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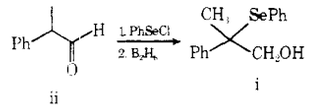

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Secondary Isotope Effects in Intramolecular Catalysis. Mono-*p*-bromophenyl Succinate Hydrolysis[1]

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Kinetic isotope effects have been measured for the intramolecular nucleophilic carboxylate-catalyzed hydrolysis, k_s, of mono-*p*-bromophenyl succinate and mono-*p*-bromophenyl succinate-d_4. The resulting isotope effect, $k_s^{H_4}/k_s^{D_4}$, equals 1.035, a *normal* effect. This is contrary to what is expected for acyl transfer reactions where the transition-state structure resembles a tetrahedral intermediate. However, the direction of the isotope effect is in agreement with a transition-state structure resembling succinic anhydride. Combining this result with previous kinetic and structural studies, a detailed transition-state structure for the hydrolysis reaction is proposed.

Intramolecularly catalyzed reactions have been studied as chemical models for reactions of an enzyme–substrate complex.[3] An additional reason to study this class of reactions is that it represents the simplest reactions in which detailed pictures of transition-state structures can be developed. Transition-state structure elucidation is facilitated in these reactions since the "diffusion complex" is already formed and thus its structure is defined.

To resolve in great detail the transition-state structure for succinate half-ester hydrolysis is an important goal for a variety of biochemical reasons. Succinates are a major tool for the reversible derivitization of bioactive agents for the purpose of improving their chemical and physical properties as drugs (thus for the design of prodrugs[4]). Hydrolytic rate studies of half-esters of succinate and of various succinate derivatives have been essential in developing theories of catalytic power.[3,5]

Half-esters of succinic acid exhibit large rate accelerations in the comparison of their intramolecularly catalyzed hydrolysis to biomolecular carboxylate-catalyzed ester hydrolysis.[6] Additional rate enhancements are observed when alkyl groups are substituted in the succinyl backbone.[7,8] Rate increases brought about by alkyl substitution are well-known phenomena in other intramolecular reactions.[9,10]

A further essential contribution to the study of these rate effects would be to examine the transition state. The kinetic isotope effects method offers a distinct advantage over alkyl substitution in that substitution of one isotope for another

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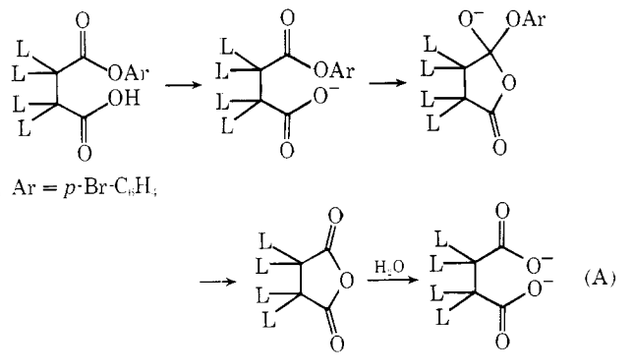
Table I. Observed First-Order Rate Constants for Hydrolysis of 5×10^{-4} M *p*-Bromophenyl Succinate and *p*-Bromophenyl Succinate-d_4 at 25.00 ± 0.02 °C in 50/50 v/v Dioxane/Water, μ = 0.65

