Kinetics of an Associative Ligand-Exchange Process: Alcohol Exchange with Arsenate(V) Triesters[1]

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Abstract: The rate of alcohol exchange with trialkyl arsenates has been studied by three techniques. Exchange of the straight-chain alcohols (ethyl, *n*-propyl, *n*-butyl, and *n*-pentyl) was studied in acetonitrile solution by using proton NMR line broadening. Activation enthalpies and entropies were found in the ranges 1 to 6 kJ mol^{-1} and −204 and −226 J mol^{-1} K^{-1}, respectively. The reactions are subject to acid catalysis for which slightly higher $\Delta H^{\ddagger}$ and less negative $\Delta S^{\ddagger}$ values were found. Methyl exchange, studied by the same technique, is about one power of ten faster. Isopropyl exchange, about three powers of ten slower, was studied in acetonitrile and dichloromethane solutions by deuterium labeling, using proton NMR. The interchange reaction of benzyl alcohol with triisopropyl arsenate in acetonitrile or dichloromethane was followed by spectrophotometry. Hydrogen bonding between alcohol and ester (which complicates order determination) was observed when reactants were at concentrations greater than about 10^{-2} M. The strongly associative mechanism is discussed.

Introduction

In order to understand the chemical basis for the very different physiological action of arsenates and phosphates,[2] it is necessary to make quantitative comparison of the behavior of arsenic(V)–oxygen bonds with that of corresponding phosphorus(V)–oxygen bonds. Such a comparison shows some similarities and differences. Since the ionization constants for the acids H_3MO_4 are almost identical, the strength of the central atom to oxygen interaction must be much alike in arsenates and phosphates. The X-ray structures of tribenzyl arsenate[3] and tribenzyl phosphate[4] are very similar. As expected, arsenic is somewhat larger than phosphorus; the As–O bonds are about 0.14 Å longer than the corresponding P–O bonds. The most significant difference between arsenates and phosphates is in the rates of As–O and P–O bond cleavage. Where data are available on comparable reactions, arsenates react five to six powers of ten more rapidly than analogous phosphates.[5] For example, phosphate esters are quite inert, but arsenate(V) esters are known to be very labile with respect to hydrolysis.[6] Recent synthetic studies have shown that arsenate(V) esters are also labile with respect to alcohol exchange.[7]

In a preliminary study,[8] we found that the rate of the exchange reaction (1) is in a region amenable to study by dynamic nuclear

$$OAs(OCH_2R)_3 + 3HOCH_2R \rightarrow OAs(OCH_2R)_3 + 3HOCH_2R \quad (1)$$

magnetic resonance spectroscopy. (In some cases acid catalysis was necessary.) The chemical shifts of the α-hydrogen atoms of the alcohol and the ester differ by about 0.5 ppm so that two distinct resonances are observed under conditions of slow chemical exchange. When the rate is increased, either by increasing the temperature or by adding an acid catalyst, the α-hydrogen lines are broadened and the rate of alcohol exchange can be determined by analysis of the line shapes.

We present here a more complete study of the alcohol–arsenate triester exchange reaction. Arsenate ester exchanges are found to be fast at room temperature, even for the sterically hindered triisopropyl arsenate. In contrast, comparable reactions of phosphate esters proceed very slowly, the reaction times probably being hours in neutral solution at 100 °C.

Experimental Section

Chemicals. Arsenate esters were prepared by the reaction of silver arsenate with an alkyl bromide or iodide.[9] All esters prepared were analyzed and characterized by NMR, IR, and mass spectrometry. In all cases where data were available in the literature, the spectra obtained were in good agreement.[10,11] Elemental analyses were also as expected. For example, Anal. Calcd for $OAs(OCH_2CH_3)_3$: C, 31.87; H, 6.69; As, 33.14. Found: C, 31.54; H, 6.91; As, 33.43.

Arsenate esters are very sensitive to atmospheric moisture; manipulations were performed by using standard inert-atmosphere techniques.[12] Solvents and alcohols were dried according to standard procedures.[13] *p*-Toluenesulfonic acid was twice recrystallized from benzene/ethanol and dried in vacuo; the crystals obtained were, however, the monohydrate, mp 105 °C. Anhydrous *p*-toluenesulfonic acid was prepared by carefully heating the pure monohydrate at 105–110 °C under vacuum for 2–4 h. The product, mp 40–42 °C, was confirmed as the anhydrous acid by its IR and NMR spectra.

Acetonitrile solutions containing *p*-toluenesulfonic acid precipitated a white solid on standing at room temperature for several days. The precipitate was identified as ammonium (*p*-toluene)sulfonate by IR and NMR as well as by elemental analysis. Anal. Calcd for $NH_4C_7H_7SO_3$: C, 44.4; H, 5.82; N, 7.40; S, 16.9. Found: C, 44.4; H, 5.77; N, 6.75; S, 16.2. The ammonium salt apparently was formed on hydrolysis of the acetonitrile solvent; the reaction was sufficiently slow that it presented no difficulties in the present experiments; however, such solutions were kept frozen in liquid nitrogen until just before use.

