shows that crystalline *cyclo*(Gly-Pro-D-Ala)$_2$ assumes a single asymmetric conformation with trans Xxx–Pro bonds and that one of the proline rings is significantly disordered.[14]

The proline C_β and C_γ spin–lattice (T_1) relaxation times (Table II) provide strong evidence that the disorder observed in the X-ray study is due to motion of one of the proline rings in the peptide. Table II shows that the Pro-2 T_1 values are an order of magnitude shorter than the corresponding Pro-1 T_1 values. This result indicates that the Pro-2 ring is considerably more flexible than the Pro-1 ring in that the spectral densities in the range of the Larmor frequency are much larger for the Pro-2 C_β and C_γ carbons than for Pro-1.

An estimate of the correlation time for the Pro-2 ring motion is made as follows: First, in accordance with the X-ray data[14] we assume a model in which the proline γ-carbon jumps between two equally populated sites. Second, the difference in angle (2θ) between C_γ–H bonds in the two sites is calculated from the coordinates of the Pro-2 C_γ and H_γ atoms.[14] This calculated value of 2θ is 60°. Finally, since the proline γ-carbon is bonded to two protons and since aliphatic carbons have chemical shift anisotropies generally less than 60 ppm, it is reasonable to assume[22] that the ^1H–^{13}C dipolar mechanism is responsible for relaxing the Pro-2 C_γ spin. We have used the approximate expression for the magic-angle spinning T_1[23] along with the measured value of T_1 of 3.5 s (Table II) to get the two possible values of the correlation time τ_c, 1.2×10^{-11} and 2.6×10^{-7} s. The motion of the Pro-2 ring also causes a substantial reorientation of the C–H bonds at the adjoining C_β carbon. This motion produces comparable carbon T_1's at both C_γ and C_β (Table II); thus there is little doubt that the assignments of the C_β and C_γ resonances at the two proline sites are correct.

To resolve the ambiguity between the two correlation times just calculated for the Pro-2 C_γ carbon, the expected T_2 values corresponding to these correlation times were also calculated. A τ_c value of 2.6×10^{-7} s corresponds to a T_2 of 3 ms, which is a factor of 5 less than that observed. Although contributions to T_2 from sources other than molecular motion[24] are present in these spectra, and although other slower modes of molecular motion could, in principle, contribute to T_2, neither of these possible contributions to T_2 can explain an observed T_2 *longer* than that expected from the τ_c since it is assumed that this τ_c describes the fastest motion. Thus, we conclude that the Pro-2 ring is undergoing fast reorientation over a 60° range ($2\theta = 60°$) with a correlation time of ca. 1.2×10^{-11} s. At that correlation time, this motion yields a T_2 which contributes less than a 1-Hz broadening to the line width. The fact that T_2 for the Pro-2 C_γ carbon corresponds to a 19-Hz line width is undoubtedly related to the influence of other broadening mechanisms referred to earlier. An analysis of the particular T_2 contributions is beyond the scope of this paper. Suffice it to say that the T_2 and line-width data combined suggest that the contribution to the Pro-1 and Pro-2 C_β and C_γ carbon line width from chemical shift dispersion and/or residual ^{13}C–^{14}N dipolar couplings is at most 0.2 ppm. In other words, the major line-width contributions are those sensed in the T_2 measurements.

Our studies show that $\Delta\delta_{\beta\gamma}$ measurements are reliable indicators of Xxx–Pro peptide bond conformation in solids and thus can be used to compare conformations of peptides in solution and in crystalline powder forms. Furthermore, they demonstrate that the disorder observed in the crystal structure of *cyclo*(Gly-Pro-D-Ala)$_2$ is a consequence of molecular motion of one proline ring in the peptide.

Acknowledgment. We thank Anita Go for synthesizing all the peptides used in the present study.

