vidual CD exciton bands correspond to that of the UV-visible spectrum of XBR,[31] the CD of A (Figure 1) or S·A (Figure 4) may be calculated and plotted as shown in Figure 10. Here the asymmetry in the curve shape is evident, and from the composite CD curve one finds $\Delta\epsilon_{max}^{455}$ −260 and $\Delta\epsilon_{max}^{395}$ +190 L·mol^{-1}·cm^{-1}. With these calculated values as references, the maximum experimental $\Delta\epsilon$ value (−135 L·mol^{-1}·cm^{-1} at 433 nm) for BR-IX + quinine in CH_2Cl_2 (Table II) corresponds to a ~50% diastereomeric excess of the complex corresponding to S·A (Figure 4).

Concluding Remarks

BR-IX and related rubins with propionic acid or propionate groups located at C-8 and C-12 tend to adopt either of two intramolecularly H-bonded enantiomeric conformations A and B (Figure 1) and as such may be viewed as racemic mixtures of interconverting mirror-image structures. Enantioselective binding to chiral solvating agents generates diastereomeric complexes, e.g., Figure 4, in which one diastereomer is favored over the other. As a consequence, BR-IX solutions become optically active in pigment and exhibit bisignate CD CEs, the intensity of which depends on the binding constant to the chiral solvating agent and its enantioselectivity. The very large bisignate CEs, previously characteristic only of albumin and other protein complexes with BR-IX,[7,8] can be detected for certain amines (cinchona alkaloids), which appear to bind to BR-IX with a high degree of enantioselectivity. We suggest that the binding enantioselectivity is high because of molecular complementarity at the dissymmetric microenvironment of the binding sites, e.g., amine salt formation stabilized by added H-bonding from a nearby secondary hydroxyl and π-π London force binding of the alkaloid quinoline aromatic system to a pigment pyrromethenone moiety. This type of chiral recognition, involving a similar sort of multiple-point binding, is probably responsible for the enantioselectivity implied by the intense bisignate ICDs of the bilirubin-albumin complex. Some of the same complementarity is potentially available at the albumin binding site, which is known to contain lysine as well as tryptophan groups.[12,13]

Conformations such as A and B (Figure 1) and S·A and S·B (Figure 4) appear to be essential in understanding the origin of the intense bisignate ICD CEs. Those bichromophoric pigments (MBR-IV, BRDME, and MBRDME) that cannot or do not adopt such conformations give only relatively weak, albeit bisignate, ICD CEs in the presence of cinchona alkaloids. Consequently, although we view all the bichromophoric pigments of this study as potential molecular excitons, only BR-IX shows bisignate ICD data characteristic of exciton systems wherein the two chromophores are held in the well-defined geometry (Figure 1 and 4) necessary for near-optimal orientation (skew angle of $\simeq$100°)[26] of their relevant electric dipole transition moments.

Acknowledgment. We thank the National Institutes of Health (Grant HD-17779) for generous support of this work. J.K.G. was on leave from Adam Mickiewicz University, Poznan, Poland (Program RP II.13.2.10), when this study was initiated.

Concertedness in Acyl Group Transfer in Solution: A Single Transition State in Acetyl Group Transfer between Phenolate Ion Nucleophiles

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Abstract: Rate constants have been measured for nucleophilic substitution of 4-nitrophenol from 4-nitrophenyl acetate by a series of phenolate anions. The Brønsted type plot is linear for unhindered phenolate ions with pK_a values significantly above and below that of the displaced 4-nitrophenol: ($\log k_{ArO} = 0.75pK^{ArOH} - 7.28$; $n = 17$, $r = 0.984$); this is consistent with a mechanism involving a single transition state or a mechanism with an intermediate that has a very low barrier to decomposition. A small change in effective charge on the carbonyl group from reactant to transition state (measured from β_{nuc} and the known β_{eq} for the overall reaction) points to an almost coupled concerted mechanism for the transfer of the acetyl function between phenolate ion nucleophiles. The conclusions of this work are consistent with previous results that indicate relatively stable tetrahedral intermediates in reactions at reactive acyl centers; a spectrum of mechanisms exists for substitution reactions of acyl functions in solution that ranges from S_N1 (or ElcB for an ester with an α-carbanion) through concerted to BAc2.

Since the discovery of carbonyl oxygen exchange in the hydrolysis of alkyl esters[1] the solution chemistry of nucleophilic displacement at carbonyl functions has been dominated by the idea of tetrahedral intermediates.[2] The concept of a stable tetrahedral intermediate has been successfully challenged for those nucleophilic substitution reactions at acyl groups that possess good leaving functions and the potential to form an acylium ion intermediate (RCO^+) that may be stabilized by charge neutralization.[3a] These well-established mechanisms represent two extremes of timing of bond formation and fission for nucleophilic substitution. A third timing possibility could exist: namely, the process where nucleophile and leaving group form and break bonds simultaneously. The spectrum of mechanisms can be represented by the schematic free energy diagram (Figure 1). A coupled concerted mechanism[3b] where there is no imbalance between bond formation and fission involves a reaction coordinate along the north-east diagonal of this diagram; concerted pathways, involving no intermediates and a single transition state, can in principle traverse any area of the diagram not possessing an energy well.

A distinction between a concerted and an associative stepwise mechanism for a displacement reaction (for example, eq 1) can be achieved by a study of substituent effects on the nucleophile. The rate-limiting step for eq 1 will be k_1 for phenolate ions strongly basic compared with 4-nitrophenolate ion and k_2 for weakly basic

(1) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.
(2) (a) McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983**, *16*, 394. (b) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Ibid.* **1981**, *14*, 306.
(3) (a) Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. (b) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

