Solvolytic Reactions of *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Tosylate[1]

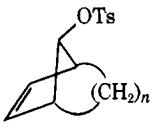
B. Andes Hess, Jr.

Contribution from the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203. *Received July 29, 1970*

Abstract: The rates of solvolysis of *endo*-bicyclo[3.2.1]oct-6-en-8-yl tosylate have been determined in acetic acid and ethanol–water mixtures. Product studies indicated that only products with the parent structure were formed. Both the results of product studies and interpretation of rate data support a significant amount of anchimeric assistance by the carbon–carbon double bond.

The apparent special stabilization of homoallylic cationic intermediates has been of interest for a number of years. The effective stabilization of the β carbon–carbon double bond appears to be greatly dependent upon the orientation of the developing cationic center and the double bond as has been demonstrated in *anti*-7-norbornenyl tosylate. Winstein, *et al.*, reported the high reactivity of the *anti*-7-norbornenyl tosylate.[2] The geometry of the 7-norbornenyl system is such that the developing cationic center is located above the carbon–carbon double bond and is symmetric with respect to the two sp^2 carbon atoms. Although the structure of the cationic intermediate has led to some controversy, recent nmr studies of the 7-norbornenyl and related ions lend strong support to a symmetrical delocalized species as the structure of the intermediate.[3]

It was of interest to us to study the ability of the carbon–carbon double bond to stabilize the positive charge with variation of the distance between the developing cationic center and the double bond while maintaining the uniqueness of the orientation of the double bond and the cationic center in the norbornenyl system. We felt that the best manner in which to do this was to vary in size the saturated bridge of **1**. While this work was in progress the solvolysis of **2** was reported.[4] Shortening of the saturated bridge brings the developing cationic



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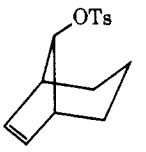
2, $n = 1$
3, $n = 2$
4, $n = 3$

center closer to the double bond. We will report here the effect of increasing the length of the saturated bridge ($n = 3$) and hence increasing the distance between the double bond and the developing cationic center. This required the synthesis of *endo*-bicyclo[3.2.1]oct-6-en-8-yl tosylate (**4**).[5]



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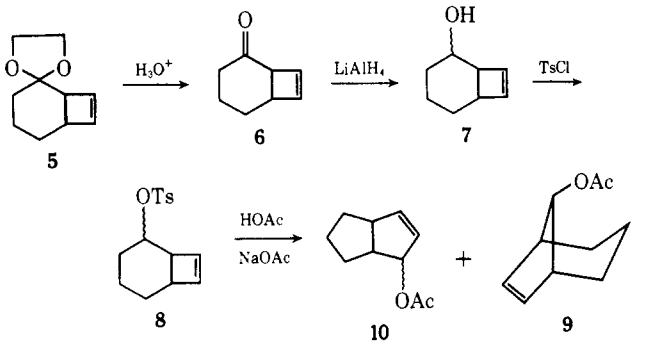
Acid hydrolysis of the ketal of bicyclo[4.2.0]oct-7-en-2-one (**5**)[6] gave the known ketone, bicyclo[4.2.0]oct-7-en-2-one (**6**).[7] Reduction of **6** with lithium aluminum hydride gave a mixture of the corresponding epimeric alcohols (**7**).[8] The tosylates of **7** were prepared and subjected to buffered acetolysis. Gas-chromatographic examination of the acetate product mixture showed two components present in a ratio of 8:2. Separation of the minor component and examination of its nmr spectrum indicated that it contained two acetates (two OCH_3 singlets) in a ratio of approximately 8:2. The nmr spectrum was identical with that reported for a mixture of the epimeric *cis*-bicyclo[3.3.0]oct-2-en-1-yl acetates (80% exo, 20% endo).[9]

The major component of the acetolysis mixture was identified as the desired *endo*-bicyclo[3.2.1]oct-6-en-8-yl acetate (**9**) by examination of its nmr spectrum and its reduction with hydrogen over palladium on charcoal followed by lithium aluminum hydride reduction to give the known *endo*-bicyclo[3.2.1]octan-8-ol.[10] The nmr spectrum of **9** had absorptions at τ 4.13 (m, 2, $CH{=}CH$), 5.25 (t, 1, $CHOAc$), 7.48 (m, 2, bridgehead), 7.94 (s, 3, CH_3), 8.20–9.08 (general absorption, 6, $(CH_2)_3$). At normal sweep width the vinyl region of **9**



5 **6** **7** **8** **10** **9**

(1) A preliminary communication on part of the work described here has been published: B. A. Hess, Jr., *J. Amer. Chem. Soc.*, **91**, 5657 (1969).