Registry No. *cyclo*(Val-Pro-Gly)$_2$, 56777-37-8; *cyclo*(Phe-Pro-D-Ala)$_2$, 85761-33-7; *cyclo*(Gly-Pro-D-Ala)$_2$, 69854-33-7.

(22) Mehring, M. *NMR: Basic Princ. Prog.* **1976**, *11*, 140–157.
(23) Torchia, D. A.; Szabo, A. *J. Magn. Reson.* **1982**, *49*, 107–121.
(24) VanderHart, D. L.; Earl, W. L.; Garroway, A. N. *J. Magn. Reson.* **1981**, *44*, 361–401.

Inhibition of Water-Catalyzed Ester Hydrolysis in Hydrophobic Microdomains of Poly(methacrylic acid) Hypercoils

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Abstract: The water-catalyzed hydrolysis of *p*-methoxyphenyl dichloroacetate (**1**) and 2,2-dichloropropionate (**2**) in aqueous solution at 25 °C is strongly retarded by neutral atactic (at) and syndiotactic (st) poly(methacrylic acid) (PMAA), but not by poly(acrylic acid) and poly(*N*-vinylpyrrolidone). The rates and thermodynamic activation parameters are consistent with binding of the substrates to hydrophobic microdomains within the PMAA hypercoil. A conformational transition of PMAA to an extended coil leads to disappearance of the rate inhibition. This transition is induced either by ionization of PMAA or, at constant pH (ca. 3), by addition of urea and can be monitored by potentiometric titrations. Solubility measurements employing the water-insoluble dye Orange OT further established hydrophobic bonding to neutral at-PMAA. Whereas inhibition of the hydrolysis of **1** and **2** in water in the presence of hydrophobic cosolvents or micelles is characterized by initial-state stabilization, it appears that the inhibition by at- and st-PMAA primarily involves destabilization of the transition state. The effect of PMAA may be explained in terms of a lack of water penetration into the hydrophobic microdomains.

Many enzyme-catalyzed hydrolysis reactions occur at hydrophobic active sites,[1] where the access and local concentration of water molecules is restricted and the substrate reactivity modified by hydrophobic interactions.[2] In an attempt to gain insight into these factors with model systems, we have investigated the neutral (i.e., water-catalyzed) hydrolysis of the acyl-activated esters **1** and **2**[4] in the presence of neutral atactic (at) and syndiotactic (st)

(1) (a) Walsh, C. "Enzymic Reaction Mechanisms"; Freeman: San Francisco, 1979. (b) Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219.
(2) Of course, the total binding potential also includes contributions from van der Waals forces, which are difficult to separate quantitatively from classical, solvent-induced hydrophobic interactions.[3]
(3) Ben-Naim, A. "Hydrophobic Interactions"; Plenum: New York, 1980; Chapters 1 and 5.
(4) The reaction proceeds via rate-determining nucleophilic attack of water on the ester carbonyl group: (a) Jencks, W. P.; Carriuolo, J. J. *J. Am. Chem. Soc.* **1961**, *83*, 1743. (b) Fife, T. H.; McMahon, D. M. *Ibid.* **1969**, *91*, 7481.

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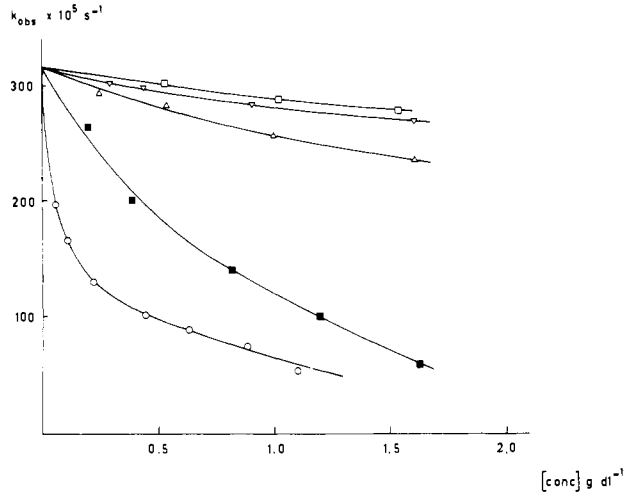

Figure 1. Pseudo-first-order rate constants (k_{obsd}) for the neutral hydrolysis of **1** in water in the presence of at-PMAA (■), st-PMAA (○), PAA (△), methacrylic acid (▽), and PVP and isobutyric acid (both □) at 25 °C and pH ca. 2.5.

