This observation permits one to study directly the kinetic isotope effect, effects of substituents, and other kinetic parameters for chromium(V). These data have been obtained and will be reported in detail subsequently. Similar behavior also has been observed using aldehydes as substrate.

Thus, the spectrophotometric study provides confirmation for the Westheimer mechanism and permits one to examine all of the steps in the reaction with the exception of the very rapid electron transfer between chromium(VI) and chromium(IV).

Acknowledgment. We are indebted to Professor J. M. Sturtevant for the use of his stopped-flow apparatus and to Professor J. H. Wang for the use of his esr spectrometer.

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2-Naphthoic Acid Derivatives as Models for the Isocarbostyril Substrates of α-Chymotrypsin (CHT)[1]

Sir:

Several efforts have been made to define that conformation (the "reactive" conformation) of methyl acetyl-L-phenylalaninate (L-APME) which is most susceptible to hydrolysis by ChT, using as a first approximation the relatively rigid geometry of D-3-carbomethoxydihydroisocarbostyril (D-CDIC).[2-5] Detailed understanding of what structural features are primarily responsible for the rapid hydrolysis of D-CDIC by ChT should greatly assist these efforts. Study of the rates of hydrolysis of **1**–**6** (Figure 1) by ChT may, for example, provide insight into the importance of the amide group in determining the reactivities of D- and L-CDIC and CIC toward the enzyme.

Table I displays the results of such a study[6-8] and reveals that the ease of hydrolysis[9] of **1**–**6** by ChT varies by more than 10^3 and is highly dependent on the nature of the ring bearing the ester groups. Particularly interesting is the observation that hydrolysis of **6** occurs with great rapidity both in an absolute sense and relative to **5**, although **5** and **6** lack the acylamino group characteristic of "specific" substrates of ChT. Ester **6** is estimated to be as reactive[9] as the *p*-nitrophenyl esters of D-3-carboxydihydroisocarbostyril or acetyl-L-phenylalanine (L-APNPE) would be under similar experimental conditions (Table I).[10] The data show that possession of a 1,2-dihydro-2-naphthoic acid-like skeleton of correct configuration is sufficient to cause the ready hydrolysis of an ester by ChT and suggest that the amido group is only a minor contributor to the reactivity of D-CDIC. Two facts other than the ease of hydrolysis of **6** support the use of **6** as a model for D-CDIC: (a) indole competitively inhibits the hydrolysis of **6** and D-CDIC, and (b) the behavior of **6** relative to **5** resembles that of D-CDIC relative to L-CDIC.

The purpose of these experiments is to define the geometry of the reactive conformation of L-APME. Figure 2 illustrates a proposed geometry which enjoys appreciable experimental support and which was obtained from the study of molecular models viewed in

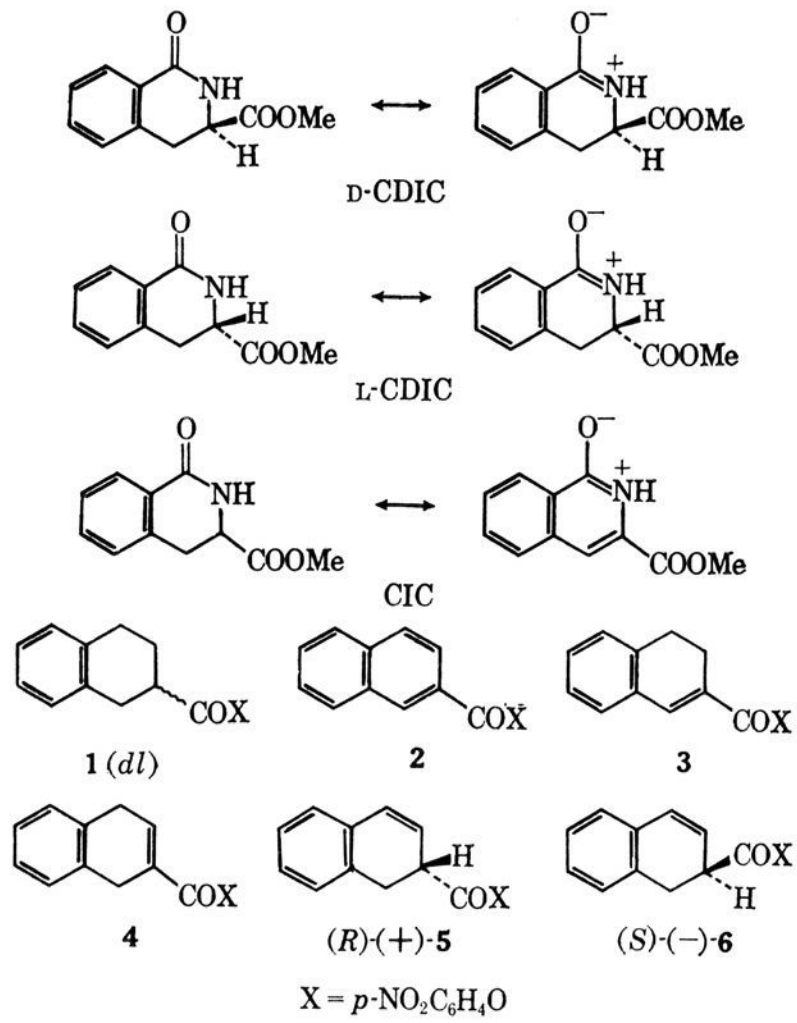


Figure 1.