(2) S. Winstein, M. Shatvsky, C. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

(3) (a) R. K. Lustgarten, P. G. Gassman, D. S. Patton, M. Brookhart, S. Winstein, H. G. Richey, Jr., and J. D. Nichols, *Tetrahedron Lett.*, 1699 (1970); (b) M. Brookhart, A. Diaz, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 3135 (1966); (c) H. G. Richey, Jr., and R. K. Lustgarten, *ibid.*, **88**, 3136 (1966); (d) H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); (e) N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 129 (1964).

(4) S. Masmune, S. Takada, N. Nakatsuka, R. Vukov, and E. N. Cain, *J. Amer. Chem. Soc.*, **91**, 4322 (1969).

(5) The synthesis and solvolytic behavior of a related compound, *endo*-bicyclo[3.2.1]octa-2,6-dien-8-yl tosylate, has been reported: G. Klump, G. Ellen, and F. Bickelhaupt, *Recl. Trav. Chim Pays-Bas*, **88**, 474 (1969).

(6) H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).

(7) C. G. Scouten, F. E. Barton, Jr., J. R. Burgess, P. R. Story, and J. F. Garst, *Chem. Commun.*, 78 (1969).

(8) A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *J. Amer. Chem. Soc.*, **84**, 4865 (1962).

(9) S. Moon and C. R. Ganz, *J. Org. Chem.*, **35**, 1241 (1970).

(10) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964).

appears to be a triplet. However, an expanded spectrum indicates that a sextuplet is present which is symmetric about its center. The pattern is characteristic of the AA′ part of an AA′XX′ spectrum. A complete analysis of the vinyl pattern was made.[11] The calculated and observed spectra are given in Table I and the assigned coupling constants are given in Table II along with those of norbornene for comparison.

Table I. Nuclear Magnetic Resonance Spectral Data for the Vinyl Region of *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Acetate

Obsd spectrum		Calcd spectrum	
Chemical shift, Hz	Rel intensity	Chemical shift, Hz	Rel intensity
346.4	0.05	346.4	0.07
351.3	1.00	351.4	1.00
352.7	1.06	352.8	0.93
353.3	1.06	353.3	0.93
354.7	0.94	354.7	1.00
359.6	0.05	359.6	0.07

Table II. Coupling Constants for *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Acetate and Norbornene

	$J_{AA'}$ [a]	J_{AX}	$J_{AX'}$
9	6.35	2.94	0.37
Norbornene[b]	5.80	2.95	0.55

[a] A and A′ are vinyl hydrogens and X and X′ are bridgehead hydrogens; in hertz. [b] P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).

Separation of the two components of the acetolysis mixture could be effected by preparative gas chromatography. However, it was found that if the acetate mixture was heated in acetic acid in the presence of *p*-toluenesulfonic acid that **10** was selectively destroyed. Hence, pure **9** could be obtained quite easily in this manner. Reduction of **9** with lithium aluminum hydride gave *endo*-bicyclo[3.2.1]oct-6-en-8-ol (**11**), which when treated with tosyl chloride in pyridine afforded the crystalline *endo*-bicyclo[3.2.1]oct-6-en-8-yl tosylate (**4**).

The rates of solvolysis of *endo*-bicyclo[3.2.1]oct-6-en-8-yl tosylate were determined in glacial acetic acid and two ethanol–water mixtures. In all cases the reactions proceeded to completion. The solvolytic rate data are summarized in Table III.

Table III. Rates of Solvolysis of *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Tosylate

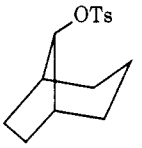
Solvent	Temp, °C	k, sec^{-1}	
Acetic acid	74.6	3.69×10^{-4}	
			$\Delta H^{\pm} = 24.1$ kcal/mol
	60.1	7.86×10^{-5}	
	50.4	2.54×10^{-5}	
			$\Delta S^{\pm} = -5.4$ eu
	25.0[a]	1.0×10^{-6}	
80% ethanol	50.4	1.44×10^{-4}	
95% ethanol	50.4	1.92×10^{-5}	
97.7% ethanol[a]	50.4	1.12×10^{-5}	

[a] Extrapolated values.

