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MECHANISTICALLY OPTIMIZED INTRAMOLECULAR CATALYSIS IN THE HYDROLYSIS OF ESTERS. GLOBAL CHANGES INVOLVED IN MOLECULAR REACTIVITY

SANTIAGO F. YUNES,[1] JOSÉ C. GESSER,[1] HERNAN CHAIMOVICH[2] AND FARUK NOME[1]*

[1] *Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC 88040-900, Brazil*
[2] *Instituto de Química, Universidade de São Paulo, São Paulo, SP, Brazil*

The hydrolysis of the 2′,2′,2′-trifluoroethyl monoester of 1,8-naphthalic acid (1) proceeds via the monoanion with the intermediate formation of the corresponding anhydride. The rate constant for the formation of 1,8-naphthalic anhydride (2) is *ca* 2500 times faster than its rate of hydrolysis. The isotope effect in the plateau region and theoretical calculations at the PM3 level suggest that elimination of the alkoxide is the rate-limiting step for the reaction. Accordingly, decomposition of the isopropyl monoester of naphthalic acid proceeds 10^4 times slower than the spontaneous decomposition of 1. The remarkably high rate of monoester decomposition derives from the special configuration of the substrates and important contributions that arise from relief of torsional strain, which clearly includes electron redistribution due to the decrease in steric hindrance to resonance and the fact that proximity obviates solvation. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

In recent decades, the fascination with enzyme catalysis has led chemists on a continuing search for simpler models where the rates and selectivity of biological catalysts are mimicked. Intramolecular accelerations are classical and simple examples of this type of work.[1–3] At present, however, there is no comprehensive theory, accepted by all involved, that can explain, or predict, the factors by which an enzymatic and/or intramolecular reaction will be faster (or slower) than the intermolecular counterpart.[4–10] Despite complications, quantitative comparisons between intra- and intermolecular reactions are commonly expressed as effective molarities (*EM*) taken as the ratios of the intramolecular rate constant (k_1, s^{-1}) to the intermolecular rate constant (k_2, $lmol^{-1}\,s^{-1}$), i.e. $EM = k_1/k_2$ (M).[2] The wide range of *EM*s for different types of reactions has generated descriptive theories where the putative causes of large *EM*s range from simple proximity to spatiotemporal descriptions.[4–11] In this paper, we report and analyze the remarkably high rate of hydrolysis of monoesters of 1,8-naphthalic acid, a system which we believe contributes significantly to the understanding of reactivity in biological systems.

EXPERIMENTAL

Materials. The isopropyl monoester of 1,8-naphthalic acid was prepared by reacting 1,8-naphthalic anhydride (**2**) with sodium isopropoxide in propa-2-nol. The reaction mixture was treated with HCl, extracted with $CHCl_3$ and finally the solvent was removed under vacuum. IR (KBr), ν_{max} 3444, 2976, 1703, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz), δ 8·17–7·26 (m, Ar*H*, 6 H), 5·33 (septuplet, CH, 1 H), 1·41 ppm (d, CH_3, 6 H); ^{13}C NMR (DMSO, 200 MHz), δ 174·2, 168·5, 134·4, 133·2, 132·2, 130·8, 130·6, 130·1, 128·8, 125·8, 125·5, 125·2, 69·4, 21·9, 21·9 ppm; analysis, calculated for $C_{15}H_{14}O_4$, C 69·76, H 5·46, O 24·78; found, C 69·58, H 5·39, O 25·02%.

The 2′,2′,2′-trifluoroethyl monoester of 1,8-naphthalic acid (**1**) was prepared *in situ* by a procedure identical with that described above. IR, ν_{max} 2977, 2946, 1735, 1568 cm^{-1}; ^{1}H NMR (CF_3CH_2OH, 200 MHz), δ 8·15–7·45 (m, Ar*H*, 6 H), 4·75 ppm (q, CH_2, 2 H); ^{13}C NMR (CF_3CH_2OH, 200 MHz), δ 177·1, 167·8, 135·8, 133·8, 132·8, 130·1, 129·7, 129·2, 128·0, 125·3, 124·5, 124·3, 123·9, 59·7 ppm.

Methods. Rates of formation of the anhydride products from monoesters of 1,8-naphthalic acid were followed

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spectrophotometrically at the wavelength maximum of **2** (340 nm) by using a Hewlett-Packard HP8452A spectrophotometer fitted with a thermostated water-jacketed cell holder. All solutions were prepared using distilled, demineralized water, which was boiled and cooled under nitrogen to remove dissolved CO_2. Reaction was initiated by injection of 10 μl of *ca* 10 mM solutions of substrates into 3 ml of buffers solution. Absorbance versus time data were stored directly on a microcomputer using a Microquímica 16 bit A/D interface board. First-order rate constants, k_{obs}, were estimated from linear plots of $\ln(A - A_t)$ against time for at least 90% reaction using an iterative least-squares program; correlation coefficients, *r*, were >0·999 for all kinetic runs.