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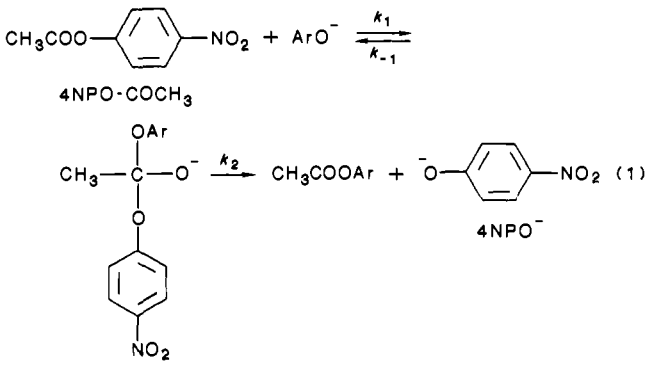
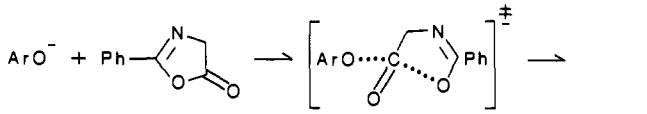


phenolate ions. Each condition predicts a different Brønsted slope for the overall rate constant because of the different electronic structures of the two transition states. A change in rate-limiting step and hence a change in Brønsted slope will occur when the basicities of leaving and attacking phenolate ions are similar (i.e., when $k_{-1} = k_2$). We cannot apply this method with precision if the nucleophiles have different structures from that of the leaving group because the pK_a at which the change in rate-limiting step occurs cannot then be predicted; the absence of a "break" will not then necessarily exclude a stepwise pathway. Nucleophiles must be chosen with basicities above and below that of the leaving group in order to observe a break in the Brønsted type plot for a stepwise process. The method, where the break point can be predicted, has been applied to sulfuryl[4] and phosphoryl[5,6] group transfer between pyridines, sulfonyl group transfer between oxyanions,[7] and acetyl group transfer between thiolate anions.[8] The observation of a break in a Brønsted relationship is excellent evidence for a stepwise process even if the break point position may not be predicted.[9,10,11-16]

The possibility of a concerted displacement of aryl oxide ions from phenyl acetates by phenoxide ions is not unreasonable. Synchronous changes in effective charge on nucleophile and leaving group in the attack of phenoxide ions on 2-phenyloxazolin-4-ones indicate a concerted displacement (eq 2).[17] Shames and Byers[18]



indicated from a consideration of their own and other work that the transition state for the rate-limiting step of hydroxide ion attack on 4-nitrophenyl esters is close to the tetrahedral adduct structure, consistent with little barrier to decomposition of such a species. Recently[19] we have shown that the transfer of the methoxycarbonyl

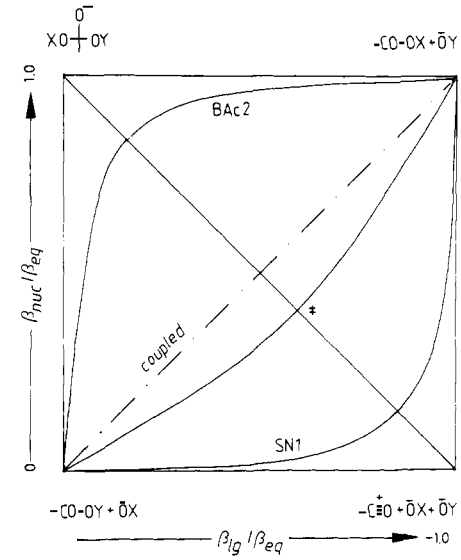
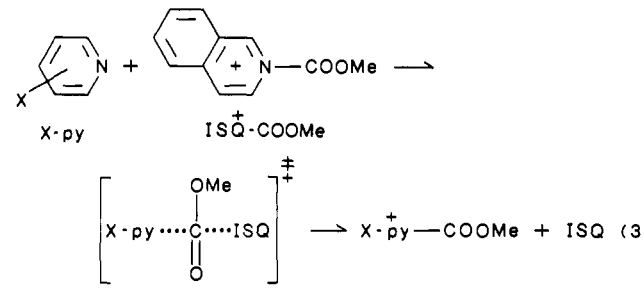


Figure 1. Schematic three-dimensional energy diagram for reaction of phenoxide ions with phenyl acetates.

function between pyridine nucleophiles possesses a concerted mechanism (eq 3).



Displacement of 4-nitrophenol from 4-nitrophenyl acetate by aryl oxide ions has been studied by Hupe and Jencks.[8] Perusal of their data indicates that the one phenolate ion less basic than 4-nitrophenoxide ion has a rate constant that fits the straight line subtended by the other phenolate rate constants in a linear Brønsted type plot. This investigation is to provide more values for weakly basic phenolate ions and thus to examine the concertedness of the reaction.

Experimental Section

Materials. Acetates were prepared by standard methods from phenols and acetyl chloride, acetyl bromide, or acetic anhydride; physical characteristics are recorded in the supplementary table. Phenols were obtained commercially and were purified by either recrystallization from a suitable solvent or sublimation. Acetic anhydride employed kinetically was of analytical reagent grade and was redistilled from K_2CO_3. Buffer materials were of analytical reagent grade or were redistilled or recrystallized from bench grade products. Acetonitrile was purified according to the method of Lewis and Smyth,[20] and water used throughout the kinetic investigation was doubly distilled from glass.

Deuterium oxide (99.8% D) and a solution of DCl in D_2O were obtained from Aldrich. Careful addition of clean sodium (0.23 g) to D_2O (20 mL) under an atmosphere of nitrogen gave NaOD solution. Both NaOD and DCl solutions were standardized with standard base or acid with phenolphthalein indicator.

Methods. Kinetics of reaction of phenolate ions with 4-nitrophenyl acetate were measured by introducing an aliquot (0.02 mL) of a stock solution of the ester in CH_3CN to buffer solution (2.5 mL) containing the phenol at the required concentration in a silica cell in the thermostated cell compartment of a Unicam SP 800 spectrophotometer. The absorbance change was recorded at 400 nm as a function of time, and the pseudo-first-order rate constant was obtained from a plot of log ($A_\infty - A_t$) against time. The buffer solution was prepared from stock solutions, one containing the phenol and buffer component and an identical solution adjusted to the same pH but without phenol. Mixing the stock

(4) Bourne, N.; Hopkins, A.; Williams, A.; *J. Am. Chem. Soc.* **1985**, *107*, 4327.
(5) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591.
(6) Skoog, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597.
(7) D'Rozario, P.; Smyth, R. L.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 5027.
(8) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(9) Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1773.
(10) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3995.
(11) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, *68*.
(12) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828.
(13) Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939.
(14) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.
(15) Battye, P. J.; Ihsan, E. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 741.
(16) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.
(17) Curran, T. C.; Farrar, C. R.; Niazy, O.; Williams, A. *J. Am. Chem. Soc.* **1980**, *102*, 6828.
(18) Shames, S. L.; Byers, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 6170.
(19) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040.
(20) Lewis, G. L.; Smyth, C. P. *J. Chem. Phys.* **1939**, *7*, 1085.