(11) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, New York, N. Y., 1962.

The sole product of the acetolysis was the parent acetate, *endo*-bicyclo[3.2.1]oct-6-en-8-yl acetate. From the ethanolyses two products were obtained, *endo*-bicyclo[3.2.1]oct-6-en-8-ol and ethyl *endo*-bicyclo[3.2.1]oct-6-en-8-yl ether.[12] In 80% ethanol the ratio of alcohol to ether was 59:41 and in 95% ethanol 22:78.

The observation that the solvolyses of **4** give only parent products with the stereochemistry of position 8 unchanged strongly suggests that the carbon–carbon double bond is participating in the solvolytic reaction of **4**. We believe that an analysis of the rate data of **4** also supports anchimeric assistance by the double bond. The best model system for rate comparison is *endo*-bicyclo[3.2.1]oct-8-yl tosylate (**12**). Although the acetolysis of **12** gives a complex mixture of products, some



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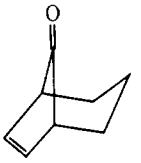
of which are rearranged products,[10] its rate of acetolysis appears to be a normal unassisted rate as indicated by Schleyer's solvolysis rate calculations.[13] The ratio of the rate of **4** to **12** is 1.9×10^5 which indicates a significant rate acceleration of **4** in its acetolysis.

Further evidence for the rate acceleration of **4** may be obtained by using the carbonyl frequency of **13** ($\nu_{C=O}$ = 1767 cm^{-1}) in Schleyer's rate treatment.[13,14] If Schley-



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er's parameters are used for *endo*-bicyclo[3.2.1]oct-8-yl tosylate and the inductive effect of the double bond is included, the log of anchimeric assistance for **4** is calculated to be 8.3. This may be compared with the log anchimeric assistance for *anti*-7-norbornenyl tosylate of 12.9.[14]

A comparison of the kinetic data for acetic acid and aqueous ethanol allows an estimation of Winstein *m* and *N* values.[15] The tosylate **4** has an *m* value of 0.68 and an *N* value of 0.44. Both values demonstrate that the solvolytic reactions of **4** are limiting.

A comparison of the rate acceleration present in **4** may be made with the rate acceleration of two other related bicyclic cyclopentenyl derivatives, **2** and **3**, as well as the parent cyclopentenyl[16] system itself (see Table IV). This requires the choice of suitable model compounds for comparison with the rates of **2** and **3**. Tosylate **14** appears to be a good model for the 7-norbornenyl tosylate;[13] the corresponding model for **2** is *exo*-bicyclo[2.1.1]hex-6-yl tosylate (**15**). However, the use of **15** as an unassisted rate model for **2** may be a poor

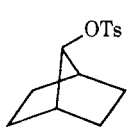
(12) Details of product isolation and identification are given in the Experimental Section.
(13) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1854 (1964).
(14) P. von R. Schleyer, *ibid.*, **86**, 1856 (1964).
(15) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948).
(16) P. D. Bartlett and M. R. Rice, *J. Org. Chem.*, **28**, 3351 (1963).

Table IV. Rate Ratios (Unsaturated–Saturated) of Related Cyclopentyl Derivatives

Compounds	k_{unsat}/k_{sat}	Ref
Cyclopentyl	0.4	*b*
endo-8-Bicyclo[3.2.1]-octyl (**4**,**12**)	1.9×10^5	This work *c*
anti-7-Norbornyl (**3**,**14**)	10^{11}	*d*
exo-6-Bicyclo[2.1.1]-hexyl (**2**,**15**)	5×10^{16} [a]	*e*

[a] k_{sat} used is a calculated unassisted rate for **15**.[13] [b] Reference 16. [c] Reference 10. [d] Reference 2. [e] Reference 4.

choice, for **15** may indeed undergo assisted solvolysis; therefore, the rate of **15** may not represent a true nonassisted rate as do the rates of **12** and **14**.[4,17,18] Com-



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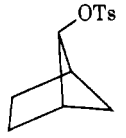

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pound **15** has an extrapolated rate of 2.24×10^{-11} at 25°. The calculated unassisted rate[13] is 2×10^{-18} which indicates, at least by the Schleyer treatment, the observed rate of acetolysis of **15** is indeed anchimerically assisted. For this reason the calculated unassisted rate of **15** is used in Table IV rather than the observed rate.

