium diisopropylamide (LDA) in 50 mL of THF. The solution was stirred for 5 min and then treated at −78 °C with a solution in 50 mL THF of 5.8 g (26.2 mmol) of 2,3-diacetoxybenzaldehyde.[28] The resulting solution was stirred at −78 °C for 0.5 h and at 0 °C for 1 h; it was the poured into 1 N HCl and extracted with dichloromethane. The combined extracts were pooled, dried ($MgSO_4$), and evaporated. The residue was dissolved in 250 mL of methanol which was then treated with a vigorous stream of HCl gas for 3 min, stirred at 25 °C for 15 min, and carefully poured into saturated aqueous $NaHCO_3$. Extraction with dichloromethane, pooling, and drying ($MgSO_4$) was followed by evaporation of the solvent in the presence of 50 g of silica gel. This was introduced at the top of a 50-g column of silica gel (EM reagents 60), and the product was recovered [4.0 g (67%); mp 206–207 °C dec] by elution with 3:1 $CHCl_3$–ETOAC, followed by evaporation: IR ($CHCl_3$) 3380, 1580 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 1.73 (m, 2), 2.23–2.80 (m, 4), 6.90 (m, 3), 10.50 (s, 1); mass spectrum, (70 eV), *m/e* (relative intensity) 228 (m^+, 98), 211 (29), 199 (100).

4-Formyl-5-hydroxyxanthene (19). A solution of 4.2 g of **18** in 500 mL of toluene containing 15.2 g of freshly prepared 30% Pd/C was heated at reflux for 1.5 h and slowly flushed with a stream of N_2. After filtration, the solvent was evaporated in the presence of 25 g of silica gel, and the residue was introduced at the top of a column containing 750 g of silica gel. The product was recovered as an oil by gradient elution with 3:1 $CHCl_3$/EtOAc and evaporation: 1.8 g (44%); IR ($CHCl_3$) 3500, 1690, 1590, 1485, 1460 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 4.05 (s, 2), 6.7–7.8 (m, 6), 8.18 (brs, 1), 10.72 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 226 (M^+, 98), 225 (100), 209 (26), 197 (51).

***N*-[α-(*tert*-Butoxycarbonyl)glycyl]-*N*-benzyl-*N*-(5-hydroxy-4-xanthenemethyl)amide.** To a solution of 238 mg (1.06 mmol) of **19** and 0.81 mL (7.3 mmol) of benzylamine in 4.5 mL of methanol that was 1.5 M in HCl were added ca. 150 0.3-nm molecular sieves and 6.3 mL of warm methanol containing 50 mg (0.73 mmol) of sodium cyanoborohydride. After 1.3 h the mixture was poured into 1 N HCl and repeatedly extracted with CH_2Cl_2; the extracts were pooled, dried ($MgSO_4$), and evaporated to yield 354 mg (95%) of secondary amine as its hydrochloride.

A mixed anhydride was prepared from 175 mg (1 mmol) of Boc-Gly-OH and 140 μL (1 mmol) of triethylamine in 3 mL of CH_2Cl_2 at 0 °C and was treated with 130 μL (1 mmol) of isobutyl chloroformate. After 10 min at 0 °C, this solution was treated with the above-described crude hydrochloride salt in 2 mL of CH_2Cl_2 containing 140 mL of triethylamine; the resulting mixture was stirred for 1 h at 0 °C and 1 h at 25 °C, diluted with CH_2Cl_2, washed with 1 N HCl, H_2O, and brine, dried over $MgSO_4$, and evaporated to give 462 mg of crude amine. Recrystallization (ether) gave 215 mg (45%) of plates: mp 169.5–170.5 °C; IR ($CHCl_3$) 3430, 1705, 1640, 1485, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9), 3.2 (s, 2), 3.96 (d, 2, J = 5 Hz), 4.30 (s, 2), 4.74 (s, 2), 5.56 (brs, 1), 6.60–7.35 (m, 11), 8.03 (s, 1); UV (MeCN) λ_{max} 285 (ϵ 5380), 340 (497). Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.86; H, 6.37; N, 5.90. Found: C, 70.56; H, 6.54; N, 5.78.