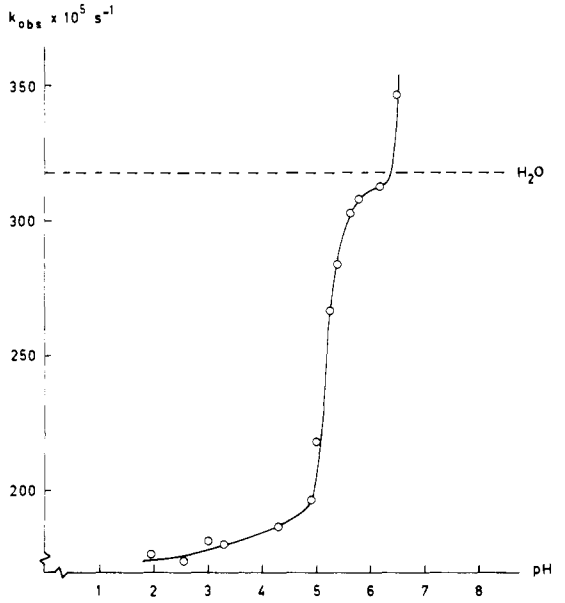

Figure 2. Pseudo-first-order rate constants (k_{obsd}) for the neutral hydrolysis of **1** in water containing 0.5 g dL^{-1} at-PMAA as a function of pH (25 °C).

poly(methacrylic (PMAA). Both forms of PMAA are known to form hydrophobic microdomains within their hypercoils[5,6] as a

$$RCCl_2CO_2C_6H_4OMe\text{-}p + H_2O \rightarrow$$
$$\mathbf{1}, R = H \qquad RCCl_2CO_2H + HOC_6H_4OMe\text{-}p$$
$$\mathbf{2}, R = Me$$

result of intramolecular hydrophobic interactions between the methyl groups. In this paper we present evidence that the inhibition of the hydrolysis of **1** and **2** can be interpreted in terms of binding of the esters to these relatively dry regions within the polymer hypercoils.

Results and Discussion

Figure 1 shows pseudo-first-order rate constants (k_{obsd}) for neutral hydrolysis of **1** in aqueous solutions containing varying

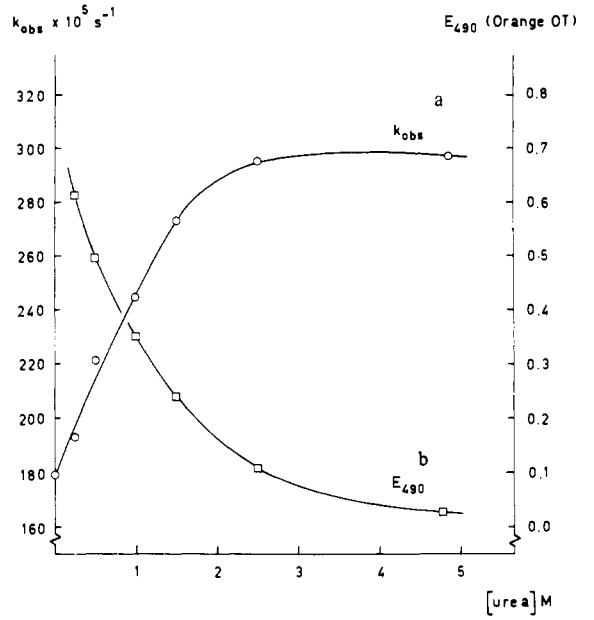

Figure 3. Effect of urea on (a) the pseudo-first-order rate constants (k_{obsd}) for the neutral hydrolysis of **1** in water in the presence of 0.5 g dL^{-1} at-PMAA and (b) E_{490} for Orange OT in water in the presence of 0.5 g dL^{-1} at-PMAA (25 °C, pH 3.3–3.8).