pH	$10^6 k_{obsd}$, s^{-1} 1, L = H[b]	$10^6 k_{obsd}$, s^{-1} 1, L = D[c]
4.71	751.3, 764.0, 757.6, 754.1, 756.6, 745.6, 767.4, 760.8, 765.8, 764.1	725.1, 735.5, 724.2, 739.8, 720.9, 724.4, 736.0, 732.1, 728.3, 728.6
Mean	758.7 ± 2.2[a]	730.4 ± 1.9
5.10	1686, 1676, 1714, 1689, 1700, 1717, 1690, 1687	1661, 1668, 1649, 1648, 1662, 1635, 1633, 1669
Mean	1695 ± 5.1	1653 ± 5
5.84	5313, 5331, 5282, 5370, 5333, 5296, 5392	5140, 5196, 5223, 5148, 5189, 5222, 5210
Mean	5331 ± 15	5190 ± 13
6.10	6584, 6687, 6633, 6586, 6691, 6687, 6621	6448, 6411, 6405, 6373, 6381, 6433, 6443
Mean	6641 ± 18	6413 ± 11
6.58	8746, 8735, 8550, 8790, 8626, 8563	8245, 8191, 8278, 8133, 8199, 8196, 8187
Mean	8668 ± 42	8204 ± 17
6.84	9194, 9149, 9166, 9120, 9130, 9135, 9153, 9122	8857, 8878, 8863, 8852, 8874, 8879, 8889, 8880
Mean	9146 ± 9	8872 ± 5
7.05	9475, 9516, 9465, 9523, 9494, 9549, 9492, 9492	9179, 9254, 9247, 9271, 9214, 9182, 9235, 9223
Mean	9501 ± 10	9226 ± 12
7.20	9600, 9564, 9513, 9497, 9481, 9631, 9594, 9595	9234, 9294, 9282, 9262, 9351, 9192, 9226, 9314
Mean	9559 ± 20	9269 ± 18

[a] Standard error of estimate. [b] Registry no. 29493-07-0. [c] Registry no. 65150-65-4.

does not change the electronic character of the reaction.[11] Consequently, isotopes are a powerful tool for probing the structure of a transition state. Development of pictures of the catalytic transition-state structure for these intramolecular reactions should greatly aid in uncovering the reasons for such large accelerations.

Previous kinetic work[7] on hydrolysis of mono-*p*-bromophenyl succinate, 1 (L = H), revealed an intramolecular catalyzed reaction when the carboxyl was ionized (eq A). This



1, Ar = *p*-Br-C_6H_4

(A)

study firmly established a mechanism proceeding via a rate-limiting formation of a cyclic anhydride intermediate.

This paper reports the measurement of a β-secondary kinetic isotope effect resulting from the replacement of protium atoms by deuterium atoms on the succinyl backbone (**1**, L = H vs. **1**, L = D). The results are used along with data from previous work[7,12] to formulate a transition-state structure for this reaction.

β Secondary Isotope Effects. Shiner[13] and his school have demonstrated the utility of β secondary isotope effects in studies of nucleophilic substitution. It has been shown in a number of cases that for S_N1 reactions (the reaction center is being converted from a tetrahedral carbon to a planar carbocation) when the protons adjacent (β) to the reaction center are replaced with deuterium atoms a decrease in the rate constant occurs; i.e., a *normal* kinetic isotope effect is observed. In carbonyl addition, the reverse is occurring (a planar, somewhat positive reaction center is converted into a more electrically neutral or negative tetrahedral structure) and an *inverse* kinetic isotope effect would be expected. A large number of examples of additions to carbonyl centers suport this expectation.[14] Typically, the equilibrium value for K^H/K^D in creating a tetrahedral center at a carbonyl carbon is 0.95 (hemiketal[14b] and ketal[14d] formation in acetone) to 0.91 (hemiketal formation in cyclopentanone[14b] and ketal formation in acetophenone[14d]) *per deuterium atom*. Most kinetic isotope effects[14c] for addition reactions to carbonyls lie between these values and 1.0. Vibrational-analysis calculations[15] on the addition of hydroxide ion to acetaldehyde and acetaldehyde-d_3 suggest a linear dependence of the magnitude of the inverse isotope effect on the bond order of the forming carbonyl carbon–hydroxide oxygen bond. These results suggest that the magnitude of the β secondary kinetic isotope effect in carbonyl addition reactions is a direct measure of the degree of tetrahedrality about the carbonyl carbon in the rate-determining transition state of biomolecular reactions. For intramolecular acyl transfer reactions, as discussed below, other sources may contribute to the isotope effect.