Table I. Nucleophilic Reactivity of Phenolate Ions against 4-Nitrophenyl Acetate[a]

entry	subst	pK_a[b]	$k_{ArO}/(M^{-1}\ s^{-1})$[c]	FB[d]	pH[e]	N[f]	[phenol]/mM[g]	$k_{obsd} \times 10^5/s^{-1}$[h]
1[k]	2,6-Me_2	10.63	0.11	0.190	10.00	4	5.0–25	135–176
2	4-Me	10.20	3.16 (1.9)[i]	0.387	10.00	5	5–20	860–2460
3	4-F	9.95	1.99	0.529	10.00	4	6–30	810–2420
4	H	9.86[i]	1.24 (0.97)[i]	0.635	10.10	5	21–53	1650–3600
5	4-Cl	9.38	0.81 (0.68)[i]	0.840	10.10	5	10–51	970–3290
6	3-Cl	9.02	0.32	0.506	9.00	4	6.6–33	138–544
7	3,4-Cl_2	8.62[j]	0.25	0.132	7.80	5	5–20	18–69
8	2-Cl	8.48	0.063	1.00	10.00	5	11–44	237–436
9	4-Ac	8.05	0.024	1.00	10.00	5	10–40	180–244
10	4-CN	7.95	0.023	0.420	7.80	4	5.4–22	6.9–22
11	2,3-Cl_2	7.71[j]	0.019	0.557	7.80	4	6.2–31	8.3–36
12	3,4,5-Cl_3	7.68[i]	0.058 (0.067)[i]	1.00	9.00	4	10.0–30	770–1880
13	4-CHO	7.66	0.014[l]	1.00	10.00	5	5–50	1610–1980
14[k]	2,6-Cl_2	6.78[j]	8.5×10^{-4}	0.918	7.80	5	10–50	1610–1980
15	2,4,5-Cl_3	6.72[j]	0.0084	0.681	7.00	5	1.6–8	1.5–3.6
16	2,3,5-Cl_3	6.43[j]	0.0038	0.807	7.00	5	2–8	1.2–2.9
17	F_5	5.49[i]	6.4×10^{-4}[l]	0.973	7.00	5	20–60	2.2–4.8
18	2,3,5,6-F_4	5.53	9.2×10^{-4}[l]	1.00	7.92	5	5.3–53	5.5–9.7
19	2,3,4,5-Cl_4	5.64	0.0012	0.88	6.5	5	0.2–1.2	0.15–0.24
20	F_5 (in D_2O)	5.49	0.0071	1.00	7.4	5	20–60	2–5

[a] 25 °C, ionic strength made up to 0.1 M with KCl; wavelength for kinetic study, 400 nm. [b] Except where stated, pK_a's are from: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; section j-187. [c] Errors in the rate constants are less than ±5%. [d] Fraction of phenol ionized. [e] Average pH; individual pH values did not differ by more than 0.02 from the average. Buffer components for pH 8 (phosphate at 0.018 M) and at pH 10 (carbonate at 0.025 M). [f] Number of data points not including duplicates. [g] Range of phenol concentrations. [h] Range of k_{obsd}. [i] Reference 8. [j] Drahanovsky, J.; Vacek, Z. *Collect. Czech. Chem. Commun.* **1971**, *36*, 3431. [k] These data not employed in Brønsted correlations owing to the possibility of general-base contributions or to steric problems with the nucleophile. [l] Calculated from the rate constant for the reverse reaction (ester with 4-nitrophenolate anion; Table II) with an equilibrium constant estimated as in the text: 4-CHO, 0.020 $M^{-1}\ s^{-1}$; F_5, $1.02 \times 10^{-3}\ M^{-1}\ s^{-1}$; 2,3,5,6-$F_4$, $1.90 \times 10^{-3}\ M^{-1}\ s^{-1}$.

solutions in the appropriate proportions gives phenol at varying concentration, with the parameters of buffer concentration, ionic strength, and pH constant. The solutions were degassed immediately prior to mixing and use.

The pH was measured before and after the kinetic runs with a Radiometer PHM 62 digital instrument equipped with a Russell CMAWL CL5 combination electrode standardized with EIL standard buffers to ±0.01 unit. Typically the pH did not alter by more than 0.02 unit. Kinetic experiments with D_2O solvent were carried out in a similar manner to those with H_2O except that low-volume, 1-cm path length cells were employed. The pDs of the solutions were estimated from the pH meter reading with the equation pD = pH meter reading + 0.4.[21]

The kinetics of very slow reactions were followed by determining initial rates of absorbance change. The final absorption was determined after rapid complete hydrolysis of an identical aliquot of the ester at high pH followed by reconstituting the pH and concentration conditions to those of the kinetic experiment. Division of the initial rate of absorbance change by the overall change in absorbance on completion of the reaction gives the pseudo-first-order rate constant. This procedure is valid since we know that the rate law is pseudo first order for the cases where complete reaction has been followed.

Reaction of 4-nitrophenolate anion with aryl acetates and acetic anhydride was followed kinetically in a similar manner by adding the acetylating agent to an equilibrated buffer solution of 4-nitrophenol. Second-order rate constants for consumption of the 4-nitrophenol were obtained from the initial rate of the absorbance decrease (at 400 nm) by division by ester (or anhydride) and nitrophenolate ion concentrations. The rate of disappearance of nitrophenolate ion absorption decreased due to hydrolysis of the acylating agent and consumption of the nitrophenol, and the initial rate was obtained with a computer program. During these experiments the pH decreased significantly due to the relatively large amounts of ester or anhydride employed that undergo a secondary hydrolysis reaction; the pH recorded is that of the initial conditions under which the rate is measured.

Product analysis was carried out for some reactions of phenols with 4-nitrophenyl acetate. A solution of 4-nitrophenyl acetate (70 mg in 3 mL of CH_3CN) was added to a solution of phenol (2 mol in 20 mL of water at pH 10); the reaction was allowed to finish and the ester product was extracted with dichloromethane (10mL), which was then dried and evaporated to give about 50 mg of an oil. The oil was shown to be phenyl acetate by comparison of its TLC and infrared spectrum with those of an authentic sample. A similar experiment was carried out on the reaction of 4-formylphenol on 4-nitrophenyl acetate at pH 8.5, and the product oil (about 55 mg) was shown to be 4-formylphenyl acetate. It proved impossible to obtain quantitative product analysis data under conditions approximating those of the kinetic experiments.

Statistical computations were carried out with a BBC microcomputer.