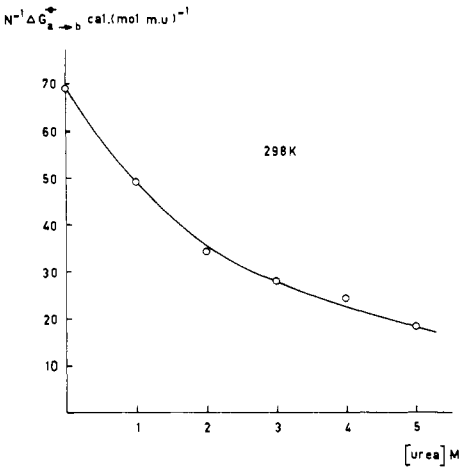

Figure 4. $\Delta G_{a\rightarrow b}^{\ddagger\circ}/N$ for at-PMAA as a function of the concentration of urea (at 25 °C).

concentrations of at- and st-PMAA.[7] The strong rate retardations contrast with the small effects induced by poly(acrylic acid) (PAA), poly(*N*-vinylpyrrolidone) (PVP), and the low molecular weight additives. Similar results were obtained for the hydrolysis of **2**. We submit that the rate inhibitions by at- and st-PMAA are due to hydrophobic bonding of the substrates in the hydrophobic microdomains of these polymers. PAA and PVP[8] do not form highly compact conformations. Analysis of the rate inhibition by at-PMAA in terms of Menger's enzyme model[9] provides the ratio of the rate constants (at 25 °C) in the aqueous phase (k_{obsd}^{w}) and in the hydrophobic domains (k_{obsd}^{HD}) for hydrolysis of **1** and **2** (**1**, $k_{obsd}^{w}/k_{obsd}^{HD} = 8.0$; **2**, $k_{obsd}^{w}/k_{obsd}^{HD} = 5.9$) as well as the ratio of the binding constants for **1** and **2** ($K_2/K_1 = 1.16$, $\Delta\Delta G^{\circ} = 86$ cal mol^{-1}, 25 °C). The latter ratio is in accord with the higher hydrophobicity of **2**.

(5) Katchalsky, A.; Eisenberg, H. *J. Polym. Sci.* **1951**, *6*, 145.
(6) (a) Leyte, J. C.; Mandel, M. *J. Polym. Sci., Part A* **1964**, *2*, 1879. (b) Mandel, M.; Stadhouder, M. G. *J. Makromol. Chem.* **1964**, *80*, 141. (c) Recently, a similar conformational transition was observed for poly(ethacrylic acid) (PEA): Sugai, S.; Nitta, K.; Ohno, N.; Nakano, H. *Colloid Polym. Sci.* **1983**, *261*, 159.
(7) In water, k_{obsd} for **1** and **2** is pH independent between pH 2.0 and 5.5.
(8) There is controversy about the effect of PVP on the three-dimensional hydrogen-bond network of water: (a) Glasel, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 375. (b) Jellinek, H. H. G. In "Water and Aqueous Solutions"; Horne, R. A., Ed.; Wiley: London, 1972; Chapter 3.
(9) Menger, F. M.; Portnoy, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 4698. The applicability of this model will be discussed in a future publication.