Kinetic Experiments. The rate of exchange of straight-chain alcohols with the corresponding arsenate esters was determined from the broadening of the ester and alcohol α-methylene proton resonances. Solutions in acetonitrile were prepared volumetrically in a drybox, transferred to 5-mm NMR tubes, and degassed by three consecutive freeze–pump–thaw cycles.

Proton NMR spectra were obtained with a Varian A60-A spectrometer equipped with a Varian temperature controller. The probe temperature was measured by the method of Van Geet.[14] Spectra were

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converted to digital form with a Hewlett-Packard 9830A calculator and 9864A digitizing board. The digitized spectra, consisting of 60–100 points, were compared with spectra which were computer-simulated[3] for various values of τ, the geometric mean of the lifetimes of the α-hydrogen atoms in the alcohol and ester environments.[15] The best value of τ was taken as that which minimized eq 2, where $y(i(\text{exptl}))$ and $y(i(\text{sim}))$ are,

$$\sum_i [y(i(\text{exptl})) - y(i(\text{sim}))]_2 \qquad (2)$$

respectively, the intensities of the experimental and simulated spectra at the frequency of the ith point. Error limits on the values of τ so obtained were approximately ±10% as calculated by the reduced χ^2 method of Bevington.[16]

The rate of exchange between triisopropyl arsenate and isopropyl alcohol was measured by following the growth of the β-proton alcohol resonance when perdeuterioisopropyl alcohol was mixed with the ester. Ester and alcohol solutions in acetonitrile or dichloromethane were prepared volumetrically in a drybox, and the ester solution was transferred to an NMR tube and sealed with a serum stopper. After thermal equilibration of the ester solution in the NMR probe, an aliquot of the alcohol solution was added by syringe and the solution mixed by shaking. Thermal equilibrium was reestablished after about 30 s, and the β-proton region of the spectrum was then repetitively scanned until the exchange reaction was complete. Typically about 20 points were obtained over a period of 10–15 min.

The ester and alcohol peak heights were measured and normalized to a constant value of $h_E + h_A$, thus averaging small fluctuations in spectrometer performance. With the assumption that the normalized peak heights are proportional to concentration, these data can be used in the McKay equation (3)[17] to obtain the rate R. The quantity $f_{ex} = h_A/h_A^\infty$,

$$-\ln(1 - f_{ex}) = \frac{3[E] + [A]}{3[E][A]} Rt = \kappa t \qquad (3)$$

the fraction of exchange, was generally not zero at the arbitrary zero of time. Thus h_A^0 and h_A^∞ were treated as parameters, and the normalized alcohol peak heights were fitted to eq 4 by using a nonlinear least-squares

$$h_A = h_A^\infty - (h_A^\infty - h_A^0)\exp(-\kappa t) \qquad (4)$$

procedure. The rate R was then computed from the concentrations and the fitted value of κ. The ester–alcohol concentration ratio should be given by $h_E^\infty/3h_A^\infty$; in most cases, the agreement was very good, justifying the assumption that peak height is proportional to concentration. In a few cases, however, disagreements between [E]/[A] and $h_E^\infty/3h_A^\infty$ were taken to indicate volumetric errors and/or hydrolysis of the ester and concentrations were corrected accordingly.

The reaction of benzyl alcohol with triisopropyl arsenate was followed spectrophotometrically at 263 nm by using a Cary 15 spectrophotometer having a thermostated cell compartment. Sample preparation was similar to that used in the NMR experiments.

Results

NMR Line-Broadening Studies. NMR spectra were obtained of acetonitrile solutions, ca. 1 M in arsenate ester and ca. 3 M in the corresponding alcohol. Spectra of trimethyl arsenate–methyl alcohol solutions showed line broadening attributable to exchange of methyl groups between ester and alcohol environments. No line broadening was detectable in the spectra of the other ester–alcohol solutions. However, addition of p-toluenesulfonic acid catalyst increased the rate of methyl alcohol exchange with trimethyl arsenate and introduced exchange line broadening in the spectra of the ethyl, n-propyl, n-butyl, and n-pentyl arsenate–alcohol solutions. No exchange line broadening was observed in spectra of isopropyl arsenate–alcohol solutions, saturated in catalyst, up to 80 °C.

Exchange in the triethyl arsenate–ethyl alcohol and tri-n-propyl arsenate–n-propyl alcohol systems was studied by using both anhydrous p-toluenesulfonic acid and the monohydrate as catalysts. The methyl and n-butyl systems were studied by using only the monohydrate, and the study of the n-pentyl system employed only the anhydrous acid. One effect of using the monohydrate as catalyst was to hydrolyze a small amount of the ester, altering the ester and alcohol concentrations and presumably introducing a small amount of arsenic acid. Ester and alcohol concentrations were corrected for this effect in the data analysis. A comparison of data for anhydrous catalyst and hydrate shows only minor differences.