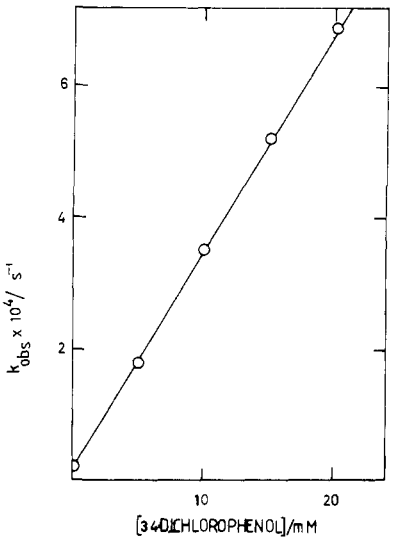


Figure 2. Reaction of 3,4-dichlorophenol containing buffers with 4-nitrophenyl acetate. Conditions are given in Table I; line is drawn from parameters in Table I.

Results

Liberation of phenolate ion from phenyl acetates in the presence of buffers with aryl oxide nucleophiles obeyed excellent pseudo-first-order kinetics up to about 90% of the total reaction. The rate constants were linearly dependent on the phenolate ion concentration (Figure 2). Details of pH, phenol concentration range, buffer, rate constant range, and number of data points are given in Table I. In the case of the slow reactions of phenolate ions with phenyl esters the initial rate was linearly dependent on the phenolate ion concentration, and the rate law was assumed to be first order in ester and phenolate ion concentrations. The data from both methods were analyzed with the reasonable assumption that only the phenolate ion reacts with the ester (eq 4).[22]

$$k_{obsd} = k_0 + k_{ArO}[ArO^-] \quad (4)$$

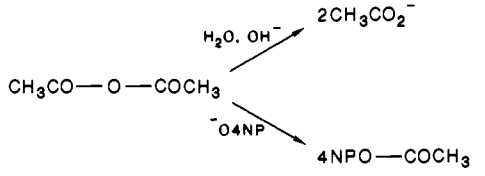
(21) D'Rozario, A. P.; Greig, D. J.; Hudson, R. F.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1981**, 590.

Table II. Rate Constants for Reaction of 4-Nitrophenolate Anion with Acetate Esters and Acetic Anhydride[a]

entry	subst	pK_{lg}[b]	$k_{ArO}/(M^{-1}\ s^{-1})$[c]	FB[d]	pH[e]	N[f]	[phenol]/mM[g]	$k_{obsd} \times 10^3/s^{-1}$[h]
1	F_5	5.49	0.65	0.420	7.00	5	0.03–0.16	0.010–0.046[j]
2	2,3,5,6-F_4	5.53	1.04	0.420	7.00	4	0.03–0.17	0.023–0.090[k]
3	4-CHO	7.66	0.0026	0.390	6.95	3	0.104–0.174	1.36×10^{-4}–1.71×10^{-4}[l]
4	acetic anhydride	4.76	25[i]	0.500	7.14	10	0.03–0.16	0.38–0.20[m]

[a–h] Footnotes *a–h* as in Table I. [i] Leppanen et al. (Leppanen, S.; Strandman, L.; Pajunen, S. T. P.; Koskikallio, J. *Acta Chem. Scand.*, **1973**, *27*, 3572) find 14.3 $M^{-1}\ s^{-1}$ at 10 °C, aqueous solution (indeterminate but low ionic strength), using a pH-stat method. [j] Concentration of ester = 1.94 mM. [k] Concentration of ester = 1.10 mM. [l] Concentration of ester =3.66–6.75 mM. [m] Concentration of acetic anhydride = 0.525 mM.

Scheme I



The second-order rate constants k_{ArO} were obtained by dividing the slope of the plot of k_{obsd} versus $[ArOH]_{total}$ by FB, the fraction of phenol present as phenolate ion. The derived values of k_{ArO} are recorded in Tables I and II and there is excellent agreement of these with data from other work where overlap is appropriate.[8]

General-base catalysis could provide an attractive pathway for weakly basic oxyanion catalysts;[23] we sought to obtain bona fide nucleophilic rate constants for low-pK_a phenolate anions in their reaction with 4-nitrophenyl acetate. It is possible to estimate the general-base component of a mixed general base/nucleophilic kinetic term by measuring the solvent deuterium isotope effect. This method possesses difficulties previously enumerated,[24] and we employ the following approach exemplified by the attack of acetate ion on 4-nitrophenyl acetate. The reverse reaction, namely, between anhydride and 4-nitrophenolate ion, can be monitored unambiguously and easily by the disappearance of 4-nitrophenol in a buffer solution containing the anhydride. The initial rate of this reaction can be determined under precisely known conditions of concentration of phenol and anhydride. As the reaction progresses, both of these quantities change according to the mechanism in Scheme I and it is difficult to obtain data from the overall time dependency; moreover, the relatively large quantities of acylating agent cause the pH to drop progressively from that under the initial conditions. The initial rate of 4-nitrophenolate ion depletion is proportional to the phenolate ion concentration, and the second-order rate constant for attack of 4-nitrophenolate ion on acetic anhydride (25 $M^{-1}\ s^{-1}$) is obtained by division of the slope of the initial rates against 4-nitrophenolate ion concentration by the concentration of acetic anhydride. The equilibrium constant for eq 5 has been obtained previously[25,26] under

$$Ac_2O + 4NPO^- \underset{k_{AcO}}{\rightleftharpoons} AcO^- + 4NPO{-}COCH_3 \quad (5)$$

similar conditions (8.85×10^6) so that substitution of the rate constant for nucleophilic attack of 4-nitrophenolate ion on acetic anhydride gives the *nucleophilic* rate constant for attack of acetate ion on 4-nitrophenyl acetate unambiguously ($k_{AcO} = 2.8 \times 10^{-6}$ $M^{-1}\ s^{-1}$). The same treatment can be applied to the rate constant for nucleophilic attack of 4-nitrophenolate ion on an aryl acetate (see Figure 3 for an example and data in Table II). In these cases the equilibrium constants for reaction (eq 6) must be *estimated*

$$ArO{-}COCH_3 + 4NPO^- \underset{k_{ArO}}{\rightleftharpoons} ArO^- + 4NPO{-}COCH_3 \quad (6)$$

from the equilibrium constant for the virtual reaction when ArO^-

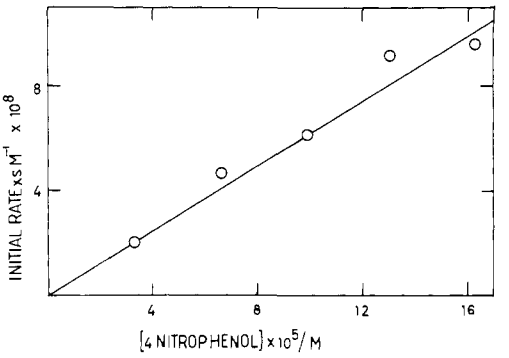


Figure 3. Rate of disappearance of 4-nitrophenolate ion in buffers containing pentafluorophenyl acetate at 1.94 mM. Conditions are given in Table I; line is calculated from data in Table I.