Table I. Thermodynamic Activation Parameters for the Neutral Hydrolysis of 1 and 2 in Aqueous Solutions of at-PMAA at 25 °C

compd	[at-PMAA], g dL^{-1}	$10^5 k_{obsd}$, s^{-1}	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	0.00	318	20.85	8.2	−42
	0.20	264	20.96	9.0	−40
	0.40	201	21.12	10.8	−35
	0.82	140	21.34	12.6	−29
	1.63	58.8	21.85	15.5	−21
2	0.00	117	21.45	7.6	−46
	0.22	89.8	21.61	9.6	−40
	0.39	71.0	21.75	10.9	−36
	0.70	53.3	21.92	13.0	−30
	1.00	38.5	22.11	15.1	−24
	1.65	22.2	22.44	17.4	−17

The effect of pH on the inhibition by at-PMAA of the hydrolysis of **1** (Figure 2) shows that above pH ca. 4.5 k_{obsd} rises sharply to the rate constant in pure water.[7] In the same pH region PMAA undergoes a conformational transition from a hypercoil to a random coil.[5,6] Above pH 6 there is a further rate acceleration due to hydroxide ion catalysis.

A similar rate increase for hydrolysis of **1**, but now at a constant pH of ca. 3.5, could be induced by addition of up to 5 M urea (Figure 3). In the absence of at-PMAA, urea has almost no effect (k_{obsd} = 331 × 10^{-5} s^{-1} in 6 M aqueous urea). Potentiometric titrations confirm the destabilizing effect of urea on the hypercoils of at- and st-PMAA.[10] In water the Gibbs free energy (at 25 °C) for the compact → random coil transition per molecular unit ($\Delta G_{a\rightarrow b}^{\ominus}/N$) amounts to 143 ± 5 cal(mol mu)$^{-1}$ for st-PMAA and 69 ± 5 cal(mol mu)$^{-1}$ for at-PMAA.[11] The effect of urea on $\Delta G_{a\rightarrow b}^{\ominus}/N$ is graphically shown in Figure 4.

The ability of neutral at-PMAA to bind relatively apolar solutes[12] was further demonstrated by solubility measurements using the hydrophobic dye Orange OT.[13] The solubility of this dye (proportional to the extinction of a saturated solution at 490 nm, E_{490}) increases almost linearly with [at-PMAA] up to at least 2 g dL^{-1} at pH ca. 3.[14] No significant solubilization occurs in the presence of PAA. The effect of urea on E_{490} in the presence of at-PMAA is also shown in Figure 3 and illustrates the decreased propensity for hydrophobic bonding of the dye upon transition to the random coil.

Isobaric activation parameters for hydrolysis of **1** and **2** in the presence of at-PMAA are listed in Table I. The changes in $\Delta G^{\ddagger}$ conceal much larger and partly compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, as is often observed for hydrolysis in highly aqueous binary solvents.[15] However, in sharp contrast to typically aqueous (TA) solutions,[16] the initial addition of at-PMAA leads to an *increase* of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (for hydrolysis of **2** in *t*-BuOH–H_2O at n_{H_2O} = 0.95, k_{obsd} = 7.97 × 10^{-5} s^{-1}, $\Delta H^{\ddagger}$ = 5.3 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = −59 eu).[17] Presumably, in the presence of at-PMAA transition state rather than initial state solvation effects exert the dominating influence on the rates. Therefore, we suggest that the rate-controlling feature is the lack of sufficient water penetration into the hydrophobic microdomains leading to deficient hydration of the transition state. That this does not lead to dramatic rate retardations is due to the largely compensating favorable changes of the $T\Delta S^{\ddagger}$ contribution. Rate-modulating effects originating from partial $\Delta H^{\ddagger}/\Delta S^{\ddagger}$ compensation are quite characteristic for reactions occurring in the fluctuating network of water–water hydrogen bonds.[15,18,19]

The present results demonstrate that hydrophobic cosolvents (in TA solutions),[15] micelles[20] and macromolecules carrying hydrophobic binding sites may all affect the rates of hydrolysis reactions in a rather similar way. But these hydrophobic effects do not necessarily have the same origin since they may primarily affect either the initial state or the transition state. These considerations also introduce a fundamental problem in the design of enzyme mimics. For those reactions in which charges are developed during the activation process, binding of the substrate(s) at a hydrophobic binding site of the model system will be accompanied by rate inhibition. Therefore, in order to obtain efficient catalysis, the enzyme mimic must be constructed in such a fashion that the transition state can be stabilized by dipolar interactions (including hydrogen bonding) with functional groups located at favorable positions near the binding site.[21]

Further studies of the effects of hydrophobic binding with PMAA and other (bio)macromolecules are in progress.