The k_{unsat}/k_{sat} rate ratios show a definite trend with the increase of the distance between the carbon–carbon double bond and the developing cationic center, *i.e.*, a decrease in the effectiveness of the double bond in its participation. Nevertheless, in **4** there appears to be a substantial effect which suggests that a delocalized intermediate may be operative in the solvolysis of **4** as well as in **2** and **3**. The intermediacy of a delocalized ion is supported by the retention of configuration in the solvolysis products of **4**.

Experimental Section

Bicyclo[4.2.0]oct-7-en-2-one (6). A solution of 9.9 g of the ketal of bicyclo[4.2.0]oct-7-en-2-one[6] and 40 ml of ether was stirred with 20 ml of 3 *N* hydrochloric acid for 2 hr. The two phases were separated, followed by ether extraction of the aqueous phase. The combined ether solutions were washed with water, 5% sodium bicarbonate, and aqueous saturated sodium chloride. After the ether was dried, distillation afforded 4.5 g (62%) of the ketone, bp 78–81° (16 mm) (lit.[7] bp 71–75° (8.5 mm)).

Bicyclo[4.2.0]oct-7-en-2-ol (7).[8] A solution of 4.5 g of bicyclo-[4.2.0]oct-7-en-2-one and 60 ml of ether was added to a stirred slurry of 1.0 g of lithium aluminum hydride and 10 ml of ether over a 15-min period. The mixture was refluxed for 0.5 hr and after addition of water, a total of 3.8 g (87%) of an oil was isolated. A small portion of alcohol was acetylated and glpc showed that the mixture was 80% endo and 20% exo.[8]

Acetolysis of the Tosylate of Bicyclo[4.2.0]oct-7-en-2-ol (80% endo and 20% exo). A. The tosylates of 1.05 g of the above mixture of alcohols were prepared in the usual manner with tosyl chloride in pyridine. The crude tosylates (1.8 g) and 1.6 g of sodium carbonate were dissolved in 175 ml of acetic acid and heated at reflux for 15 hr. The reaction mixture was cooled and diluted with water. The aqueous mixture was extracted with pentane and the combined pentane solutions were washed with water and 5% aqueous sodium bicarbonate, dried, and evaporated to give 1.0 g of a dark oil. Distillation gave 0.85 g of a colorless oil (bp 37–40° (0.2 mm)). Gas-chromatographic examination indicated that two components were present in a ratio of 8:2. Separation was effected by preparative glpc with a 5 ft × 3/8 in. 20% TCEP column at 159°. A total of 540 mg of the major component and 100 mg of the minor component was obtained.

A small portion of the major component was reduced first with hydrogen and 5% palladium on charcoal, and secondly with lithium aluminum hydride to give a tan solid. Purification by glpc gave a colorless solid, mp 198–199° (sealed capillary). The reported melting point of *endo*-bicyclo[3.2.1]octan-8-ol is 200.2–201°.[10] Hence, the major component of the above acetate mixture was identified as *endo*-bicyclo[3.2.1]oct-6-en-8-yl acetate: nmr (CCl_4) τ 4.13 (m, 2, C*H*=C*H*), 5.25 (t, 1, C*H*OAc, J = 5 Hz), 7.48 (m, 2, bridgehead), 7.94 (s, 3, CH_3), and 8.20–9.08 (m, 6, $(CH_2)_3$).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.45.

The minor component was identified as bicyclo[3.3.0]oct-2-en-1-yl acetate by comparison of its nmr spectrum with the reported spectrum.[9]

B. The crude tosylates (7.6 g) of the bicyclo[3.2.1]oct-6-en-8-ols were heated at reflux in buffered acetic acid (350 ml) for 7 hr, 3.4 g of *p*-toluenesulfonic acid was added, and refluxing was continued for an additional 3 hr. Work-up as in A gave 3.4 g of distilled product which was pure *endo*-bicyclo[3.2.1]oct-6-en-8-yl acetate (**9**).