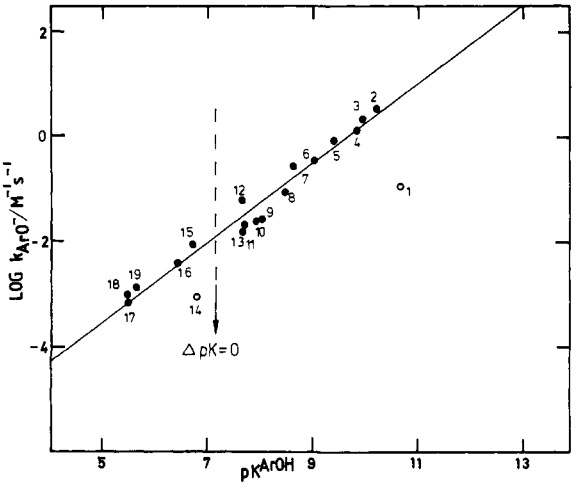


Figure 4. Brønsted type dependence of k_{ArO} for nucleophilic attack of phenolate ions on 4-nitrophenyl acetate. Conditions are given in Table I; line is calculated from eq 8. The identity of the points is given in Table I; only the filled circles are used in the correlation.

is 4-nitrophenoxide ion ($K = 1$) and the β_{eq} for variation of the equilibrium constant with pK_a of the leaving phenol (1.7).[26] The value of k_{ArO} determined in this way for the attack of 4-formyl phenolate ion on 4-nitrophenyl acetate agrees well with that determined directly; it is unlikely that the direct determination yields a rate constant with any general-base component. The tetrafluoro- and pentafluorophenolate ion attack on 4-nitrophenyl acetate have rate constants that agree when determined directly and indirectly (see Table I).

The deuterium oxide solvent isotope effect on the reaction of pentafluorophenolate ion with 4-nitrophenyl acetate is approximately unity (Table I), confirming the absence of general-base catalysis by the oxyanion.

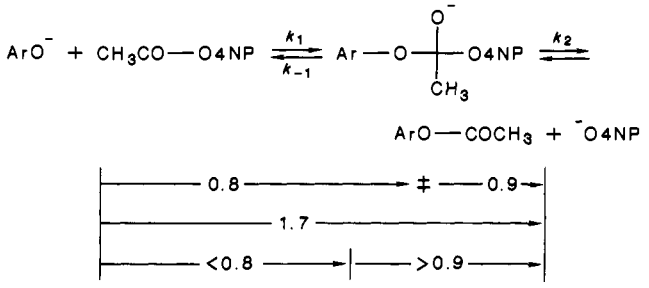
The rate constants for attack of phenolate ions on 4-nitrophenyl acetate are displayed in Figure 4 and obey an excellent Brønsted rate law. The data were force fitted to eq 7, obtained from eq

$$k_{ARO}/k_0 = 10^{\beta_1 \Delta pK}/(1 + 10^{\Delta\beta\Delta pK}) \quad (7)$$

1, where $\Delta\beta = \beta_{-1} - \beta_2$ and $\Delta pK = pK_a^{ArOH} - pK_a^{4\text{-nitrophenol}}$; the values of β_1, β_{-1}, and β_2 refer to the Brønsted equations governing k_1, k_{-1}, and k_2, respectively. The fitting procedure employed a

(22) Bruice, T. C.; Lapinski, R. *J. Am. Chem. Soc.* **1958**, *82*, 2265.
(23) Chrystiuk, E.; Jusoli, A.; Santaflanos, D.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 163.
(24) Khan, S. A.; Kirby, A. J. *J. Chem. Soc. B* **1970**, 1172.
(25) Jencks, W. P.; Barley, F.; Barnett, R.; Gilchrist, M. *J. Am. Chem. Soc.* **1966**, *88*, 4464.
(26) Gerstein, J.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 4655.

Scheme II



"grid-search" program that scanned values of $\Delta\beta$ from −0.3 to 0 in units of 0.05, β_1 from 0.6 to 0.9 in units of 0.05, and log k_0 from −1.5 to −2.5 in units of 0.05. The set of parameters best fitting the points as determined by the above procedure ($\beta_1 = 0.75$, $\Delta\beta = 0$, log $k_0 = -1.65$) agree almost perfectly with those derived by a regular linear regression analysis (eq 8).

$$\log k_{ArO} = (0.75 \pm 0.04)pK^{ArO} - (7.28 \pm 0.28) \quad (r = 0.986) \quad (8)$$

Discussion

Evidence for a Single Transition State. The Brønsted plot of log k_{ArO} versus the pK_a of the unhindered phenol for nucleophilic attack on 4-nitrophenyl acetate is linear from pK_a = 5.5 to pK_a = 10.2 (Figure 4). There is no evidence for a break at the predicted break point of 7.14. We therefore conclude that the reaction has a single transition state as evidenced from a single electronic requirement for nucleophiles with basicities above and below that of the leaving group.

An alternative explanation of the linearity is that there is a very small $\Delta\beta$ value (eq 7) indistinguishable, experimentally, from zero. The error in determining $\Delta\beta$ is no greater than 0.1 so that if there are two transition states the effective charge difference should be no greater than required by an equivalent small (~6%) structural difference of 0.1 in 1.7; the value 1.7 is the effective charge change in the overall reaction. Conservatively, the present results indicate that at *least* the mechanism is in the borderline region between stepwise and concerted. The case of closely similar transition-state structures has been discussed recently by Dietze and Jencks.[27]

Reference to Figure 4 indicates that the value of β_{nuc} for a mechanism with a putative tetrahedral intermediate is approximately 0.8 in the region ($\Delta pK < 0$) where k_2 is rate limiting (taking only those values of k_{ArO} in this region). Thus β_{eq} for formation of the tetrahedral intermediate should be less than 0.8 from ester and the variant phenolate ion level. The β_{eq} for formation of variant ester product and 4-nitrophenolate ion from the tetrahedral adduct should be greater than 0.9 (Scheme II). Since the bond to the aryl oxyanion nucleophile forms in step k_1, this step would be expected to show a larger change in effective charge than in the k_2 step, where there is little bonding change in this bond. The above inequalities cannot hold for the stepwise path and are consistent with the mechanism where the transition states for both k_1 and k_2 are identical (i.e., there is only one transition state) or are very closely related.