Experimental Section

Materials. Sodium acetate (NaOAc) and acetic acid (HOAc) were purified as described previously.[16] Potassium chloride (KCl, Baker, reagent grade) was dried in an oven at 130 °C for 24 h. Dioxane was distilled from lithium aluminum hydride. Mono-*p*-bromophenyl succinate was prepared from *p*-bromophenol and succinic anhydride by a method developed for monophenyl succinate.[17] Mono-*p*-bromophenyl succinate-d_4 was prepared in a similar manner from *p*-bromophenol and succinic anhydride-d_4.[18] This half-ester contained 93 atom % D as determined by mass spectral analysis.

Buffer solutions were prepared by mixing an appropriate amount of 0.100 M HOAc in 50/50 v/v dioxane/water with 0.650 M KCl solution and an appropriate amount of 0.100 M NaOAc in 50/50 v/v dioxane/water with 0.650 M KCl. The pH was measured with a combination electrode and the value converted to a_H.

Instrumentation. Rate measurements were made spectrophotometrically, employing a Cary 16 UV–visible spectrophotometer interfaced to a Hewlett-Packard 2100A minicomputer. Output of the photomultiplier tube, consisting of a 60-Hz pulse train of alternating sample and reference pulses, was conveyed to an Analogic 5800N analogue-to-digital converter through a synchronizer circuit which identified the pulses. Fifteen measurements of the height of both reference and sample pulses were averaged across each cycle and values of the absorbance were calculated from the logarithm of the ratio of these averages. Run times were divided into 1000 segments and absorbances were then time-averaged across each segment. Run times were typically 5 half-lives of the particular reaction being observed. The 1000 data points were analyzed by a nonlinear least-squares method to give the observed rate constant. The standard error of estimate for an individual rate constant within a single run was normally ±0.08%.

Kinetics Procedure. Experiments were conducted in thermostated cell holders and were initiated after thermal equilibration. A 6×10^{-2} M ester solution (25 μL) in dioxane was injected into a cu-

Table II. Catalytic Constants and Isotope Effects for *p*-Bromophenyl Succinate-d_4 Hydrolyses[a]

	10^6k_s, s^{-1}			10^6K_a, M		
	h_4	d_4	$k_s^{h_4}/k_s^{d_4}$	h_4	d_4	$K_a^{h_4}/K_a^{d_4}$
Eq 1	9982 (±36)	9641 (±47)	1.035 (±0.006)	1.630 (±0.030)	1.628 (±0.040)	1.001 (±0.031)
Eq 2	9999 (±42)	9650 (±63)	1.036 (±0.008)	1.613 (±0.014)	1.621 (±0.022)	0.995 (±0.016)

[a] Standard error of estimate in parentheses.

vette containing 3 mL of buffer. An increase in absorbance was monitored at 280 mm.

Results

First-order rate constants for the hydrolysis of *p*-bromophenyl succinate and *p*-bromophenyl succinate-d_4 are given in Table I. A careful examination of these data reveals that for a given pH value, there is no overlap in ranges of the observed rate constants, k_{obsd}, for succinate and succinate-d_4. This indicates that the reliability of our measurements of k_{obsd} at a given pH value is excellent. The standard error of estimate for the mean value of a given set of rate constants ranged from ±0.06% to ±0.48% with an average of ±0.23%. These results attest to the reality of the isotope effect and the quality of our kinetics procedure.