Addition of anhydrous catalyst to acetonitrile solutions of the ester alone or alcohol alone resulted in no apparent change in the NMR spectra. Addition of the monohydrate to ester solutions, on the other hand, resulted in some ester hydrolysis, and the spectra showed line broadening due to exchange with the alcohol formed by hydrolysis.

Typical exchange-broadened spectra for the triethyl arsenate–ethyl alcohol system are shown in Figure 1 as a function of temperature and in Figure 2 as a function of catalyst concentration at fixed temperature. Spectral changes observed as a function of temperature were, in all cases, completely reversible. It should

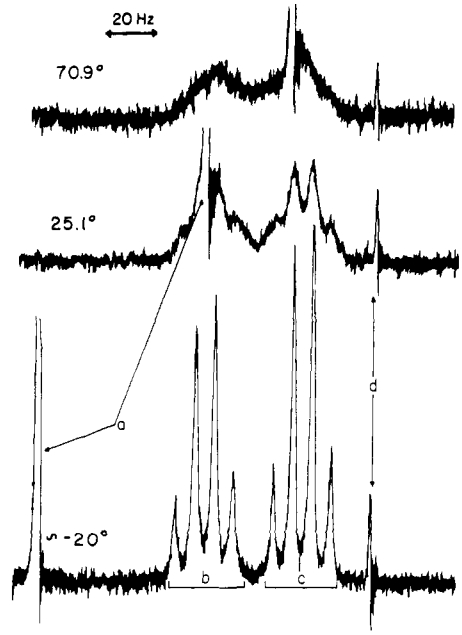

Figure 1. Temperature dependence of the α-methylene proton resonance of an acetonitrile solution of triethyl arsenate (1.0 M), ethyl alcohol (3.0 M), and p-toluenesulfonic acid (0.35 M): (a) hydroxyl proton resonance, (b) ester α-methylene protons, (c) alcohol α-methylene protons, and (d) acetonitrile ^{13}C satellite.

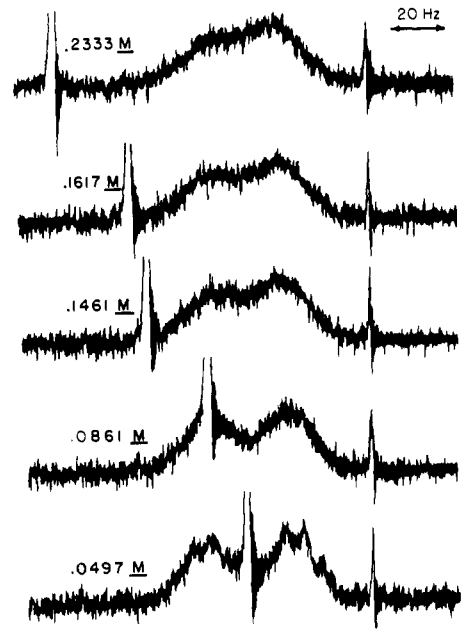

Figure 2. NMR spectra of the ethyl alcohol–arsenate system at 60 °C at various concentrations of p-toluenesulfonic acid catalyst. Peaks are as assigned in Figure 1.

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Table I. Observed Lifetimes for Triethyl Arsenate–Ethyl Alcohol Exchange

T/°C	t/ms	T/°C	t/ms
	$[C_7H_7SO_3H]$ = 0.045 M[a]		
25.1	24.5	57.3	16.5
34.5	22.0	67.1	16.0
48.9	17.0	70.9	18.5
	$[C_7H_7SO_3H]$ = 0.078 M[b]		
21.8	21.0	57.3	13.0
35.3	17.5	67.1	11.0
48.9	14.0	71.7	11.0
	$[C_7H_7SO_3H]$ = 0.132 M[c]		
22.6	16.0	58.2	10.0
34.9	13.0	67.1	9.0
48.9	11.0	73.4	8.0
	$[C_7H_7SO_3H]$ = 0.146[d]		
20.9	14.5	58.2	10.0
34.9	13.0	67.1	9.0
48.9	10.0	74.3	8.0
	$[C_7H_7SO_3H]$ = 0.211 M[e]		
20.9	12.5	57.3	7.5
34.5	10.0	67.1	6.5
46.3	8.5	75.1	6.0