The Acetate Nucleophile and General-Base Catalysis. Bordwell and co-workers[28] have stressed that in order to be sure of nonlinearity in a free energy relationship it is essential to choose species of similar structure for the variant group. We have elected to use only the phenolate anions in the correlations; steric hindrance due to ortho substituents is not felt in the reactivity as evidenced by the fit of 2-chlorophenolate data to the Brønsted regression for meta and para substituents (Figure 4). Introducing two ortho substituents depresses the reactivity of the nucleophile; the 2,6-dichloro and 2,6-dimethyl points can be used as upper limits for general-base incursion. It is thus unlikely that the pentafluoro-, tetrafluoro-, trichloro-, and tetrachlorophenolate ions (with basicity lower than the leaving group) react as general-base catalysts; these points do not lie above the regression line for the more basic nucleophiles that act only via the nucleophilic pathway. This is further confirmed by the observation of no solvent deuterium oxide effect for the pentafluorophenolate anion and the excellent agreement of the experimentally determined k_{ArO} values with those estimated semiempirically for nucleophilic attack (see Table I and the Results). There may be something special about the halophenolate ions that we have not appreciated, but halophenolate ions with high basicity (e.g., 3-Cl, 4-F, 4-Cl) appear to react normally. We are therefore convinced that the points for ΔpK less than zero are bona fide nucleophilic and that the overall relationship is indeed linear.

The acetate nucleophile has a reactivity against 4-nitrophenyl acetate well below that (1.5 powers of ten lower) expected on the basis of its pK_a according to the Brønsted equation for phenolate ion attack on the ester. A plot of the logarithm of equilibrium constants for hydrolysis of acetic acid derivatives is gratifyingly linear (Figure 5) except for the acetic anhydride case, where the species is some 3 powers of ten more energetic than expected on the basis of the pK_a of the acetic acid leaving group. We cannot offer any rational explanation of this exceptional behavior except to note that the structure of the oxyanion in a carboxylate ion is not the same as that in a phenolate alcoholate ion. The plot of log k_{ArO} against the logarithm of the equilibrium constant for the reaction will be linear, but in this case the acetate point will be too reactive to fit. We have not included statistical corrections in these plots, but these will not affect the results for the acetate significantly.

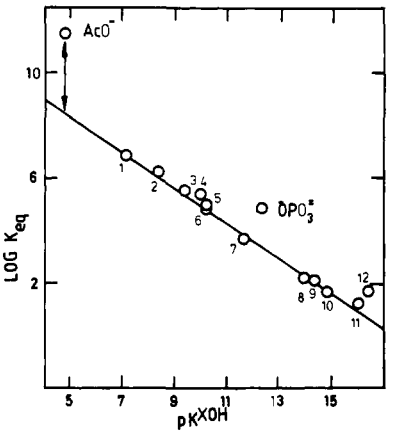
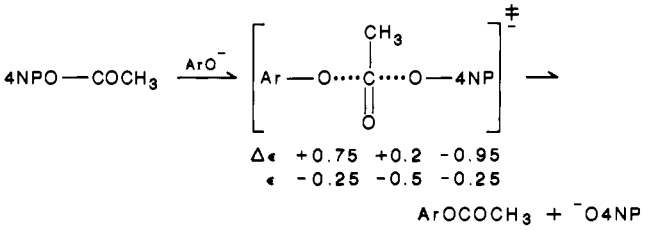


Figure 5. Brønsted dependence of the equilibrium constant for the reaction $CH_3CO\text{–}OX + H_2O \rightleftharpoons CH_3CO\text{–}OH + XOH$. The activity of water is defined as unity and the data are taken from ref 25 and 26; when X = H the equilibrium constant is 55.5. T = 25 °C but the ionic strengths are slightly variant. The identities of the points are as follows: (1) 4-nitrophenol, (2) 3-nitrophenol, (3) 4-chlorophenol, (4) phenol, (5) 4-methylphenol, (6) 4-methoxyphenol, (7) 2,2,2-trifluoroethanol, (8) choline, (9) 2-chloroethanol, (10) 2-methoxyethanol, (11) ethanol, and (12) water; acetic acid and the dianion of phosphoric acid are labeled separately.

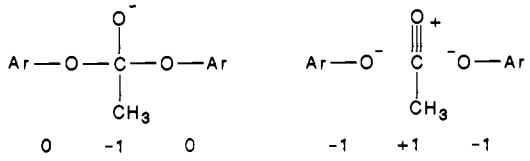
Scheme III



Transition-State Structure. The effective charges on the attacking and leaving oxygen may be derived from the β_{nuc} for attack of phenolate ions on the 4-nitrophenyl acetate and β_{eq} for the overall reaction (1.7). The effective charge is depicted in Scheme III, where $\Delta\epsilon$ represents the *change* in effective charge from the ground state. Since the transition state must lie on the north–west

(27) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4549.
(28) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224.

diagonal of Figure 1 and presumably occupies a *narrow band* thereon, it is essentially symmetrical and we can determine the effective charge on the leaving atom. Assuming the additivity of effective charge holds, we can show that while large changes occur on entering and leaving oxygen atoms, relatively small change occurs on the carbonyl group; in other words, the charge gained on the leaving group is almost balanced by the charge lost on the nucleophile, consistent with a coupled concerted mechanism. The effective charges (ϵ; see Scheme III) on the transition state indicate that the structure is between the following two canonical extremes represented with their respective charges.



In considering a strict comparison between these canonical extremes and the transition state, one should realize that the charges of the former are nominal, based on "absolute" charge; we cannot, as yet, predict what the corresponding effective charges will be compared with the unit charge defined in the standard ionization. Solvation will certainly modify the charges in the canonical structures.

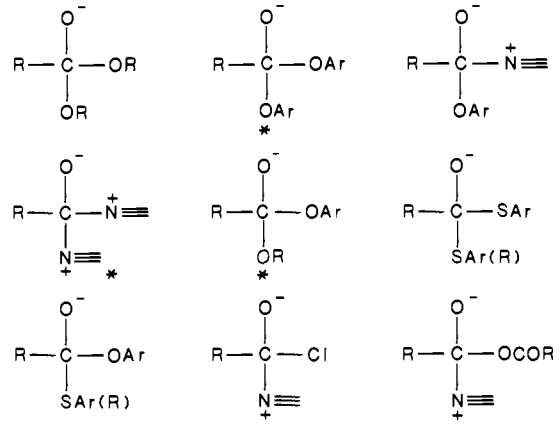
The change in effective charge on the carbonyl function (+0.2) is significantly less than that in the transfer of the methoxycarbonyl group between pyridine nucleophiles.[19] We predict that the methoxyl function has little effect because of the relatively small reactivity differences between methoxycarbonyl and acetyl (alkaline hydrolysis of the ethyl esters has similar rate constants[29]). We concluded[19] that the carbonyl group in the transfer between pyridines has acylium ion character; the extra negative charge in the transfer between phenolate ions probably encourages a more coupled concerted pathway with less acylium ion character.