Experimental Section

Materials. The esters **1** and **2** were prepared by using standard procedures.[4,22] PVP (Kollidon-K90 from BASF, $\bar{M}_v$ = 60.3 × 10^4) was precipitated twice from chloroform–ether. PAA, st-PMAA,[23] and at-PMAA were prepared by standard methods. The $\bar{M}_v$ and tacticity (NMR) of the PMAA's were determined after quantitative conversion into poly(methyl methacrylate) with diazomethane.[5] at-PMAA: $\bar{M}_v$ = 26.3 × 10^4; triad composition, isotactic, 12%; heterotactic, 44%; syndiotactic, 44%. St-PMAA: $\bar{M}_v$ = 6.7 × 10^4; triad composition, isotactic, 0%; heterotactic, 7%, syndiotactic, 93%. 1-(*o*-Tolylazo)-2-naphthol (Orange OT) was synthesized from *o*-toluidine and β-naphthol.[24] The water used in all experiments was demineralized and distilled twice in an all-quartz distillation unit. All solutions were made up by weight.

Kinetic Measurements. Pseudo-first-order rate constants for the neutral hydrolysis of **1** and **2** (k_{obsd}; ± 1.5%) were determined between 25 and 45 °C by following the change in absorbance at 288 nm.[17] About 5 μL of a concentrated stock solution of **1** or **2** in acetonitrile was added to the reaction medium in 1-cm quartz cells placed in the thermostated (±0.05 °C) cell compartment of a Varian Cary-210 spectrophotometer. Substrate concentrations were in the range 10^{-4}–10^{-5} M. The thermodynamic activation parameters were obtained from rate constants at four different temperatures in the range 25–45 °C. Excellent Eyring plots were found. The estimated error in $\Delta G^{\ddagger}$ is ±0.02 kcal mol^{-1}, in $\Delta H^{\ddagger}$ ± 0.3 kcal mol^{-1}, and in $\Delta S^{\ddagger}$ ± 1 eu.

Solubility Measurements. Solutions (5 mL) containing 5 mg of Orange OT were kept at 25 °C for several weeks and stirred occasionally.

(10) Compare: Dublin, P.; Strauss, U. P. *J. Phys. Chem.* **1973**, *77*, 1427.

(11) The following data were reported previously: syn-PMAA ($\bar{M}_w$ = 9.0 × 10^3), $\Delta G_{a\rightarrow b}^{\ominus}/N$ = 185 ± 5 cal(mol **mu**)$^{-1}$; at-PMAA ($\bar{M}_w$ = 3.4 × 10^5), $\Delta G_{a\rightarrow b}^{\ominus}/N$ = 184 ± 6 cal (mol mu)$^{-1}$. No triad compositions were given. See: Crescenzi, V.; Quadrifoglio, F.; Delben, F. *J. Polym. Sci., Polym. Phys. Ed.* **1972**, *10*, 357. For at-PEA, $\Delta G_{a\rightarrow b}^{\ominus}/N$ is much higher than for at-PMAA; see ref 6c.

(12) (a) Barone, G.; Crescenzi, V.; Pispisa, B.; Quadrifoglio, F. *J. Macromol. Chem.* **1966**, *1*, 761. (b) Barone, G.; Crescenzi, V.; Liquori, A. M.; Quadrifoglio, F. *J. Phys. Chem.* **1967**, *71*, 2341. (c) Morcellet-Sauvage, J.; Morcellet, M.; Loucheux, C. *Makromol. Chem.* **1982**, *183*, 839.