General Procedure for Formation of 8, 10, 12, or 14 from Hydroxy Aldehydes. The Schiff base is formed from primary amine and hydroxy aldehyde in acetonitrile or methanol over 30 min at 25 °C; this species is reduced without purification in ethanol or methanol with sodium borohydride or sodium cyanoboro-

(25) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967); I. M. Kolthoff and T. B. Reddy, *Inorg. Chem.*, **1**, 189 (1962).
(26) C. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974).
(27) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947); L. Bardou, J. Elguero, and R. Jaquier, *Bull. Soc. Chim. Fr.*, 297 (1967).
(28) Prepared by the reaction of 2,3-dihydroxybenzaldehyde with a twofold excess of acetic anhydride in refluxing acetic acid and used as the oil obtained after aqueous workup.

Table IV. Properties of Amides 9, 11, 13, and 15

amide	acyl	amine	mp, °C	calcd C	calcd H	calcd N	calcd m/e	found C	found H	found N	found m/e
9a	acetyl	Gly	170-172	60.50	5.36	11.76	357.132 47	60.46	5.38	11.77	357.135 47
9b	acetyl	L-Ala	90-92	61.45	5.70	11.31	371.148 12	61.29	5.76	11.19	371.150 32
9c	acetyl	L-Val	75-76	63.15	6.31	10.52	399.179 42	63.15	6.59	10.30	399.177 55
9d	Cbz-Gly	Gly	60-62	61.65	5.17	11.06	506.180 15	61.49	5.20	11.12	506.182 76
9e	Cbz-L-Ala	Gly	72-74	62.30	5.42	10.76	520.195 80	61.73	5.69	10.48	520.193 51
9f	Cbz-L-Val	Gly	70-71	63.49	5.88	10.21	548.227 10	63.34	5.99	10.29	548.228 04
9g	Cbz-L-Ala	L-Val	58-60	64.04	6.09	9.96	562.242 75	63.98	6.20	9.77	562.242 08
11a	acetyl	Gly	68-70				416.173 60				416.173 72
11b	acetyl	L-Ala	oil				430.189 25				430.190 46
13a	acetyl	Gly	100-101	62.13	6.83	5.57		62.16	6.72	5.61	
13b	acetyl	L-Ala	86-87	63.37	7.23	5.28		63.06	7.35	5.37	
13c	acetyl	L-Val	116-117	65.51	7.90	4.77		65.32	8.10	4.78	
15a	acetyl	Gly	oil				301.131 4				301.137 5
15b	acetyl	L-Ala	58				315.147				315.148

[a] Molecular ion from high-resolution mass spectrometry.

hydride in the presence of a weak acid (acetic acid or conjugate acid of excess amine). The crude secondary amine was obtained by evaporation, solution in CH_2Cl_2, washing with H_2O, drying, and evaporation; it is used without further purification. Acylation with di-*tert*-butyl dicarbonate generates a (*tert*-butoxycarbonyl)urethane; acylation with a mixed carbonic–carboxylic anhydride of a (*tert*-butoxycarbonyl)amino acid (or with a mixture of 1 equiv each of the α-Boc amino acid, dicyclohexylcarbodiimide, and *N*-hydroxybenzotriazole) generates an amide. Acylation of the phenolic hydroxyl is carried out in pyridine with acetic anhydride at 25 °C for 1–2 h or with the mixed anhydride of a [(benzyloxy)carbonyl]amino acid. Treatment with HCl in dioxane for 30 min at 25 °C, followed by freeze-drying gives the hydrochloride salts of **8**, **10**, **12**, or **14**, which were characterized spectroscopically and by conversion to amides **9**, **11**, **13**, or **15**, which were characterized spectroscopically and by elemental analysis (Table IV). The following experimental procedure is representative.