Equation 1 is the rate law for the hydrolysis of the *p*-bromophenyl succinate esters,[7] where k_s is the rate constant for spontaneous hydrolysis, K_a is the dissociation constant of the carboxyl group, and a_H is the activity of hydrogen ion.

$$k_{obsd} = k_s \frac{K_a}{K_a + a_H} \quad (1)$$

Values of k_s and K_a are determined by a nonlinear least-squares procedure[19] and reported in Table II. Since an analysis of variance among pH levels for an entire data set for each compound reveals that the variation in pH is 99.99% of the variation in k_{obsd}, the small error associated with a mean value of k_{obsd} is highly insignificant in fitting the curve described by eq 1. Thus, the values reported in Table II are determined from a fit of the mean values of k_{obsd} and measured values of a_H. Standard error of estimates for k_s and K_a reveal that most of the error occurs in determining K_a and that the values for k_s are quite accurate (±0.36% and ±0.49%). Estimation of the error in the isotope effects follows from the standard equation for propagation of error in a ratio.[20] The errors associated with the isotope effects on k_s and K_a are ±0.6% and ±3.1%, respectively.

Alternatively, eq 1 can be rearranged to a linear form, eq 2, and solved by linear least-squares analysis.

$$k_{obsd} = k_s - \frac{1}{K_a}(k_{obsd}a_H) \quad (2)$$

The values of k_s and K_a reported in Table II are determined from a fit of the mean values of k_{obsd} and measured values of a_H. The values obtained for k_s and K_a are essentially identical to those produced in the fitting of the data to eq 1. Estimates of error are handled in a similar manner as described above. The errors associated with the isotope effects on k_s and K_a are ±0.8% and ±1.6%, respectively.

Discussion

The mechanism described by eq A suggests the formation of an intermediate tetrahedral compound preceding formation of succinic anhydride. It has previously been suggested[21] that the breakdown of the tetrahedral intermediate to form the cyclic anhydride is the rate-limiting step. This proposal is largely based on the sensitivity of the rate on the nature of the departing aryloxide ion. If this breakdown step is rate limiting, then a significant amount of bond breaking to the aryloxide is expected in the transition state. This thought is well-supported when previous kinetic data for a series of monoaryl succinates[12] are examined. Regression of log k_s on pK_a of the leaving group yields a slope of −1.17, which indicates bond cleavage is well-advanced in the transition state.

Structure–reactivity correlations of this type are normally utilized for the reverse reaction, nucleophilic attack on a carbonyl.[22] Slopes of plots of log (rate constant) vs. pK_a of the attacking nucleophile are defined as β_n. Values of β_n are expected to lie between 0 and 1.7.[22b] For strongly basic nucleophiles attacking carbonyl groups, β_n values of 0.3–0.7 are typical.[21a] This is interpreted as an indication that bond formation has occurred only to a modest extent, i.e., an "early" transition state. Large β_{lg} values, 1.4–1.0, would be expected for the reverse reaction, the departure of a strong basic group to form a carbonyl. β values of this magnitude have only been observed in intramolecular nucleophilic attack of carboxylate on ester groups.[21] It is concluded then that the rate-limiting transition state for the hydrolysis of **1** occurs "late" in the breakdown step.

Isotope Effects. The kinetic isotope effect, $k_s^{h_4}/k_s^{d_4}$, is 1.035 (1.008 per deuterium), a *normal* isotope effect. This is in marked contrast to the expected isotope effect for acyl transfer (vide supra), if the rate-limiting transition-state structure resembles a tetrahedral intermediate. An explanation of this *normal* isotope effect is that in the rate-controlling transition-state structure the backbone hydrogens are in a "looser" vibrational force field than in the reactant. Another explanation would be that the small *normal* isotope effect arises from contributions of the ratio of imaginary frequencies.[23] Possibly, both factors contribute in this case. In any case the effect is inconsistent with a near-tetrahedral structure for the transition state.

But how could one account for a "looser" vibrational force field about the backbone hydrogens? One possible implication is that a relief of steric interactions has taken place in going from reactant state to transition state. Such a relief of ground state strain has been suggested as the driving force behind rate accelerations observed for ring closing reactions when the succinyl backbone is substituted with alkyl groups (L = alkyl), but this steric relief has been theorized as absent for the unsubstituted case (L = H).[3] In fact, some have proposed that there is an *increase* in steric interactions between the backbone hydrogens when the anhydride ring is formed.[24] The conclusion from the observation of a *normal* isotope effect is that this latter proposal is incorrect. An alternative possibility is that an increase in hyperconjugation (leading to a decrease in force constants) arises in an anhydride-like transition state relative to the reactant. Such an effect would have to outweigh any increased steric interaction which again suggests that the steric effect, if adverse, is small.