The transfer of phosphoryl and sulfuryl groups between pyridines or phenolate ions suffers very large changes in effective charge on the central acyl function[4-6] consistent with "uncoupled" bond formation and fission. The sulfonyl group transfer between aryl oxide nucleophiles suffers little change in effective charge,[7] consistent with a "coupled" mechanism.

As the ArO^- ligands become more nucleophilic the transition state should become more like the tetrahedral intermediate and bond fission and formation should become less coupled. This is in agreement with the nonactivated esters' participating in stepwise displacements and with the observation that hydroxide ion attack on activated esters has a transition state close to the tetrahedral structure.[18] Carbonyl groups with weakly basic ligands have transition states tending towards the southeast corner of the energy profile (Figure 1). Such systems comprise for example strong-acid-catalyzed ester exchange and hydrolysis of hindered benzoates[30a] or acyl group transfer between pyridine nucleophiles.[19]

Concerted Carbonyl Group Transfer. Moodie, Castro, and co-workers[10-16] have provided excellent evidence that pyridine attack on activated esters involves "stable" tetrahedral adducts. Thioanion attack with oxyanion leaving group can also involve the participation of a tetrahedral intermediate.[8] The pattern of mechanisms is collected in Chart I, where the tetrahedral intermediates, putative or otherwise, are illustrated. The instability of the tetrahedral adduct from pyridine and *N*-acylpyridinium ion compared with pyridine and esters is possibly due to electrostatic stabilization in the latter.[19] The tetrahedral adduct from ester and aryl oxide ion has no potential for gross electrostatic stabilization. The observation of relatively stable thio analogues is explained on the basis that the divalent sulfur group is well-known to stabilize adjacent negative charge,[30b] and it would seem unlikely that the charge on the oxyanion should not overlap with the acceptor orbitals on the sulfur to provide such a stabilization.

Chart I[a]



[a] The starred tetrahedral adducts are deemed to be kinetically unstable.

Although Shames and Byers[18] indicate that the transition state for the attack of hydroxide ion on aryl esters is close to the tetrahedral structure, the process could still be concerted. The present results support a previous conclusion that the attack of phenoxide ions on oxazolinones is concerted with ring fission[17] and a hypothesis of Gaetjens and Morawetz[31] that expulsion of aryl oxide ions by anhydride formation of aryl glutarates and succinates is concerted. Our original explanation of these mechanisms[17] on the basis that an acylium ion could be stabilized by the anionic nucleophiles is not now necessary.

Other areas where concertedness has been postulated recently with reasonably conclusive evidence are the hydrazinolysis of acylimidazoles,[32] the solvolysis of benzoyl chlorides,[33] and gas-phase acyl group transfer.[34] We have previously discussed arguments for concertedness based on estimated constants for decay of tetrahedral adducts too great to support a stepwise mechanism.[19]

Conclusion

The idea of a concerted mechanism for transfer of the carbonyl group has been discussed by Ingold,[35] by Dewar,[36] and, more recently, by Jencks and Gilchrist.[37] The last authors indicated that evidence was not then available to distinguish concerted from a stepwise path for reactions of activated esters. The problem with investigating timing in this system is that the transition states for both paths are related and techniques for measuring bond order (for example, isotope effect, polar effects, and volumes and entropies of activation) require some theoretical estimate of these values at the extremes of the mechanism. These methods will be of necessity ambiguous unless, as in the present case, one can predict a change in rate-limiting step. We cannot exclude, in the light of this statement, that the mechanism is either concerted with a single transition state or stepwise with two closely similar transition states. It is impossible in our opinion to experimentally distinguish between these two possibilities, which are in the borderline region, and the question is not an appropriate one. A similar situation holds for the sulfuryl and phosphoryl group

(29) Williams, A.; Salvadori, G. *J. Chem. Soc. B* **1971**, 2401.
(30) (a) Bender, M. L.; Ladenheim, H.; Chen, M. C. *Ibid.* **1961**, *84*, 123. (b) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic: New York, 1965.
(31) Gaetjens, E.; Morawetz, H. *J. Am. Chem. Soc.* **1960**, *82*, 5328.
(32) Page, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8828.
(33) (a) Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Chem. Commun.* **1984**, 387; *J. Chem. Soc., Perkin Trans. 2* **1985**, 983. (b) Bentley, T. W.; Harris, H. C. *Ibid.* **1986**, 619.
(34) (a) Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 2124. (b) Pau, J. K.; Kim, J. K.; Caserio, M. C. *Ibid.* **1978**, *100*, 3831. (c) Takashima, C.; Josē, S. M.; do Amaral, A. T.; Riveros, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1255. (d) Han, C.-C.; Brauman, J. I. *J. Am. Chem. Soc.* **1987**, *109*, 589.
(35) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969.
(36) Dewar, M. J. S. *The Electronic Theory of Organic Chemistry*; Oxford University Press: Oxford, 1948.
(37) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

transfer experiments.[4,5,6] In general, we envisage acyl group transfer reactions in solution possessing mechanisms with pathways that could take any direction in the energy contour diagram of Figure 1. We propose that there is smooth transition between the mechanisms resultant upon the changing energetics of the discrete intermediates.

It requires care to extrapolate the results of this study to enzyme mechanisms. Almost certainly the hydrolysis of peptides by serine proteinases will involve a stepwise path because of the stabilizing effect of the zwitterionic species ($R^+NH_2C(R)O^-$–O–enzyme) in the reaction. The oxyanion cavity[38] could stabilize the negative charge on the intermediate tetrahedral adduct in the serine protease catalyzed acyl transfer from esters.

(38) (a) Fersht, A. R.; Blow, D. M.; Fastrez, J. *Biochemistry* **1973**, *12*, 2035. (b) Robertus, J. D.; Kraut, J.; Alden, R. A.; Birktoft, J. J. *Ibid.* **1972**, *11*, 4293.