***endo*-Bicyclo[3.2.1]oct-6-en-8-ol (11).** A solution of 3.8 g of **9** in 60 ml of ether was added to a stirred slurry of 1.0 g of lithium aluminum hydride and 200 ml of ether over 30 min. After the reaction mixture was heated at reflux for 30 min, work-up with 3 *N* hydrochloric acid gave 2.7 g of a crude solid. This was recrystallized from pentane to give 2.2 g (78%) of a colorless solid: mp 169.5–171°; nmr ($CDCl_3$) τ 4.11 (m, 2, C*H*=C*H*), 5.92 (t, 1, C*H*OAc, J = 5 Hz), 7.42 (s, 1, O*H*), 7.68 (m, 2, bridgehead), 8.0–9.1 (m, 6, $(CH_2)_3$).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.26; H, 9.74.

***endo*-Bicyclo[3.2.1]oct-6-en-8-yl Tosylate (4).** To a solution of 1.18 g of *endo*-bicyclo[3.2.1]oct-6-en-8-ol and 10 ml of pyridine cooled in an ice–salt bath was added 1.91 g of tosyl chloride. After standing in a refrigerator for 48 hr, the normal work-up gave 2.14 g of a white solid, mp 50–63°. Two recrystallizations from pentane gave 1.58 g (60%) of a white solid: mp 68.5–70°; nmr ($CDCl_3$) τ 2.42 (m, 4, aromatic), 4.19 (m, 2, C*H*=C*H*), 5.34 (t, 1, C*H*OTs, J = 5 Hz), 7.53 (s, 3, CH_3), ~7.58 (m, 2, bridgehead), 8.0–9.1 (m, 6, $CH_2)_3$).

Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52; S, 11.52. Found: C, 64.55; H, 6.61; S, 11.60.

Acetolysis of *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Tosylate. Solutions of the tosylate (0.025 *m*) in buffered glacial acetic acid containing about 1% acetic anhydride were prepared. Sealed ampoules were prepared which contained approximately 3.3 ml of the solution. They were placed in a constant temperature oil bath and allowed to equilibrate for at least 20 min. They were removed at known times, cooled in an ice bath, and broken open; 3 ml was titrated with standard *p*-toluenesulfonic acid in glacial acetic acid. Bromophenol blue was used as the indicator.

Ethanolysis of *endo*-Bicyclo[3.2.1]oct-6-en-8-yl Tosylate. The ethanolysis was carried out in the same manner as the acetolysis using 80% (density of 0.84934) and 95% ethanol in which a slight excess of sodium metal had been dissolved. Titrations were performed with standard hydrochloric acid using bromothymol blue as the indicator.

Product Studies. A. Acetic Acid. A solution of 200 mg of the tosylate **4** in 30 ml of glacial acetic acid buffered with potassium carbonate was heated at reflux for 1 hr. Work-up provided a colorless oil. Its glpc showed only one component on several columns and its nmr spectrum was identical with that of *endo*-bicyclo[3.2.1]octan-6-en-8-yl acetate.

B. Ethanol. The ethanolysis product studies were carried out in a manner similar to the acetolysis product study. In both the 80 and the 95% ethanolyses two products were obtained. Separation by glpc afforded an oil and a solid. The oil was identified as ethyl *endo*-bicyclo[3.2.1]oct-6-en-8-yl ether by its nmr spectrum. The solid, mp 169–171°, was identified by its nmr spectrum and its mixture melting point with *endo*-bicyclo[3.2.1]oct-6-en-8-ol. The 80% ethanolysis gave a ratio of ether to alcohol of 41:59 and the 95% ethanolysis, a ratio of 78:22.

Bicyclo[3.2.1]oct-6-en-8-one (13). A solution of 1.35 g of chromium trioxide, 3.3 ml of water, and 1.1 ml of sulfuric acid was added dropwise to a stirred solution of 1.0 g of *endo*-bicyclo[3.2.1]-oct-6-en-8-ol and 4 ml of acetone at 15° over a period of 45 min.

(17) K. B. Wiberg, R. A. Fenoglio, V. Z. Williams, and R. W. Ubersax, *J. Amer. Chem. Soc.*, **92**, 568 (1970).
(18) K. B. Wiberg and B. A. Hess, Jr., *ibid.*, **89**, 3015 (1967).