(13) Estimated pK_a ca. 10.

(14) Comparison of the E_{490} values at [at-PMAA] = 0.5 g dL^{-1} in H_2O and D_2O reveals that the solubility is higher in D_2O by a factor of 1.6 (25 °C). Strengthening of the hydrophobic bonding in D_2O is also indicated by the increase of the solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) for hydrolysis of **2** from 3.3 in H_2O to 5.6 in D_2O containing 0.5 g dL^{-1} at-PMAA. Under conditions of almost complete binding ([at-PMAA] = 1.5 g dL^{-1}) k_{H_2O}/k_{D_2O} is 3.6. For a discussion of hydrophobic interaction in D_2O, see: Oakenfull, D. G.; Fenwick, D. W. *Aust. J. Chem.* **1974**, *27*, 2149.

(15) Engberts, J. B. F. N. In "Water. A Comprehensive Treatise"; Franks, F., Ed.; Plenum: New York, 1979; Chapter 6.

(16) TA solutions are highly aqueous mixtures of water with a hydrophobic organic cosolvent. Franks, F., in reference 15, 1973, Vol. 2, Chapter 1; 1975, Vol. 2, Chapter 1.

(17) Holterman, H. A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1982**, *104*, 6382.

(18) For a recent discussion of the thermodynamic properties of neutral solutes in water, see: Mirejovsky, D.; Arnett, E. M. *J. Am. Chem. Soc.* **1983**, *105*, 1112.

(19) Initial-state stabilization by hydrophobic interactions in TA solutions is partly attenuated in rate effects because of unfavorable enthalpic contributions.

(20) The binding sites of substrates in the Stern layer of micelles are usually immersed in highly aqueous environments: (a) Menger, F. M.; Yoshinaga, H.; Venkatasubban, K. S.; Das, A. R. *J. Org. Chem.* **1981**, *46*, 415. (b) Fadnavis, N.; Engberts, J. B. F. N. *Ibid.* **1982**, *47*, 152.

(21) Enzymes usually speed hydrolytic reactions at hydrophobic binding sites by general-base catalysis and by electrostatic and/or hydrogen-bonding stabilization of the transition state involving interactions with nearby α-amino acid constituents.

(22) Holterman, H. A. J. Ph.D. Thesis, University of Groningen, The Netherlands, 1982.

(23) Koetsier, D. V. Ph.D. Thesis, University of Groningen, The Netherlands, 1981.

(24) Williams, R. J.; Philips, J. N.; Mysels, K. J. *Trans. Faraday Soc.* **1955**, *51*, 728.

After filtration, the absorbance of the saturated solution was determined at 490 nm.

Potentiometric Titrations were carried out automatically in thermostated (25.00 ± 0.05 °C) titration cells, under an atmosphere of nitrogen.

Registry No. 1, 26921-58-4; **2**, 75265-14-4; (at)(PMAA) (homopolymer), 25087-26-7; (st)(PMAA) (homopolymer), 25750-36-1; poly(acrylic acid) (homopolymer), 9003-01-4; poly(*N*-vinylpyrrolidone) (homopolymer), 9003-39-8; Orange OT, 2646-17-5.

Absolute Configuration of Epoxyeicosatrienoic Acids (EETs) Formed during Catalytic Oxygenation of Arachidonic Acid by Purified Rat Liver Microsomal Cytochrome P-450[1]

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Received November 2, 1983

Abstract: Incubation of arachidonic acid with a reconstituted enzymatic system containing a purified preparation of the major, phenobarbital-inducible form of rat liver microsomal cytochrome P-450, NADPH, cytochrome b_5, and NADPH-cytochrome P-450 reductase affords as the principal products four regioisomeric *cis*-epoxides: 5,6-, 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acids (EETs). Their absolute configurations were established by conversion to the corresponding hydroxyeicosatetraenoic acid (HETE) methyl esters, derivatization with dehydroabiethylisocyanate, and chromatographic analysis. Except for 5,6-EET, the cytochrome P-450 catalyzed epoxidation is highly enantioselective.