[a] $[C_2H_5OH]$ = 3.19 M, $[(C_2H_5O)_3AsO]$ = 0.92 M. [b] $[C_2H_5OH]$ = 3.18 M, $[(C_2H_5O)_3AsO]$ = 0.92 M. [c] $[C_2H_5OH]$ = 3.17 M, $[(C_2H_5O)_3AsO]$ = 0.92 M. [d] $[C_2H_5OH]$ = 3.25 M, $[(C_2H_5O)_3AsO]$ = 0.90 M. [e] $[C_2H_5OH]$ = 3.39 M, $[(C_2H_5O)_3AsO]$ = 0.85 M.

be noted that the hydroxyl proton resonance, seen in Figures 1 and 2, moves upfield with increasing temperature and downfield with increasing catalyst concentration. This resonance was always narrow compared with the exchange-broadened peaks and did not materially interfere with the line shape analysis. Values of the mean lifetime τ, obtained from the computer analysis of the spectra of the triethyl arsenate–ethyl alcohol system, are given in Table I. Similar data for the other ester–alcohol systems studied are available as supplementary material.

With the assumption that the exchange process is first order in both ester and alcohol (see below), the exchange rate is given by eq 5 and 6. The pseudo-first-order rate constants, τ_A^{-1} and

$$\text{rate} = k_{obsd}[E][A] \quad (5)$$

$$\text{rate} = \tau_A^{-1}[A] = 3\tau_E^{-1}[E] \quad (6)$$

τ_E^{-1}, are related to the geometric mean lifetime τ by eq 7 and 8,

$$\tau_E^{-1} = p_A\tau^{-1} \quad (7)$$

$$\tau_A^{-1} = p_E\tau^{-1} \quad (8)$$

where p_E and p_A are the mole fractions of α-methylene protons in the ester and alcohol environments, respectively. The observed rate constant may thus be related to τ by eq 9. Observed rate

$$k_{obsd} = \tau^{-1}/([E] + [A]/3) \quad (9)$$

constants for ethyl alcohol exchange with triethyl arsenate are plotted vs. the concentration of *p*-toluenesulfonic acid in Figure 3. Similar plots are obtained for the other ester–alcohol mixtures.

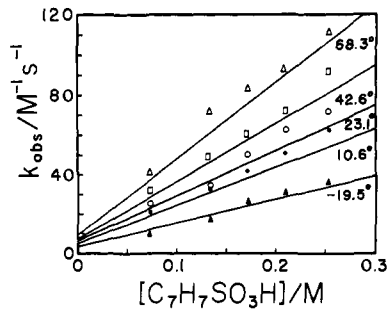

Figure 3. k_{obsd} as a function of *p*-toluenesulfonic acid concentration at various temperatures for triethyl arsenate–ethyl alcohol exchange. The straight lines correspond to the least-squares parameters of Table II.

In all cases, the observed rate was found to be linear in catalyst concentration, but with a nonzero intercept at zero catalyst concentration

$$k_{obsd} = k_u + k_c[C_7H_7SO_3H] \quad (10)$$

suggesting that exchange takes place via two independent parallel paths, an acid-independent path with rate constant k_u, and an acid-catalyzed path with rate constant k_c. Data at a single temperature could be fitted to eq 10 to extract k_u and k_c. However, since temperatures sometimes varied from run to run, this procedure was not possible without interpolation. To avoid interpolation errors, we adopted the following data analysis procedure. By applying absolute rate theory to eq 10, we may express k_{obsd} as eq 11, where k_B is Boltzmann's constant, h is Planck's constant,

$$k_{obsd} = (k_BT/h)[\exp(\Delta S_u^{\ddagger}/R)\exp(-\Delta H_u^{\ddagger}/RT) + [C_7H_7SO_3H]\exp(\Delta S_c^{\ddagger}/R)\exp(-\Delta H_c^{\ddagger}/RT)] \quad (11)$$

$\Delta S_u^{\ddagger}$ and $\Delta H_u^{\ddagger}$ are the entropy and enthalpy of activation for the uncatalyzed pathway, and $\Delta S_c^{\ddagger}$ and $\Delta H_c^{\ddagger}$ are the entropy and enthalpy of activation for the acid-catalyzed pathway. The values of k_{obsd} were fitted to eq 11 by using a nonlinear least-squares procedure[3] to obtain the activation parameters given in Table II.

With the exception of the methyl ester, which undergoes exchange significantly more rapidly, there is no discernible trend in the activation parameters. Within experimental error, the enthalpy and entropy of activation for the uncatalyzed pathway are 3 kJ mol^{-1} and −210 J K^{-1} mol^{-1} while for the acid-catalyzed pathway the activation parameters are, respectively, 12 kJ mol^{-1} and −160 J K^{-1} mol^{-1}. The methyl ester exchange appears to differ primarily in having lower enthalpies of activation for both the uncatalyzed and acid-catalyzed pathways.

Since all NMR line-broadening experiments used the same nominal ester and alcohol concentrations, the geometric mean lifetimes do not permit the determination of kinetic orders. Although in principle this information is obtainable from experiments in which concentrations are varied, in practice the experimental signal-to-noise ratio permitted only small variations in concentration. The high concentrations used would make the interpretation of the results of such an experiment somewhat questionable in any case. Thus this line of experiments was not pursued.