After additional stirring for 1.5 hr at room temperature, excess sodium bisulfite was added. Ether (15 ml) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted several times with ether. The combined ether phases were washed with 20% aqueous potassium carbonate solution, dried, and evaporated to give 600 mg of a soft solid. This was sublimed to give 360 mg (37%) of a colorless solid; a small portion was purified by glpc for analysis: mp 108–110° (sealed capillary); nmr (CCl_4) τ 3.79 (m, 2, vinyl), 7.32 (m, 2, bridgehead), 7.8–8.7 (m, 6, $(CH_2)_3$); ir (CCl_4) 1767 cm^{-1} (C=O).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.84; H, 8.37.

Acknowledgment. This work was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

Studies of the Chymotrypsinogen Family. XII. "A" Type Substates of α-Chymotrypsin at Neutral and Alkaline pH Values[1]

Yung Dai Kim and Rufus Lumry*

Contribution from the Laboratory for Biophysical Chemistry, Chemistry Department University of Minnesota, Minneapolis, Minnesota 55455. *Received April 14, 1970*

Abstract: Time-dependent changes in the yield of indole fluorescence from α-chymotrypsin (α-CT) have been analyzed to show the existence of new substates of the best-folded state (state A) in the pH region from 7 to 10. Temperature studies provide values for enthalpy and entropy changes which characterize the interconversions of the substates. The slow processes produced by pH change at alkaline pH values are not accompanied by large changes in the latter quantities. These processes are partially controlled by two acid groups which become deprotonated cooperatively at about pH 9. Thermodynamic and rate information is provided for these processes and estimates of the contributions to the enthalpy and entropy changes from the protein–water subsystem and the protolysis groups are made. Near pH 8 there is a temperature-dependent process between substates A_bH_2 and A_fH_2 with relatively large enthalpy and entropy changes. This process, which has a half-conversion temperature of about 25°, has been shown to be of the two-state type and it has the characteristics which might be expected for a conformation change of considerable size. δ-Chymotrypsin shows similar substate versatility whereas chymotrypsinogen A and catalytically inactive derivatives of α-CT demonstrate no pH dependence of the fluorescence. In the alkaline pH region the substate behavior of δ-CT was similar to that of α-CT but was more closely first order in hydrogen ion activity than second order. As a general rule changes in ORD, fluorescence, and catalytic activity with pH are closely correlated.

The behavior of α-chymotrypsin (α-CT) above pH 7.5 reveals a variety of interesting features which have already proved to be of value in detecting structural variations participating in the catalytic process of this enzyme.[2-9] As judged by studies with "good" ester substrates, the protein is maximally active in the region from about pH 7 to about pH 8. K_m has its minimum values and the maximum velocity parameter, V_{max}, achieves its highest values in this region. Although V_{max} remains substantially constant with some ester substrates up to about pH 10, K_m increases with an apparent pK_a value of approximately 9.[2,9] This decrease has been shown to measure the change from a state of strong affinity for substrates and competitive inhibitors to a state of lower affinity. The number and characteristics of the acidic and basic groups which participate in chymotryptic catalysis have not been established. Different authors have used different substrates, different experimental conditions, and different postulated mechanisms in analyzing their data.

Studies of the behavior of α-CT at alkaline pH values by physical methods also have not led to firm conclusions. The optical rotation was first shown by Rupley, Dreyer, and Neurath[10] to be pH dependent. Hess and coworkers[11] and Parker and Lumry[12,13] extended these studies to include the dispersion of optical rotation of the protein and several of its derivatives. Both optical rotation and optical rotatory dispersion demonstrated pH-dependent behavior in the region from pH 8 to 10.

Parker and Lumry were hesitant about attributing their ORD observations to a change in protein conformation. Hess and coworkers[5-7,11] were less so and since then have provided a considerable body of additional evidence to support their contention that the pH-

(1) The work in this paper is from the Ph.D. Dissertation of Yung Dai Kim, University of Minnesota, 1968; the results were presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967. This work was supported by the National Science Foundation, Grant No. GB7896, and Atomic Energy Commission, Grant No. AT(11-1)-894. This is paper No. 57 from this laboratory. Please request reprint by this number.

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