Acknowledgment. We are grateful to the Science and Engineering Research Council and to the Government of Saudi Arabia (S.B.-S.) for partial support of this work.

Registry No. 2,6-$Me_2C_6H_3O^-$, 25117-01-5; 4-$MeC_6H_4O^-$, 22113-51-5; 4-$FC_6H_4O^-$, 32376-34-4; $C_6H_5O^-$, 3229-70-7; 4-$ClC_6H_4O^-$, 24573-38-4; 3-$ClC_6H_4O^-$, 18938-14-2; 3,4-$Cl_2C_6H_3O^-$, 45670-76-6; 2-$ClC_6H_4O^-$, 29650-97-3; 4-$AcC_6H_4O^-$, 18983-84-1; 4-$NCC_6H_4O^-$, 14609-76-8; 2,3-$Cl_2C_6H_3O^-$, 96541-70-7; 3,4,5-$Cl_3C_6H_2O^-$, 60154-34-9; 4-$OHCC_6H_4O^-$, 18938-17-5; 2,6-$Cl_2C_6H_3O^-$, 53330-27-1; 2,4,5-$Cl_3C_6H_2O^-$, 45773-92-0; 2,3,5-$Cl_3C_6H_2O^-$, 100414-67-3; $C_6F_5O^-$, 26910-95-2; 2,3,5,6-$F_4C_6HO^-$, 91178-72-2; 2,3,4,5-$Cl_4C_6HO^-$, 68743-35-1; 4-$O_2NC_6H_4OAc$, 830-03-5; C_6F_5OAc, 19220-93-0; 2,3,5,6-C_6HF_4OAc, 110079-43-1; 4-$OHCC_6H_4OAc$, 878-00-2; 4-$O_2NC_6H_4O^-$, 14609-74-6; AcOAc, 108-24-7.

Supplementary Material Available: Table of physical properties of substituted phenyl acetates (1 page). Ordering information is given on any current masthead page.

Chiral Intermediates in Thiamin Catalysis. The Stereochemical Course of the Decarboxylation Step in the Conversion of Pyruvate to Acetaldehyde

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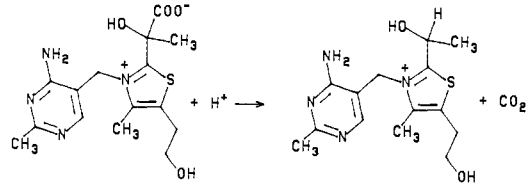
Contribution from the Lash Miller Chemical Laboratories, Department of Chemistry, University of Toronto, Toronto, Canada M5S 1A1. *Received March 31, 1987*

Abstract: The stereochemical course of the nonenzymic decarboxylation of the adduct of pyruvate and thiamin was determined. Racemic ethyl 2-(lact-2-yl)thiamin was resolved as the 2,3-dibenzoyltartrate salt under slightly acidic conditions. The specific rotations of the free enantiomers of ethyl 2-(lact-2-yl)thiamin are +8.4 ± 0.1° and −8.4 ± 0.1°. These were converted to the parent acid, 2-(lact-2-yl)thiamin, by acid hydrolysis. The (+) ethyl ester gave the (−) acid ($[\alpha]^{25}_D$ −4.7 ± 0.1°) while the (−) ethyl ester gave the (+) acid ($[\alpha]^{25}_D$ = +4.7 ± 0.1°). The acids were allowed to undergo spontaneous decarboxylation under a variety of conditions: aqueous solution, ethanol solution, dimethylformamide solution, and dimethylformamide solution containing brucine. Under all conditions the product was racemic 2-(1-hydroxyethyl)thiamin. These results require that the reaction proceed via an achiral intermediate or rapidly equilibrating achirally solvated enantiomeric intermediates. Since it is known that enzymic reactions produce a single enantiomer of 2-(1-hydroxyethyl)thiamin, the stereospecificity of the enzymic reaction is due to the chirality of the protein and not the intrinsic mechanism of the decarboxylation reaction.

The catalytic pathway of pyruvate decarboxylases involves two chiral intermediates derived from the combination of the substrate with thiamin diphosphate. The chiral adduct of thiamin diphosphate and pyruvate, 2-(lact-2-yl)thiamin diphosphate, exchanges carbon dioxide for a proton to produce a second chiral intermediate, 2-(1-hydroxyethyl)thiamin diphosphate.[1-4] The reaction of thiamin with pyruvate in the absence of enzyme produces similar adducts, 2-(lact-2-yl)thiamin ("lactylthiamin") and 2-(1-hydroxyethyl)thiamin ("hydroxyethylthiamin").



The decarboxylation of lactylthiamin formally involves substitution of a proton for carbon dioxide, with the potential intermediacy of a species which is the conjugate base of the product. Although thiamin is achiral, lactylthiamin and hydroxyethylthiamin are both chiral with the stereocenter located at the carbon atom at which the substitution occurs. Hydroxyethylthiamin diphosphate isolated from a subunit of pyruvate dehydrogenase (lacking subunits necessary for formation of acetyl-coenzyme A) has been shown to be a single enantiomer[5] and this is likely to result from the reaction of a single enantiomer of enzyme-bound lactylthiamin diphosphate. However, it is not clear if the stereochemical purity of the hydroxyethylthiamin diphosphate is a consequence of enzymic catalysis or an inherent property of the substitution process.

In order to study the stereochemical course of the nonenzymic reaction, it is necessary to have available the separated enantiomers of lactylthiamin and to relate the outcome of the reaction to the stereochemistry of the product. We have recently reported the resolution of the enantiomers of hydroxyethylthiamin and the determination of the absolute stereochemistry of the (+) and (−) enantiomers.[6,7] In this paper we report the isolation of the

(1) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
(2) Krampitz, L. O. *Thiamin Diphosphate and Its Catalytic Functions*; Marcel Dekker: New York, 1970.
(3) Kluger, R. *Ann. N.Y. Acad. Sci.* **1982**, *378*, 63.
(4) Kluger, R. *Chem. Rev.*, in press.
(5) Ullrich, J.; Mannschreck, A. *Eur. J. Biochem.* **1967**, *1*, 110.
(6) Kluger, R.; Karimian, K.; Gish, G.; Pangborn, W. A.; DeTitta, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 618. The title and caption to Figure 1 contain a typographical error. The enantiomer of HETI shown has a *negative* (but very weak) specific rotation (circular dichroism is preferred for the assignment), as stated in the rest of the paper. This material results from (+)-hydroxyethylthiamin and the configuration at the stereocenter is *R* as indicated. We thank Professor W. Shin for noting the error.

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