***N*-[(*tert*-Butoxycarbonyl)-L-valinyl]-*N*-benzyl-*N*-(2-acetoxy-5-nitrobenzyl)amide.** A solution of 2.0 g (12 mmol) of 5-nitrosalicyaldehyde and 1.28 g (12 mmol) of benzylamine in 25 mL of MeCN was stirred for 5 min and then filtered. The Schiff base was recrystallized from hot $CHCl_3$ to give 1.64 g (54%) of product, mp 150–153 °C. This substance was dissolved in 25 mL of THF, and 8 mL of absolute EtOH was added at 25 °C, followed by 0.22 g (5.8 mmol) of $NaBH_4$ in small portions over the course of 20 min. After the mixture was stirred for 2 h, the solvent was removed under vacuum, and the residue was partitioned between ETOAC and H_2O. The oganic phase was washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in 25 mL of MeOH that was previously saturated with HCl and heated to 70 °C for 30 min. Evaporation and trituration with ether yielded 1.2 g (62%) of the hydrochloride salt of *N*-(2-hydroxy-5-nitrobenzyl)benzylamine, mp 223–226 °C. The free base was obtained as an oil by neutralization of the salt with aqueous sodium hydroxide, extraction with CH_2Cl_2, drying, and evaporation. A solution of this crude amine (0.97 g, 3.8 mmol) in 10 mL of freshly distilled DMF containing 0.60 g (2.8 mM) of (*tert*-butoxycarbonyl)-L-valine and 0.8 g of *N*-hydroxybenzotriazole was treated with 0.84 g of dicyclohexylcarbodiimide. After 24 h at 25 °C, the urea was removed by filtration, the solvent was evaporated, and the residue was dissolved in 50 mL of ETOAC. The solution was filtered, washed with H_2O (4 × 15 mL), 20 mL of 5% $KHSO_4$ solution, 10 mL of 5% $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and evaporated to give the crude product as a yellow oil which was purified by column chromatography on silica gel, eluting with 95:5 $CHCl_3$–MeCN. The yield of oily product was nearly quantitative: ^1H NMR ($CDCl_3$) δ 0.90 (dd, 6), 1.50 (s, 9), 1.98 (m, 1), 4.40–4.90 (m, 6), 5.20 (br d, 1), 6.95 (d, J = 9 Hz, 1), 7.30 (s, 5), 7.8 (d, 1), 8.10 (dd, J = 9 Hz, 1), 10.5 (br s, 1). The resulting amide (1.4 g, 3.0 mmol) was dissolved in 3 mL of dry pyridine, and 0.71 mL of acetic anhydride was added. After 24 h at 25 °C, the solvent was removed under vacuum, and the residue was taken up in 50 mL of CH_2Cl_2. Washing with 0.5 M citric acid, water, and brine, drying ($MgSO_4$), and evaporation gave an oil which crystallized from EtOAc–petroleum ether to give the product: 1.2 g (80%); mp 80–83 °C; ^1H NMR ($CDCl_3$) δ 1.00 (d, 6), 1.50 (s, 9), 2.00 (m, 1), 2.35 (d, 3), 4.30–5.10 (m, 6), 5.40 (br d, 1), 7.30–7.50 (m, 5), 8.20 (s, 1), 8.30 (dd, 1); mass spectrum (70 eV), *m/e* (relative intensity) 50 (M^+, 0.3), 91 (58). Anal. Calcd for $C_{26}H_{33}N_3O_7$: C, 62.51; H, 6.66; N, 8.41. Found: C, 62.70; H, 6.74; N, 8.39.

***N*-(Acetoxy-L-valinyl)-*N*-benzyl-*N*-(2-hydroxy-5-nitrobenzyl)amide (9c).** The above-described *tert*-butoxycarbonyl derivative (100 mg) was dissolved in 2 mL of dioxane that had been saturated with HCl, and after 30 min at 25 °C the solution was frozen in liquid nitrogen and allowed to thaw under vacuum. The dry hydrochloride salt of **8c** was triturated with ether to give a white powder: 82 mg; IR (KBr) 3420, 2800–3100, 1765, 1650, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (dd, 6), 2.10 (m, 1), 2.25 (d, 3), 3.40 (br s, 1), 4.1–5.2 (m, 4), 7.30 (br s, 5), 8.00 (s, 1), 8.10 (d, 1), 8.50 (br s, 2).

