pendently favorable factors, among which the high acidity of the esters II (IIb is ~20% dissociated in DMF 0.2 *M* in Et_3N), the inhibitory effect of acids on the racemization of peptide esters,[9] the reluctance of salts of II to assume a second negative charge, and their high aminolytic reactivity[10] all figure prominently.

Further investigations into the mechanism of these processes and their general applicability to peptide coupling reactions are in progress and will be reported subsequently.

Acknowledgment. The support of the U. S. Public Health Service through Grants GM 13453-01 and -02 is gratefully acknowledged.

(9) *Cf.* D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2745 (1967).

(10) For a discussion of propinquity catalysis, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., 1966, pp 150–169.

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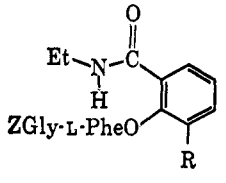
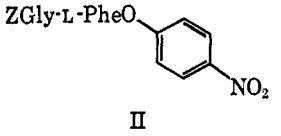
Specific Base Catalysis of Azlactone Formation

Sir:

Recent work[1,2] has established azlactones as essential intermediates in the racemization of many peptide activated species. While this and earlier work has made clear a dependence of azlactone formation on the presence of base, the precise nature of the dependence has not been explored. By analogy with Winstein's work on the cyclization of 2-benzamidoethyl tosylates,[3] one would anticipate for a primary or secondary amide a dual nucleophilicity, dependent on the relative concentrations of neutral amide and amide anion present in the reaction medium. We wish to present evidence which supports the presence of equilibrated amide anions as the reactive intermediates leading to azlactone formation from four peptide activated esters.



Ia, R=H
b, R=OMe
c, R=Me



II

Table I presents first-order rate constants observed for the triethylamine-catalyzed racemization of O-(carbobenzoxyglycyl-L-phenylalanyl)-N-ethylsalicylamide (Ia)[4] in dimethylformamide containing tri-

(1) M. Goodman and K. C. Steuben, *J. Org. Chem.*, 27, 3409 (1962); M. Goodman and L. Levine, *J. Am. Chem. Soc.*, **86**, 2918 (1964); M. Goodman and W. J. McGahren, *ibid.*, **87**, 3028 (1965).

(2) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964); I. Antonovics and G. T. Young, *Chem. Commun.*, 398 (1965).

(3) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(4) Ia, mp 140–141°, $[\alpha]^{22}D$ −21.7° (*c* 2.2, CH_3CN); Ib, mp 149–150°, $[\alpha]^{25}D$ −25.2° (*c* 2.0, DMF); Ic, mp 125–126°, $[\alpha]^{25}D$ −47.8° (*c* 2.0, DMF); these esters were prepared in optically pure form by reaction of the sodium salt of ZGly-L-PheOH in an aqueous pyridine buffer with the appropriate 7-substituted N-ethylbenzisoxazolium salt.[5,6]

(5) Satisfactory elemental analyses were obtained for all new compounds.

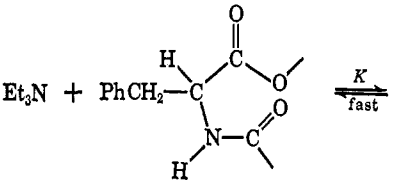
(6) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

Table I[a]

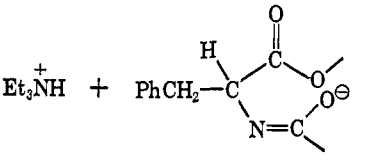
$[Et_3N]$	$[Et_3N^+H]$[b]	$[Et_3N]/[Et_3N^+H]$	First-order[c] rate constant, min^{-1}	Calcd rate[d]
0.2	No salt	...	12×10^{-2}	
0.2	0.000	...	20×10^{-2}	
0.2	0.01	20	3.0×10^{-2}	3.0×10^{-2}
0.2	0.015	13.3	2.4×10^{-2}	2.1×10^{-2}
0.2	0.02	10	1.7×10^{-2}	1.7×10^{-2}
0.2	0.05	4	0.86×10^{-2}	0.83×10^{-2}
0.2	0.2	1	0.38×10^{-2}	0.37×10^{-2}
0.4	0.04	10	1.9×10^{-2}	
0.1	0.01	10	1.7×10^{-2}	
0.05	0.005	10	1.5×10^{-2}	
0.02	0.002	10	1.1×10^{-2}	

[a] Temperature 25°, DMF solvent. [b] Unless otherwise specified, sufficient $Et_4N^+BF_4^-$ was added to bring the total salt concentration to 0.2 *M*. [c] Ester concentration 10–20 mg/ml; rates followed polarimetrically, first-order rate law followed for at least three half-lives. [d] For rates at 0.2 *M* Et_3N, a plot of the observed first-order rate constant *vs.* $[Et_3N]/[Et_3N^+H]$ was linear with a slope, k_a, of 1.4 $\times 10^{-3}$ min^{-1} and a zero intercept, k_b, of 2.3×10^{-3}. Calculated rate = $k_a[Et_3N]/Et_3N^+H] + k_b$.