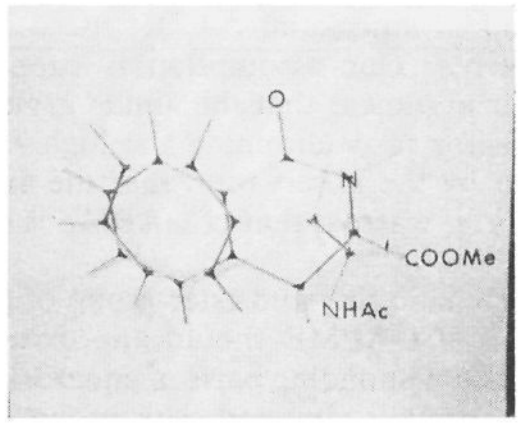


Figure 2. Photograph of Drieding models illustrating a possible reactive conformation of L-APME superimposed on equatorial D-CDIC.

(1) Supported by Grant AM 08005-03 of the U. S. Public Health Service.

(2) G. Hein and C. Niemann, *Proc. Natl. Acad. Sci. U.S.*, **47**, 1341 (1961); *J. Am. Chem. Soc.*, **84**, 4487, 4495 (1962).

(3) E. S. Awad, H. Neurath, and B. S. Hartley, *J. Biol. Chem.*, **235**, PC35 (1960).

(4) I. B. Wilson and B. F. Erlanger, *J. Am. Chem. Soc.*, **82**, 6422 (1960).

(5) M. S. Silver, *ibid.*, **88**, 4247 (1966).

(6) The substrates were prepared by conventional methods and gave satisfactory microanalyses. Rotations for 1% solutions of the optically active compounds in $CHCl_3$ were as follows: acid precursor of **5**, $[\alpha]^{25}D$ +259.6° (lit.[7] +158.7°); acid precursor of **6**, $[\alpha]^{25}D$ −282.5°; **5**, $[\alpha]^{21}D$ +171.4°; **6**, $[\alpha]^{25}D$ −197.5°. The kinetic behavior of **5** and **6** shows that **6** is only 82% (−) isomer, so either the acid was not completely resolved or extensive racemization occurred in the preparation of the ester. The hydrogenation experiment described later suggests that the latter may be correct. The ease of racemization and rearrangement of 1,2-dihydro-2-naphthoic acid derivatives probably explains the low rotation of the (+)-acid isolated by Pickard and Yates.[7]

(7) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **95**, 1011 (1909).

(8) The kinetic methods employed were identical with those of ref 5.

(9) All comparisons of reactivity in this communication are based on k_0/K_0.

(10) Detailed comparisons of k_0 and K_0 await data for the methyl esters analogous to **5** and **6** and for the *p*-nitrophenyl esters analogous to D- and L-CDIC. We believe these data will support the substance of our argument.

Table I. Kinetic Parameters for Some α-Chymotrypsin-Catalyzed Reactions[a]

Substrate	Runs	$10^6[S]_0$, M	$10^6[E]_0$, M	$10k_0$, sec^{-1}	10^5K_0, M	k_0/K_0, M^{-1} sec^{-1}	Relative reactivity[b]
1	24	2.77–15.7	6.88	2.28 ± 0.14	1.05 ± 0.11	2.17×10^4	1×10^2
2	15	2.88–7.01	55.7	0.42 ± 0.00	1.05 ± 0.10	3.96×10^3	2×10
3[c]						$\sim 3 \times 10^3$	2×10
4	22	3.11–16.6	55.7	0.32 ± 0.02	1.00 ± 0.08	3.18×10^3	2×10
5	17	2.38–12.7	11.5	1.24 ± 0.07	0.35 ± 0.05	3.59×10^4	2×10^2
5[d]	28	2.38–12.7	55.4	0.042 ± 0.007	0.25 ± 0.01	1.65×10^3	
6	23	2.69–13.5	1.09	69.8 ± 3.1	0.41 ± 0.05	1.70×10^6	1×10^4
6[d]	24	2.69–13.5	11.1	1.61 ± 0.02	0.18 ± 0.01	9.0×10^4	
D-CDIC[e]				227	52.7	4.31×10^4	4×10^3[f]
L-CDIC[e]				1.24	11.7×10^2	1.06×10	1[f]
CIC[e]				1.34	141	9.50×10	9[f]
L-APNPE[g]				770	2.4	3.21×10^6	1×10^4[h]
NPA[i]						9.00×10^2	5