The hydrochloride salt (65 mg, 0.15 mmol) was dissolved in 10 mL of MeCN and 21 μL (0.15 mmol) of triethylamine was added. After 30 min at 25 °C the solvent was evaporated, and the residue was taken up in CH_2Cl_2. The solution was washed with water and brine, dried (Na_2SO_4), and evaporated. Trituration with CH_2Cl_2–pentane gave 46 mg (77%) of a yellow powder (**9c**): mp 75–76 °C; IR ($CHCl_3$) 3420, 3100, 2960, 1660, 1600, 1480, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (dd, 6), 2.00 (s and m, 4), 4.45 (d, 2), 4.75 (s, 2), 5.1 (m, 1), 6.4 (br d, 1), 7.00 (d, J = 9 Hz, 1), 7.4 (br s, 5), 7.85 (d, 1), 8.15 (dd, 1), 10.7 (s, 1). Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52. Found: C, 63.15; H, 6.59; N, 10.30.

Kinetic Procedures. Reagent or spectro grade solvents were used without further purification. Approximate rate constants were obtained by ^1H NMR spectroscopy with the acetate esters by observation of the relative intensities of the resonances attributable to the acetyl methyls of the starting materials and products. Rate constants reported in Table I were measured by UV spectrophotometry at the long-wavelength maximum for the phenolic product in each solvent. Satisfactory linear plots of ln $(A_t - A_\infty)$ were obtained to 3 half-lives. For stopped-flow runs, the drive syringes were filled with freshly prepared solutions, one containing 10^{-5}–10^{-4} M substrate as the hydrochloride in a solution to which 1 drop of 6 N HCl had been added per 100 mL of solution and the other containing 10 times the substrate concentration of triethylamine. Varying the triethylamine concentration more than tenfold had no effect on the observed rate constant.

Half-lives measured by ^1H NMR in $CDCl_3$ or $(CD_3)_2SO$ for **12** and **14** at 0.05–0.3 M concentrations were observed to be smaller than those measured at (1–2) × 10^{-4} M by UV photometry; the largest difference was observed for **12c** in Me_2SO ($t_{1/2} \simeq 0.5$ min at 0.06 M and 6 min at 2 × 10^{-4} M). The effect was never large enough to be consistent with simple second-order kinetics, and we interpret these results in terms of intermolecular base catalysis at high concentrations which competes with simple or solvent-catalyzed intramolecular acyl transfer. As seen in Table I for entries **12b** and **12c**, simple base catalysis in water is observed for these systems, but solvent catalysis by Me_2SO is not.

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Registry No. **8a**, 75830-06-7; **8b**, 75847-34-6; **8c**, 75830-07-8; **8c**·HCl, 75830-08-9; **8d**, 75830-09-0; **8e**, 75830-10-3; **8f**, 75830-11-4; **8g**, 75830-12-5; **9a**, 75830-13-6; **9b**, 75830-14-7; **9c**, 75830-15-8; **9d**, 75830-16-9; **9e**, 75830-17-0; **9f**, 75830-18-1; **9g**, 75830-19-2; **10a**, 75830-20-5; **10b**, 75830-21-6; **10c**, 75862-66-7; **11a**, 75847-35-7; **11b**, 75830-22-7; **11c**, 75830-23-8; **12a**, 75830-24-9; **12b**, 75830-25-0; **12c**, 75830-26-1; **13a**, 75830-27-2; **13b**, 75830-28-3; **13c**, 75830-29-4; **14a**, 75847-36-8; **14b**, 75830-30-7; **15a**, 75830-31-8; **15b**, 75830-32-9; **16**, 67985-75-5; **18**, 75830-33-0; **19**, 75830-34-1; 2-(isopropoxymethylene)cyclohexanone, 15839-23-3; benzylamine, 100-46-9; *N*-[α-(*tert*-butyloxycarbonyl)glycine]-*N*-benzyl-*N*-(5-hydroxy-4-xanthene)methylamide, 75830-39-6; *N*-benzyl-*N*-(5-hydroxy-4-xanthene)methylamine·HCl, 75830-35-2; 5-nitrosalicylaldehyde, 97-51-8; 5-nitrosalicylaldehyde benzylamine Schiff base, 53848-16-1; *N*-[(*tert*-butoxycarbonyl)-L-valinyl]-*N*-benzyl-*N*-(2-acetoxy-5-nitrobenzyl)amide, 75830-36-3; *N*-(2-hydroxy-5-nitrobenzyl)benzylamine·HCl, 75830-37-4; *N*-(2-hydroxy-5-nitrobenzyl)benzylamine, 75830-38-5; (*tert*-butoxycarbonyl)-L-valine, 13734-41-3.