RESULTS AND DISCUSSION

The velocity of the decomposition of the monoester **1**, when compared with the rate of decomposition of the corresponding anhydride **2**, permitted the demonstration of the formation of the intermediate. The calculated rate constants for the descending limb of the kinetics shown in Figure 1 (inset) are identical with those measured with authentic 1,8-naphthalic anhydride. It is clear, therefore, that the hydrolysis of the 2′,2′,2′-trifluoroethyl monoester of 1,8-naphthalic acid occurs with the intermediate formation of the corresponding anhydride. The rate constant for the first step, which leads to the formation of naphthoic anhydride, is *ca* 2500 times faster than the hydrolysis of **2**. Hence, the rate constant for the *trans*-acylation reaction can be obtained without interference from the hydrolysis of the anhydride (Scheme 1). The pH–rate constant profile for the hydrolysis of **1** exhibits a plateau around pH 4–6 (Figure 1), which indicates that the spontaneous decomposition of the monoester monoanion is the main mechanistic pathway (Scheme 1).

The pH–rate constant profile for the hydrolysis of **1** can be quantitatively fitted using equation (1), which satisfies Scheme 1:

$$k_{obs} = k_1/(1 + [H^+]/K_a) \quad (1)$$

Treatment of the experimental data with equation (1) renders values of $k_1 = 1{\cdot}49 \times 10^{-1}\ s^{-1}$ and a kinetic $pK_a = 3{\cdot}47$. The pK_a obtained agrees well with that expected for **1** based on $pK_a = 3{\cdot}67$ for 1-naphthoic acid[12] and the expected substituent effect for the electron-withdrawing 8-substituent. The absence of a kinetic solvent isotope effect ($k_{H_2O}/k_{D_2O} = 1{\cdot}01$ in the plateau region) is consistent with either the formation or the decomposition of the tetrahedral intermediate as the rate-limiting step of the reaction, since in both cases either a hydrogen atom or a water molecule is not involved in the route to the transition state.

Despite all the difficulties in comparing bimolecular and monomolecular reactions, there is general agreement that at least the reaction pathways of the reactions to be compared must be identical. Using the commonly used reference phthalic acid monomethyl ester (*EM* is assumed to be 10^9 M for all phthalate esters; the reference intermolecular reaction is the nucleophilic attack of acetate on phenylacetate[2]), the *EM*s obtained with **1** are in excess of 10^{13}. Indeed, the rate constant in the plateau region (k_1) for the formation of the anhydride from the monoester of **1** is 10^4 times faster than

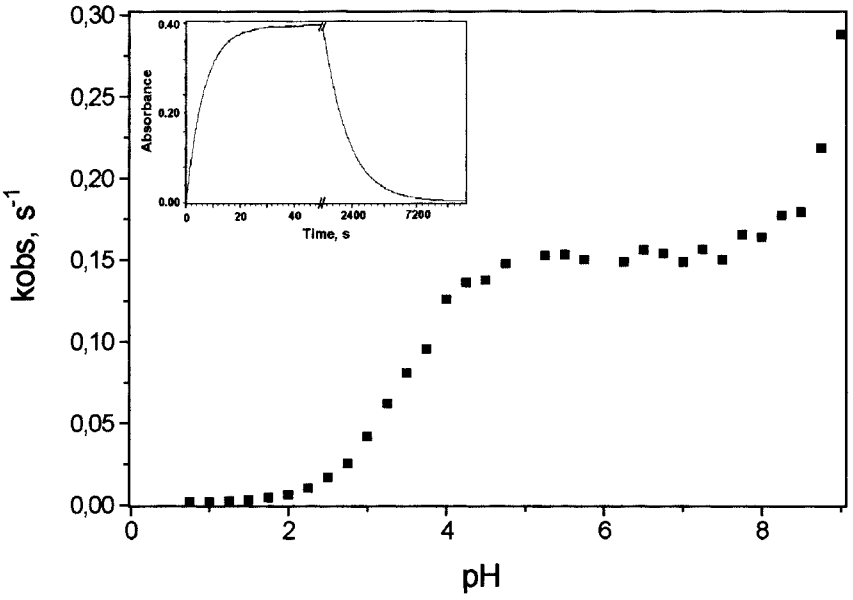
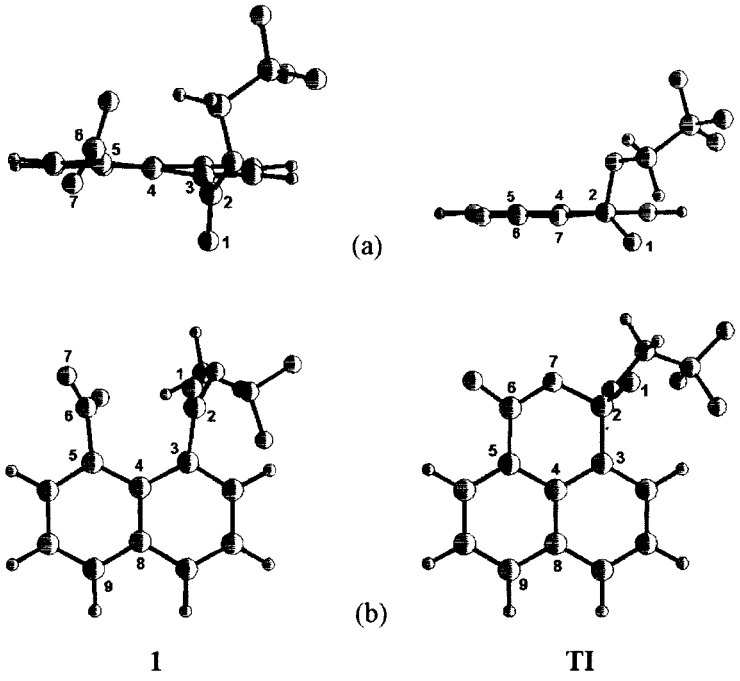