Isotope-Exchange Kinetics. Since exchange in the isopropyl arsenate–alcohol system proved too slow for study by NMR line

Table II. Rate Constants and Activation Parameters for ROH–$OAs(OR)_3$ Exchange

R	k_u[a]	$\Delta H_u^{\ddagger}$[c]	$\Delta S_u^{\ddagger}$[d]	k_c[b]	$\Delta H_c^{\ddagger}$[c]	$\Delta S_c^{\ddagger}$[d]	no. of runs
methyl[e]	194	−3 ± 2	−211 ± 7	1630	6 ± 2	−165 ± 5	23
ethyl[e]	16	4 ± 3	−209 ± 8	133	11 ± 2	−167 ± 6	30
ethyl[f]	6	6 ± 5	−210 ± 16	236	7 ± 2	−176 ± 2	54
n-propyl[e]	13	1 ± 3	−221 ± 8	72	18 ± 3	−150 ± 8	25
n-propyl[f]	6	1 ± 10	−226 ± 35	445	10 ± 2	−160 ± 6	24
n-butyl[e]	15	6 ± 3	−204 ± 9	89	12 ± 2	−166 ± 7	30
n-pentyl[f]	8	3 ± 4	−216 ± 15	521	12 ± 1	−153 ± 2	52
isopropyl	0.014	18 ± 3	−220 ± 8				

[a] Uncatalyzed rate constant, M^{-1} s^{-1}, at 25 °C. [b] Catalyzed rate constant, M^{-2} s^{-1}, at 25 °C. [c] kJ mol^{-1}. [d] J mol^{-1} K^{-1}. [e] Catalyst added as *p*-toluenesulfonic acid monohydrate. [f] Catalyst added as anhydrous *p*-toluenesulfonic acid.

Table III. Isopropyl Arsenate–Isopropyl Alcohol Exchange Rates in CD_3CN

T/°C	[E]/ M[a]	[A]/ M[a]	$\Delta[A]_{corr}$/ M[b]	10^3rate/ M s^{-1}	10^2k_2/ M^{-1} s^{-1}
41.2	0.089	0.102	0.001	0.30 ± 0.01	3.3
41.2	0.096	0.225	0.024	0.48 ± 0.03	2.2
41.2	0.087	0.364	−0.038	0.71 ± 0.04	2.0
41.2	0.093	0.523	0.021	0.96 ± 0.04	2.0
41.2	0.085	0.691	0.089	1.13 ± 0.07	1.9
39.3	0.048	0.280	0.005	0.67 ± 0.02	5.0
39.3	0.073	0.277	0.002	0.84 ± 0.02	4.2
39.3	0.103	0.288	0.013	1.02 ± 0.04	3.4
39.3	0.122	0.269	0.004	1.10 ± 0.03	3.4
39.3	0.154	0.265	−0.010	1.20 ± 0.05	3.1
41.9	0.146	0.473	−0.001	1.46 ± 0.02	2.1
53.1	0.144	0.480	0.006	2.26 ± 0.04	3.3
33.9	0.142	0.488	0.014	1.32 ± 0.03	1.9
22.6	0.141	0.488	0.014	1.00 ± 0.03	1.5
40.5	0.149	0.466	−0.008	1.54 ± 0.04	2.2
1.0	0.104	0.590	0.051	9.0 ± 1.0[c]	15
1.0	0.098	0.386	0.116	12.2 ± 1.4[c]	32
1.0	0.098	0.479	0.086	8.0 ± 1.4[c]	17
−2.2	0.119	0.336[e]	0.004	5.6 ± 0.9[d]	14
−2.2	0.106	0.375[e]	0.035	7.0 ± 1.0[d]	18
−2.2	0.116	0.346	0.006	4.6 ± 0.2[d]	12
−2.2	0.117	0.343	0.003	4.7 ± 0.3[d]	13

[a] Ester and alcohol concentrations, corrected from nominal values to match NMR peak height ratio. [b] Correction to alcohol concentration. [c] 0.042 M *p*-toluenesulfonic acid monohydrate. [d] 0.021 M *p*-toluenesulfonic acid (anhydrous). [e] Initial alcohol was C_3D_7OH.