Carbanions. Electron Transfer vs. Proton Capture. 7. Electron-Transfer Oxidation of an Amino Acid Derived Carbanion

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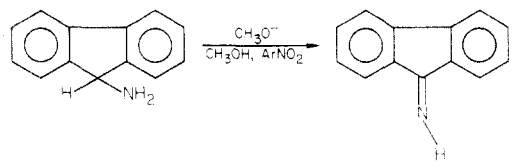
The dimethylamide of phenylalanine, **1**, reacts with potassium *tert*-butoxide and nitrobenzene in *tert*-butyl alcohol at 50 °C in an argon atmosphere. The products are potassium nitrobenzenide ($PhNO_2^-K^+$) and degradative fragments of the amino amide, including ammonia, dimethylamine, potassium benzoate, potassium carbonate, and potassium cyanide. The yields of these isolated degradation products are relatively low when the reaction is run anaerobically but are improved when the reaction is carried out under oxygen. The oxygen-mediated reaction does not produce cyanide or nitrobenzenide but its products are otherwise the same with the addition of oxalate. Conversions are essentially quantitative when the oxygen-mediated reaction is followed by vigorous, acid-catalyzed, hydrolytic workup. The reaction is believed to begin with the one-electron oxidation of the α-amino carbanion, proceeding through a ketimine and/or an enamine which is rapidly oxidized to the eventual products. The rate of oxidation of **1** is approximately the same as its ionization rate but the reaction becomes less efficient if the *N*-pivalyl derivative of **1** is used. Experiments with the dimethylamide of alanine give qualitatively similar results, with potassium formate replacing potassium benzoate in the products.

Introduction

In a study dealing with the electron-transfer oxidation of 9-substituted fluorenes by base and aromatic nitro compounds, we observed that 9-aminofluorene is cleanly dehydrogenated as shown in eq 1.[1] Evidence was presented that the mechanism involves proton and electron transfer in the sequence $A_{BH}D_{CH} + A_{CA}D_{C\cdot A} + A_{C\cdot A}D_{CA} + A_{BH}D_{NH}$, where A is the electron acceptor and B is a base.[2] An analogous mechanism is possible for flavin-mediated biological oxidations[3] and the connection has been strengthened in a recent study[4] which showed that 9-methoxyfluorenide ion reacts with a model flavin system in a manner analogous to its reaction with nitrobenzene.[5]



(1)

We decided to study the reaction of an amino acid derived carbanion with nitrobenzene. It is obvious that such a remotely analogous system could, at best, provide only permissive evidence for the involvement of carbanion electron transfer in the action of amino acid oxidases. Moreover, a base of the strength found necessary for carbanion formation from **1** is an unlikely resident of an enzyme cavity. One might argue that this fact militates against the proposal of free α-amino carbanions as intermediates in the biological mechanism. The transformation to be described nevertheless represents a new reaction of amino acid derivatives.

Results

The search for an appropriate amino acid derivative started with an attempt to form a carbanion directly from the amino acid. It was found that alanine itself showed no deuterium incorporation after treatment with 0.5 N potassium *tert*-butoxide in *tert*-butyl alcohol-*d* for 4 days at 65 °C. The presence of a carboxylate anion in this substrate apparently makes the energy requirements of the carbanionic charge prohibitive under conditions where we could expect nitrobenzene to survive. Similar results were obtained with Cbz and *t*-Boc derivatives. We were reluctant to experiment with amino acid esters because of the possible complications of transesterification and peptide formation. We therefore settled on the dimethylamide. Most of the work to be described was carried out with the dimethylamide of phenylalanine, **1**.

Anaerobic Reaction. When **1** was treated with potassium *tert*-butoxide in *tert*-butyl alcohol at 50 °C under argon, roughly 4 mol of nitrobenzene were consumed per

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