A relatively "freer" environment of the methylene hydrogens in the anhydride form could be supported by experimental structural data on succinic anhydride[24] and succinate dianion[26] as well as theoretical structural data on succinic anhydride and succinic acid.[27] All the methods reveal that the nearest neighbor contact distances are longer in the anhydride than in an acyclic form. This lengthening of nearest neighbor interactions is a result of the "fanning out" of the pairs of methylene hydrogens in the cyclic form relative to the open chain. Although the hydrogens are eclipsing in the anhydride,

their nearest neighbor interactions are with two other hydrogens and an oxygen, whereas in the open chain structure (assuming a staggered conformation) the nearest neighbors are a hydrogen, a carbon, and an oxygen.

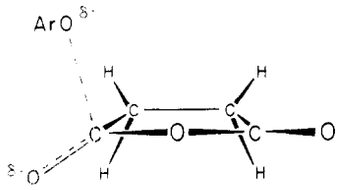
Evaluation of contact distances is only suggestive of the "looser" environment for the backbone hydrogens in the anhydride compared to the acyclic form. A better method would involve a complete vibrational analysis. Vibrational studies[28] on succinic anhydride and succinic-d_4 have been performed as well as similar studies on succinic acid and its deuterated analogues.[29] Unfortunately, missing frequencies preclude a total vibrational analysis.

The isotope effect of *unity* on the acid dissociation constant, K_a, of **1** is unexpected. The isotope effect on K_a for acetic acid and acetic-d_3 acid is 1.035.[30] However, the uncertainty associated with the isotope effect on the K_a of **1** (see Table II) is too great to allow for speculation on the origin of such a result.

Transition-State Structure. A quantitative way of looking at the transition-state structure is to compare the value of β_{lg} to the maximum possible value. This ratio of β_{lg} values yields the fraction of bond cleavage that has occurred in the transition state. The bond order of the breaking bond is equal to $1 - (\beta_{lg}/-1.7)$. For monoaryl succinate hydrolysis the bond order of the breaking bond is 0.31. Substitution of this value in Pauling's bond order equation,[31] eq 3, and utilizing 1.41 (single bond C–O) for D_1 give a breaking C–O bond distance of 1.77 Å.

$$D_n = D_1 - 0.71 \text{ Å} \log n \quad (3)$$

The isotope effect suggests a planar anhydride-like ring structure, so that the picture of the transition-state structure that emerges is represented by **2**. The planar ring structure



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is further supported by calculations[27] on a reverse reaction, addition of $^-$OH to succinic anhydride, which occurs with no change in the planarity of the ring atoms.

Summary and Conclusion. The β secondary isotope effect probe of transition-state structure in the hydrolysis of **1** suggests that relief of ground state steric interactions is important in driving the ring closure when L = H just as when L = alkyl. Consequently, the dominant factor affecting rate accelerations in reactions described by eq 1 is the equilibrium driving force for ring closure. Isotope effects are consistent with the conclusion from structure–reactivity relations that the transition state is "late", resembling an alkoxide ion and succinic anhydride. Since the isotope effect, which probes force-constant alterations near the carbonyl, and the structure–reactivity probe, which measures charge development in the leaving group, yield similar conclusions, these two processes (force-constant alteration at carbonyl and leaving group charge development) appear to be highly *coupled* along the reaction path.

References and Notes

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$$\left[\frac{(172 + 100.1)/(172 \times 100.1)}{(172 + 104.1)/(172 + 104.1)}\right]^{1/2} = 1.012$$
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