Table IV. Isopropyl Arsenate–Isopropyl Alcohol Exchange Rates in CH_2Cl_2

T/°C	[E]/ M[a]	[A]/ M[a]	$\Delta[A]_{corr}$/ M[b]	10^3rate/M s^{-1}	10^2k_2/ M^{-1} s^{-1}
38.7	0.041	0.225	0.017	0.58 ± 0.05	6.3
38.7	0.041	0.373	0.014	0.73 ± 0.07	4.8
38.7	0.042	0.571	0.009	0.92 ± 0.06	3.8
38.7	0.040	0.763	0.017	1.00 ± 0.12	3.3
38.7	0.043	0.937	0.004	1.12 ± 0.04	2.8
40.0	0.379	0.112	0.006	3.1 ± 0.8	7.3
40.0	0.373	0.236	0.014	6.4 ± 0.6	7.3
40.0	0.369	0.355	0.036	8.0 ± 0.8	6.1
40.0	0.351	0.585	0.089	11.0 ± 1.5	5.4
40.0	0.334	0.777	0.108	13.5 ± 1.4	5.2

[a] Ester and alcohol concentrations, corrected from nominal values to match NMR peak height ratio. [b] Correction to alcohol concentration.

broadening, this reaction was followed by an isotope-exchange technique. Acetonitrile or dichloromethane solutions of triisopropyl arsenate were mixed with perdeuterioisopropyl alcohol, and the β-proton ester and alcohol resonances were followed as functions of time. Since the NMR lines remained sharp in this experiment, it was possible to work at lower concentrations of ester and alcohol and to vary the concentrations over nearly an order of magnitude. The exchange rates from these experiments, determined by using eq 3 and 4, are given in Tables III and IV for the acetonitrile and dichloromethane data, respectively. The ester and alcohol concentrations given in the tables were corrected as described in the Experimental Section. If the correction resulted from hydrolysis, the magnitude of the alcohol correction, which is shown in the tables, is equal to the concentration of acidic protons generated.

Since ester and alcohol concentrations could be varied over a considerable range, it was hoped that the kinetic orders could be uniquely determined. Thus in one series of kinetic runs (the first five entries in Table III), the alcohol concentration was varied from 0.1 to 0.7 M while the ester concentration was held at about 0.09 M. A plot of log (rate) vs. log [A] gave an apparent order in alcohol of 0.71. A second series (the next five entries in Table III) varied the ester concentration at constant alcohol concentration and gave an apparent order in ester of 0.55. Reproducibility between series of kinetic runs was often poor; for example, the rates measured in the second series given in Table III are about 50% greater than might be expected from the series 1 runs. Nonetheless, several other series of kinetic runs confirmed the apparent orders in ester and alcohol as substantially less than 1. The dichloromethane data shown in Table IV give similar low orders in alcohol; in this case, however, plots of log (rate) vs. log [A] are significantly nonlinear.

Table V. Isopropyl Arsenate–Benzyl Alcohol Exchange Rate Data

T/°C	[E]/ mM	[A]/ mM	k_2/M^{-1} s^{-1}	solvent	no. of runs
13.9	37.4	3.32	0.42 ± 0.02	CH_3CN	3
18.9	37.4	3.32	0.54 ± 0.01	CH_3CN	1
23.6	37.4	3.32	0.64 ± 0.04	CH_3CN	3
27.3	37.4	3.32	0.70 ± 0.03	CH_3CN	2
31.1	37.4	3.32	0.88 ± 0.07	CH_3CN	1
15.7	59.5	3.44	0.39 ± 0.06	CH_3CN	3
15.7	59.5	3.44[a]	0.39 ± 0.04	CH_3CN	3
10.0	41.4	3.71	0.122 ± 0.004	CH_2Cl_2	2
14.6	41.4	3.71	0.153 ± 0.013	CH_2Cl_2	2
19.1	41.4	3.71	0.174 ± 0.008	CH_2Cl_2	2
23.8	41.4	3.71	0.201 ± 0.002	CH_2Cl_2	1
20.0	4.9	0.59	0.53 ± 0.03[b]	CH_3CN	3
20.0	9.9	0.59	1.08 ± 0.07[b]	CH_3CN	3
20.0	19.8	0.59	1.76 ± 0.01[b]	CH_3CN	3
20.0	49.3	0.59	3.54 ± 0.15[b]	CH_3CN	3

[a] BzOD. [b] Initial rate in arbitrary units.

One series of kinetic runs, with 0.48 M isopropyl alcohol and 0.14 M triisopropyl arsenate in acetonitrile, covered the temperature range 22–53 °C and permitted the determination of activation parameters. With the assumption that the reaction is first order in alcohol and in ester, these data gave $\Delta H^{\ddagger} = 18 \pm 3$ kJ mol^{-1} and $\Delta S^{\ddagger} = -220 \pm 8$ J mol^{-1} K^{-1}. Comparison of these parameters with those determined for the straight-chain alkoxyl-group-exchange reactions (Table II) suggests that the exchange mechanism must be qualitatively similar.

Two series of kinetic runs (the last seven entries in Table III) show that the isopropyl alcohol–arsenate exchange is catalyzed by *p*-toluenesulfonic acid. The exchange rate found in these series is 10–20 times faster than would be expected in the absence of catalyst. The last series of four experiments demonstrates a kinetic isotope effect for the acid-catalyzed exchange, $k_H/k_D = 1.3 \pm 0.2$.