Figure 1. Effect of pH on the first-order rate constant for the hydrolysis of the 2′,2′,2′-trifluoroethyl monoester of 1,8-naphthalic acid. The inset shows the absorbance at 340 nm as a function of time

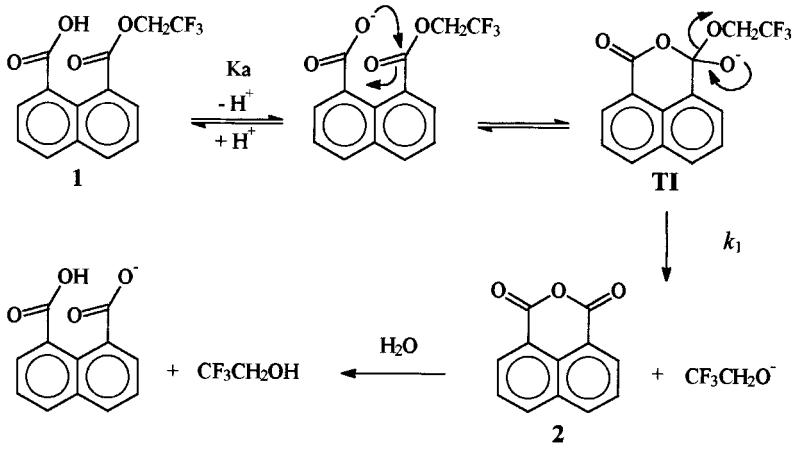
the hydrolysis of 2′,2′,2′-trifluoroethyl hydrogenphthalate,[13] 150 times faster than the hydrolysis of 2′,2′,2′-trifluoroethyl hydrogen-3,6-dimethylphthalate[14] and comparable to the highest rate accelerations obtained for similar reactions in highly strained or sterically constrained systems.

Semi-empirical quantum chemical calculations of the intramolecular reaction at the PM3 level,[15] using the MOPAC[16] program package (version 6·0), are highly informative. In all cases, the PRECISE keyword was used and full geometry optimization was carried out (Fletcher–Powell algorithm) without symmetry constraints. The location of the transition state was done using the Eigenvector Following method. The characterization of both kinds of stationary points, minimal and transition states, was carried out by diagonalizing their Hessian matrices and looking for zero and one-negative eigenvalues, respectively. Examination of the contour plots, obtained under the conditions described above, indicates that neither the carboxylate nor the ester groups in **1** are in the plane of the naphthalene ring (Figure 2). The distance between the van der Waals radius of the carboxylate oxygen atom (O-7) and the carbonyl carbon (C-2) in the ester moiety is 0·17 Å, which is smaller than the van der Waals radius of water, precluding the presence of a solvent molecule between the reactive groups. Also, similarly to the case of 1,8-diaminonaphthalenes, there is a lack of planarity of the naphthalene ring.[17] In the route to the transition state, as the carboxylate anion approaches the neighboring carbonyl, the energy increases and the transition state for the formation of the tetrahedral intermediate is reached. The calculated enthalpy of activation [5·19 kcal mol^{-1} (1 kcal = 4·184 kJ)] is well below the experimentally determined activation energy ($\Delta H^{\neq} = 14{\cdot}45$ kcal mol^{-1} and $\Delta S^{\neq} = -12{\cdot}9$ e.u. were experimentally determined for the hydrolysis of **1** in the plateau region). In the tetrahedral intermediate (TI), formed in the initial addition reaction, the torsional strain has been considerably relieved, allowing the positioning of the