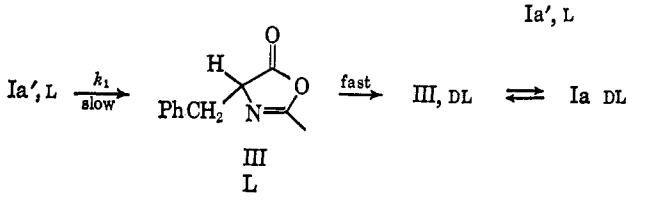
ethylammonium fluoroborate. The observed linear dependence of rate on the amine:amine salt ratio, together with the striking insensitivity of rate to the absolute amine concentration at constant amine:amine salt ratio, are most easily interpreted as requiring the intermediacy of a conjugate base of Ia. A scheme consistent with this result is shown below.[7]



Ia, L



Ia′, L



III
L

$$d[DL\text{-Ia}]/dt = k_1[L\text{-Ia}'] = k_1K[L\text{-Ia}][Et_3N]/Et_3\overset{+}{N}H] \quad (1)$$

Similar behavior is observed for the esters Ib, Ic, and II (Table II). It is of interest that the intercepts, k_b, which are the limiting rates expected at constant amine concentration as the amine salt concentration is raised, most include all general base catalyzed terms; their magnitudes therefore bound the rates of simple base-catalyzed enolization for these esters. Although these results must be generalized with caution since they stand in contrast to other well-known salt effects on peptide racemization,[2] it would appear that in DMF tertiary amine catalyzed racemization of peptide phe-

(7) Although the formation of azlactones need not result in racemization, the reaction conditions of this study (polar solvent, excess of nonnucleophilic base) ensure that II racemizes faster than it reacts with phenolate anion, and therefore that k_1 is rate-determining.[1]

Table II[a]

Ester	$k_{rac} = k_a[Et_3N]/[Et_3N^+H] + k_b$ k_a, min^{-1}	k_b, min^{-1}	$k_{coupling}$,[b] M^{-1} min^{-1}	$k_{coupling}/k_a$
Ia	1.4×10^{-3}	2.3×10^{-3}	8.7×10^{-1}	600
Ib	2.3×10^{-4}	2.3×10^{-5}	2.1×10^{-1}	930
Ic	2.9×10^{-5}	2.3×10^{-5}	4.8×10^{-2}	1600
II	3.8×10^{-3}	1.4×10^{-2}	19.3	5100

[a] Rates followed polarimetrically; Et_3N = 0.2 *M*, Et_3N^+H + Et_4N^+ = 0.2 *M*, temperature 25°, DMF, anion = BF_4^-, 0.01 ≤ $[Et_3N^+H]$ ≤ 0.2 *M*; k_a and k_b obtained as described in Table I, footnote *d*. [b] Rates of the reaction, ester + GlyOEt → ZGly-Phe-GlyOEt + phenol; rates followed by ultraviolet photometry in DMF, 30°; ester, 1–2 × 10^{-4} *M*; GlyOEt, 0.01–0.5 *M*; reactions were first order in ester to at least three-half-lives, first order in amine over at least a 3-fold concentration range.

nolic esters can be slowed by as much as 50-fold by the addition of the corresponding ammonium fluoroborate salt.

Included in Table II are rates of combination of the esters Ia–c and II with ethyl glycinate in DMF. Since the value of *K* in (1) should not vary significantly for these esters, the values of k_a may be taken as measures of the relative reactivities of the esters Ia–c and II toward an internal oxygen nucleophile. Comparing these values with the rates of reaction with an external amine, one finds a surprisingly good correlation, despite considerable variation of reactivity and structure.