[a] Procedures were identical with those described in ref 5 and k_0 and K_0 are the usual steady-state parameters. Reactions were carried out at 25.3°, pH 7.95, in 20% methanol–3% acetonitrile unless otherwise indicated. [b] Based on k_0/K_0 under the conditions specified in *a*. [c] Estimated for a sample that contained considerable **4**. [d] At pH 5.4. [e] Reference 2, pH 7.9, 25°, water. [f] Estimated for the corresponding *p*-nitrophenyl ester assuming a100-fold increase for the change in leaving group and a 5-fold decrease for the solvent effect. [g] From B. Zerner, R. P. M. Bond, and M. L. Bender, *J. Am. Chem. Soc.*, **86**, 3674 (1964), pH 7, 25°, 3% acetonitrile. [h] Assuming a 2-fold increase for the pH correction and a 2.9-fold decrease for the solvent change. [i] Reference 5.

the light of (prejudices) (1–4) below. The four basic assumptions which furnished the ingredients for construction of Figure 2 are:

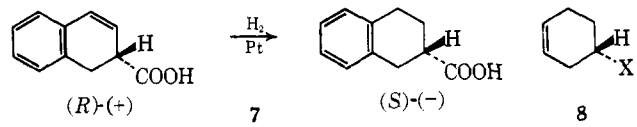
(1) The equatorial D-CDIC hypothesis is correct: that conformation of D-CDIC with an equatorial ester group (equatorial D-CDIC) is the one which undergoes hydrolysis by ChT and which should serve as the basic model for the reactive conformation of L-APME.[5]

(2) The amide groups of the reactive conformation of L-APME and of equatorial D-CDIC need not be oriented similarly. This assumption is supported both by the earlier argument that the amide group is not an important factor in determining the high reactivity of D-CDIC and by the observation that the amide group of D-CDIC is *cis* whereas that of L-APME is presumably *trans*.[5]

(3) The aromatic ring and ester group of the reactive conformation of L-APME should approximately coincide with the corresponding parts of equatorial D-CDIC.

(4) If the aromatic ring and ester group of any conformation of D-APME and the corresponding parts of equatorial D-CDIC are made to coincide, the acetamino side chains of D-APME and of the reactive conformation of L-APME should not have the same spatial orientation. This condition is introduced to reflect the stereospecific hydrolysis of L-APME by ChT.[11] Doubtless a similar procedure will yield a different model for the reactive conformation of L-APME if (1) is replaced by the axial D-CDIC hypothesis.[5]

If D-CDIC and **6** are truly analogous, **5** and **6** should have the absolute configurations indicated in Figure 1. Only tentative independent support for these assignments is now available. Dihydro acid of $[\alpha]^{25}D$ +93.5° (*c* 0.8, $CHCl_3$) was quantitatively hydrogenated (**7**) to tetrahydro acid with $[\alpha]^{25}D$ −18.1° (*c* 2, $CHCl_3$), which should have the (*S*) configuration if the carbon–carbon double bond of cyclohexene derivatives of type **8** and the benzo group of the tetrahydro acid may be equated.[12–14]



(*R*)-(+) **7** (*S*)-(−) **8**

Acknowledgments. All computations were performed at the University of Massachusetts Computer Center in Amherst. Mr. Stelios Arghyros assisted in the design of Figure 2, and Professor C. Peter Lillya measured many nmr spectra for us.

(11) If the phenyl and ester groups of D-APME are superimposed on the corresponding groups of the models shown in Figure 2, two extreme cases are observed. If the methylene groups of D- and L-APME coincide, the acetamino chain of D-APME lies in the direction of the hydrogen atom of the asymmetric carbon of L-APME, while if the methylene groups of D-APME and D-CDIC coincide, it lies in the direction of the CH→NH bond of D-CDIC.

(12) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959), has discussed the evidence that cyclohexene compounds of configuration **8** will be more levorotatory than their epimers.

(13) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **89**, 1101 (1906), claim that completely resolved tetrahydro acid had $[\alpha]D$ −51.8° (*c* 1.4, $CHCl_3$). If this is true, the hydrogenation experiment leads to the prediction that completely resolved dihydro acid should have $[\alpha]D$ ±268°, in good agreement with our observed value for the (−) isomer.[6]

(14) The absolute configurations D. Battail-Robert and D. Gagnaire [*Bull. Soc. Chim. France*, 208 (1966)] have assigned to the 1,2,3,4-tetrahydro-2-naphthols are in accord with this argument.

(15) The Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Katahira-cho, Sendai, Japan.

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Polar and Solvent Effects on Homolytic Abstraction of Benzylic Hydrogen of Substituted Toluenes by *t*-Butoxy Radical

Sir:

In a number of cases polar substituent effects have been discerned in reactions in which a free radical attacks a molecule. For attack on benzylic hydrogen atoms, bromine[1] and chlorine[2] atoms and *t*-butoxy,[3,4] trichloromethyl,[5] and peroxy radicals[2] give rise to rate data best correlated by σ^+ parameters[6] except in the case of *t*-butoxy. Since the *t*-butoxy radical is elec-

(1) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354 (1963).
(2) G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964).
(3) C. Walling and B. B. Jacknow, *ibid.*, **82**, 6113 (1960).
(4) R. D. Gilliom and B. F. Ward, Jr., *ibid.*, **87**, 3944 (1965).
(5) E. S. Huyser, *ibid.*, **82**, 394 (1960).
(6) The σ^+ correlations to free-radical reactions were introduced first by G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).