Transesterification Kinetics. The reaction of benzyl alcohol with triisopropyl arsenate was followed by monitoring the absorbance change at 263 nm. When the ester:alcohol mole ratio was about 10:1, reaction 12 went essentially to completion as

$$\text{BzOH} + \text{OAs(O-}i\text{-Pr)}_3 \rightarrow i\text{-PrOH} + \text{OAs(O-}i\text{-Pr)}_2\text{(OBz)} \quad (12)$$

indicated by the NMR spectrum of the product mixture. Plots of ln $(A_\infty - A_t)$ vs. time were cleanly linear over more than 2 half-lives, indicating that the reaction is first order in alcohol under these conditions. The method of initial rates was employed to determine the order in ester. In a series of experiments where the alcohol concentration was 5.88×10^{-4} M and the ester concentration ranged from 4.94×10^{-3} to 4.93×10^{-2} M, the rate was linear in ester concentration at lower ester concentrations, but the order in ester appears to fall at the higher concentrations. Data from these experiments are given in Table IV. Activation parameters were determined for the reaction both in acetonitrile and in dichloromethane solvents: $\Delta H^{\ddagger} = 27 \pm 2$ kJ mol^{-1} and $\Delta S^{\ddagger} = -158 \pm 5$ J mol^{-1} K^{-1} for the reaction in acetonitrile and $\Delta H^{\ddagger} = 22 \pm 2$ kJ mol^{-1} and $\Delta S^{\ddagger} = -183 \pm 8$ J mol^{-1} K^{-1} in dichloromethane. At 25 °C, the transesterification rate is more rapid in acetonitrile ($k = 0.67$ M^{-1} s^{-1}) than in dichloromethane ($k = 0.21$ M^{-1} s^{-1}).

Comparison of the rates of the reaction of triisopropyl arsenate with benzyl alcohol and with benzyl alcohol-*d* shows no kinetic isotope effect, $k_H/k_D = 0.98 \pm 0.18$.

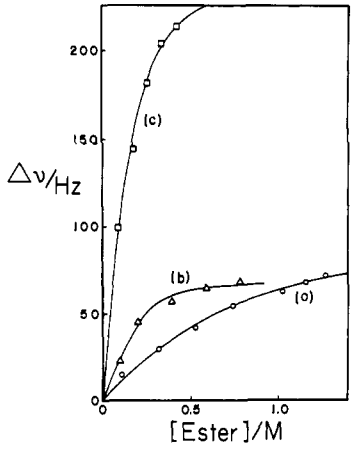

Figure 4. Shift of the hydroxyl proton resonance on addition of triisopropyl arsenate to (a) 0.927 M isopropyl alcohol in acetonitrile, (b) 0.496 M isopropyl alcohol in dichloromethane, and (c) 0.291 M *p*-toluenesulfonic acid in acetonitrile. Solid curves are least-squares fitted to the data points shown.

Formation of Hydrogen-Bonded Complexes. The deviations seen from simple second-order kinetics at higher concentrations of ester and alcohol could be a consequence of complex formation, presumably by hydrogen bonding of the alcohol to the unique oxygen of the ester. Such bonding has been reported for triethyl arsenate[18] and is known for the analogous phosphate esters.[19]

In order to confirm this possibility and to determine the degree to which hydrogen bonding occurs between ester and alcohol in the mixtures used in the kinetic studies, we measured the NMR chemical shift of the hydroxyl proton of isopropyl alcohol in both acetonitrile and dichloromethane solvents. The results are summarized in Figure 4 for data obtained at 40 °C. In both solvents, sizable shifts of the hydroxyl proton resonance are observed as a function of ester concentration, suggesting the formation of hydrogen-bonded complexes. From the shape of the curves shown in Figure 4, it is evident that the complex is more stable in dichloromethane than in acetonitrile, as might be expected.

The data were first fitted to eq 13, where x_C is the mole fraction

$$\Delta\nu = x_C\Delta\nu_C \tag{13}$$

of alcohol in a 1:1 hydrogen-bonded complex and $\Delta\nu_C$ is the shift of the resonance frequency between free alcohol and complex. The fit was poor. However, if a 2:1 alcohol–ester complex was also considered, the data could be fitted within experimental error to eq 14. Here it was assumed that the complex formation constants

$$\Delta\nu = (x_{C1} + x_{C2})\Delta\nu_C \tag{14}$$

are related by the statistical factor $K_1/K_2 = 4$ so that the data again were fitted to only two parameters: $K_1 = 2.2 \pm 0.6$ and $\Delta\nu_C = 106 \pm 10$ Hz for the acetonitrile data and $K_1 = 36 \pm 19$ and $\Delta\nu_C = 70 \pm 2$ Hz for the dichloromethane data.