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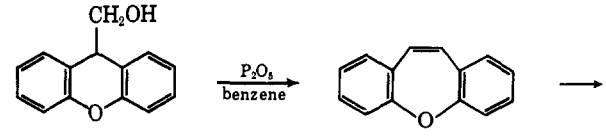
A Valence Tautomer of Pyrene *cis*-15,16-Epoxide

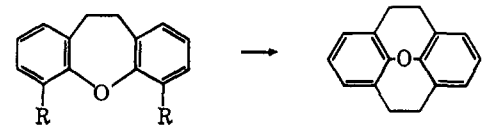
Sir:

Recently we reported the synthesis of *trans*-15,16-dimethyldihydropyrene[1] and its photoisomerization to the corresponding metacyclophane valence tautomer.[2] Since then, syntheses of other examples of *trans*-15,16-dihydropyrenes have been described,[3,4] but as yet no example has been reported of a *cis*-15,16-dihydropyrene derivative. We now wish to record the synthesis of 8,16-oxido[2.2]metacyclophane-1,9-diene (VIII), a valence tautomer of *cis*-pyrene 15,16-epoxide.

The starting material for this synthesis was xanthene-9-carbinol (I), which undergoes an acid-catalyzed rearrangement in essentially quantitative yield to give dibenz[b,f]oxepine (II).[5] Reduction of II gave the corresponding dihydro derivative III as a colorless oil, bp 100–103° (0.2 mm).[6] Treatment of III with *n*-butyllithium followed by carbonation, according to the procedure used by Gilman for carbonating diphenyl ether,[7] gave the corresponding dicarboxylic acid which, by reaction with diazomethane, led to the dimethyl ester IV as white crystals, mp 94.5–95.0°, in 39% over-all yield. Reduction of IV with lithium aluminum hydride provided the diol V as white crystals, mp 123–124°, in 98% yield. Conversion of V to the corresponding dibromide VI, white crystals, mp 124–125°, was accomplished in 90% yield using phosphorus tribromide. Cyclization of VI with phenyllithium to the corresponding metacyclophane VII, mp 94.0–95.5°, occurred smoothly in 75% yield.



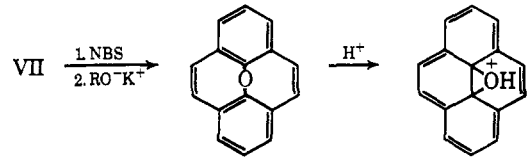
I II



VII

III, R = H
IV, R = CO_2Me
V, R = CH_2OH
VI, R = CH_2Br

Although VII is a metacyclophane derivative, the oxygen bridge forces the two benzene rings into a *cis* relationship in contrast to the normal *trans* geometry of [2.2]metacyclophanes.[8] Further, it could be expected that the *cis* geometry of VII would allow normal benzylic substitution. This was found to be the case. Treatment of VII with 2 equiv of N-bromosuccinimide gave the corresponding dibromide as a mixture of two stereoisomers. Without separation, this mixture was then subjected to reaction with potassium *t*-butoxide in *t*-butyl alcohol to yield the desired unsaturated derivative, VIII, as white crystals, mp 119–120°. In support of its structural assignment, VIII showed an A_2B multiplet (6 H) at τ 2.66–3.30 and a singlet (4 H) at τ 2.92. Also, the ultraviolet absorption spectrum of VIII showed absorption maxima in cyclohexane at 239 (ϵ 15,700) and 302 mμ (ϵ 16,300), indicating conjugation between the aromatic rings and the unsaturated side chains.[9]



VIII IX

Although the spectral data clearly establish that VIII is the correct structure of our product and that spontaneous valence tautomerization to the corresponding pyrene 15,16-epoxide structure does not occur, it was of interest to see whether conditions might be found for accomplishing this valence tautomerization. Our initial attempts employing light and heat have been

(1) V. Boekelheide and J. B. Phillips, *Proc. Natl. Acad. Sci. U. S.*, **51**, 550 (1964).
(2) H. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Am. Chem. Soc.*, **87**, 130 (1965).
(3) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).
(4) H. B. Renfroe, L. A. R. Hall, and J. A. Gurney, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Paper O-184.
(5) F. Anet, *Can. J. Chem.*, **35**, 1084 (1957).
(6) Satisfactory elemental analyses have been obtained for all of the compounds reported in this communication.
(7) K. Oita and H. Gilman, *J. Am. Chem. Soc.*, **79**, 339 (1957).
(8) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *ibid.*, **83**, 943 (1961).
(9) The mass spectrum of VIII shows the expected parent molecular ion at *m/e* 218, with an even more intense signal at 202 corresponding to loss of oxygen.