Selected torsion angles (degrees)		
	1	**TI**
O_1-C_2-C_3-C_4	80.2	131.1
O_7-C_6-C_5-C_4	-114.9	-0.7
C_5-C_4-C_8-C_9	-7.5	0.8
C_3-C_4-C_8-C_9	172.8	-179.2

Figure 2. Projection of **1** and **TI** illustrating the lack of planarity of the naphthalene ring. (a) Lateral view and (b) projection in the naphthalene ring plane. Selected torsional angles are given



Scheme 1

carbonyl group coplanar with the aromatic ring. Also, the coplanarity of the naphthalene ring is increased considerably. When the decomposition of TI is examined, a value of 13·99 kcal mol^{-1} is obtained for the enthalpy of activation (calculated enthalpies of activation are generally smaller than the experimental values), a result which clearly indicates that the rate-limiting step for the *trans*-acylation corresponds to the unimolecular decomposition of TI.

The absence of isotopic effect in the plateau region is consistent with the theoretical calculations and suggests that the reaction should depend strongly on the nature of the leaving group. Indeed, decomposition of the isopropyl monoester of naphthalic acid[11] ($k = 1{\cdot}5 \times 10^{-4}$ s^{-1} at 50 °C) proceeds 10^4 times slower than the spontaneous decomposition of **1**.

In the present case, the remarkably high rate of monoester decomposition derives from the very special configuration of the substrates. Even the simple PM3/MOPAC calculations described above show that in substrate **1** the steric crowding of the reaction region is sufficient to exclude water molecules from part of the reaction region is sufficient to exclude water molecules from part of the reaction center, therefore generating a highly reactive carboxylate oxygen. Although solvent can hydrogen bond both of the reactive moieties of the substrate, there is not enough space to position a water molecule between the groups and, therefore, the nucleophilic attack becomes facile. Reaching the tetrahedral intermediate, a considerable part of the torsional strain is relieved. As a consequence, decomposition of the tetrahedral intermediate is then rate limiting.

The central point here, that has led to much discussion in trying to define the source of acceleration in intramolecular catalysis, is that is certainly involves a matter of distance and time. Here we are not proposing, as Menger clearly stated, that 'intramolecular reactions occur at enzyme-like rates when van der Waals contact distances are imposed for finite times upon reactive groups.[10] Indeed, for any reaction to occur the reactive partners must initially approach the van der Waals sum of radii and proceed further to the equilibrium bonding distance. Certainly, a considerable part of the rate acceleration stems from putting the reagents at an appropriate distance for the reaction to occur. It is likely that, owing to the high amount of energy expended on desolvation of a carboxylate group, the attack of a dissociated carboxylic acid on an unactivated ester in water is essentially forbidden, in aqueous solutions, and no bimolecular counterpart for this reaction has therefore been described. In fact, general base catalysis is the natural mechanistic option in aqueous solutions.

Enzymes and nature do not define proximity in terms of a definitive number of ångstroms between the amino acid residue participating in the reaction and the reactive center in the substrate. In aspartic proteases a single water molecule is bridging two aspartic residues,[1] and the 'proximity' in this particular case is such that it allows the nucleophile to become activated, and in a proper spatial orientation, only on the reaction coordinate leading to the transition state.

Clearly, the chemistry which actually occurs in aqueous solutions for the 'analogous bimolecular reaction' is completely different from the chemistry in our model system, from a mechanistic point of view. What we are stating here is that enzyme-like catalytic accelerations are experimentally obtained only when a variety of factors affect the reaction rate. In this sense, only full comprehension of the 'global changes involved in molecular reactivity' will finally lead to a proper understanding of enzyme catalysis. Clearly, the rate of any particular reaction cannot be analyzed in terms of the reactive groups only. Rate accelerations may be caused by a wide variety of factors related to structural changes and electron redistribution processes along the reaction coordinate, involving the complete molecule and not only the reactive center. In accord with the essence of the transition-state theory, unless all the molecular changes involved along the reaction coordinate are taken into account, we will not understand

why reagents lead to products at enzyme-like rates. In our case, important contributions arise from the relief of torsional strain, which clearly includes electron redistribution due to the decrease in steric hindrance to resonance, and the fact that proximity obviates solvation. Clearly, improvement of our understanding of enzyme catalysis, through the study of model systems, involves a full comprehension of the global changes in electronic distribution on the route to the transition state.

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