A thorough knowledge of the arachidonic acid cascade is vital to our understanding of polyunsaturated fatty acid metabolism and its relationship to physiological and disease processes.[3] Recently, evidence has been presented from studies using reconstituted[4] and microsomal cytochrome P-450[5] as well as intact cells[6] for an additional route to eicosanoids. Designated the epoxygenase pathway,[7a] this route is catalyzed by cytochrome P-450 and is distinct from the well-established lipoxygenase and cyclooxygenase pathways of the arachidonate cascade. In addition to various lipoxygenase-type[8] and ω/ω - 1 oxidation products,[9] the epoxygenase pathway generates several novel metabolites,[4-6] some of which have been shown by us to have potent biological activity in vitro.[7] The validity of these observations has been confirmed with the in vivo detection of epoxygenase metabolites in mammalian tissue.[10]

As part of a comprehensive study of polyunsaturated fatty acid metabolism by cytochrome P-450 and as an aid to structural studies of other epoxygenase metabolites, we report herein the absolute configuration of the arachidonate metabolites 5,6-, 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid (EETs) produced by

Scheme I

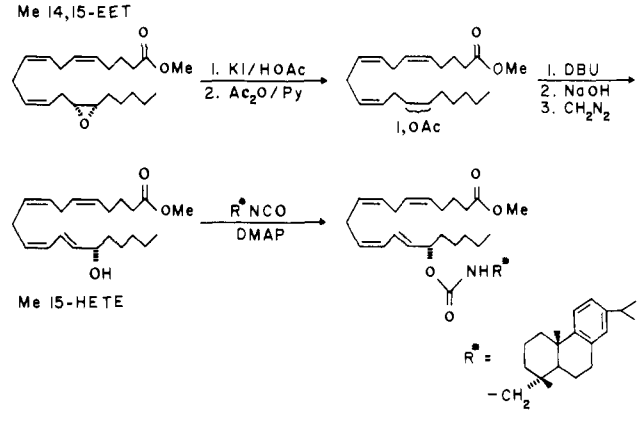

Table I. Enantioselectivity of Arachidonate Epoxygenation

EET	*R*, *S* (%)	*S*, *R* (%)
5, 6	61	39
8, 9	97	3
11, 12	3	97
14, 15	80	20

(1) Presented in part at the 185th ACS National Meeting, Seattle, Washington, March 20-25, 1983.
(2) (a) Molecular Genetics. (b) Internal Medicine. (c) Biochemistry.
(3) Recent reviews: Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, *Aug. 16*, 30-44. Samuelsson, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 902-910. Bailey, D. M.; Casey, F. B. *Ann. Rep. Med. Chem.* **1982**, *17*, 203-217.
(4) (a) Capdevila, J.; Parkhill, L.; Chacos, N.; Okita, R.; Masters, B. S. S.; Estabrook, R. W. *Biochem. Biophys. Res. Commun.* **1981**, *101*, 1357-1363. (b) Oliw, E. H.; Guengerich, F. P.; Oates, J. A. *J. Biol. Chem.* **1982**, *257*, 3771-3781.
(5) (a) Capdevila, J.; Chacos, N.; Werringloer, J.; Prough, R. A.; Estabrook, R. W. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5362-5366. (b) Chacos, N.; Falck, J. R.; Wixtrom, C.; Capdevila, J. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 916-922. (c) Morrison, A. R.; Pascoe, N. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7375-7378.
(6) Oliw. E. H.; Moldéus, P. *Biochim. Biophys. Acta* **1982**, *721*, 135-143.
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