A similar experiment was performed in which the acidic proton chemical shift was measured as a function of triisopropyl arsenate concentratin for acetonitrile solutions of *p*-toluenesulfonic acid at 40 °C. These data are also plotted in Figure 4. The shifts observed in this case are considerably larger but again suggest the formation of hydrogen-bonded complexes. Fit of the data to eq 14 is fairly good and results in the parameters: $K_1 = 17 \pm 16$ and $\Delta\nu_C = 254 \pm 5$ Hz.

Ester Self-Association. Infrared studies suggest that some association of arsenate esters to form oxygen-bridged dimers occurs at −80 °C.[11] However, freezing-point depression studies of benzene solutions of triisopropyl arsenate here failed to give any indication of ester dimerization, even up to 1 M ester. Although this hardly eliminates an ester dimer as a kinetic intermediate, we have no evidence, kinetic or otherwise, to suggest the involvement of such a species.

Discussion

The general nature of the mechanism of the arsenate ester–alcohol exchange reactions may be inferred from the activation parameters and the dependence of rate on the alkyl group. The low enthalpies of activation and very negative entropies of activation can only be rationalized in terms of an associative mechanism (A or I_a in the terminology of Langford and Gray).[20] This consideration would require that at least one molecule of ester and one of alcohol participate in the transition state which most likely involves 5-coordinate arsenic. The rate of ester–alcohol exchange is strongly dependent on the number of β-carbon atoms. Increasing the number from zero (methyl) to one (the straight-chain alkyl groups) decreases the rate by about an order of magnitude while a further increase to two β-carbon atoms (isopropyl) decreases the rate by three powers of ten. This effect is undoubtedly steric in origin and is to be expected for a highly associative process.

Although this picture of the mechanism is almost certainly qualitatively correct, the details appear to be complicated. Kinetic studies of the reaction of triisopropyl arsenate with benzyl alcohol showed that the reaction is cleanly first order in alcohol and, at least at the lower end of the concentration range, first order in ester as well. In the studies of isopropyl alcohol exchange with triisopropyl arsenate, on the other hand, the apparent kinetic orders are less than one for both alcohol and ester. The difference between these experiments lies in the concentration ranges used. In the transesterification reaction, the alcohol and ester concentrations were in the ranges 0.6–3.3 mM and 5–50 mM, respectively. Under these conditions, hydrogen bonding between alcohol and ester is of only marginal significance. In the isopropyl arsenate–alcohol exchange experiments, both ester and alcohol concentrations were greater than 0.1 M and a large fraction of the limiting reagent was involved in hydrogen bonding.

If the exchanging alcohol molecule is first hydrogen bonded to the ester, one might expect a rate law of the form

$$\text{rate} = k_1[\text{E}\cdot\text{A}] + k_2[\text{E}\cdot 2\text{A}] \tag{15}$$

With such a rate law, one would expect the apparent order in alcohol to be one at low concentrations, as observed, but, if $k_2 > k_1$, the order should increase at higher concentrations. In fact, the observed order decreases at higher concentrations, suggesting that hydrogen bonding is a competing process rather than a step in the exchange reaction. In this case, the expected rate law would be of the form

$$\text{rate} = k_1[\text{E}][\text{A}] + k_2[\text{E}\cdot\text{A}][\text{A}] + k_3[\text{E}\cdot 2\text{A}][\text{A}] \tag{16}$$

Since

$$[\text{A}] = [\text{A}]_0 - [\text{E}\cdot\text{A}] - 2[\text{E}\cdot 2\text{A}] \tag{17}$$

it is evident that, if $k_1 \simeq k_2 \simeq k_3$, the apparent order in alcohol, determined by the dependence of rate on $[\text{A}]_0$, should be less than 1. Since the apparent order in ester is also less than one, it is necessary that $k_1 > k_2 > k_3$.

In principle, it should be possible to test this kinetic model quantitatively, but the number of parameters necessarily involved—three rate constants and two equilibrium constants—would require a large amount of very good data and experimental problems intervene. In practice, it is virtually impossible to completely eliminate ester hydrolysis. Although the concentrations of ester and alcohol can be corrected for hydrolysis by using the NMR peak heights, hydrolysis must produce some mixture of arsenic acid and the mono- and diesters. These species (all fairly acidic) would be expected to catalyze the ester–alcohol exchange in a way analogous to the observed catalysis by *p*-toluenesulfonic acid. Indeed, the rate of alcohol exchange tended to increase with the degree of hydrolysis in the isopropyl system. This problem, though understood qualitatively, made detailed quantitative

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analysis of the kinetic data difficult, if not impossible.

The absence of a kinetic isotope effect suggests (but does not prove) that proton transfer occurs after the rate-determining formation of a 5-coordinate intermediate (eq 18). This mech-

$$\begin{array}{l} OAs(OR)_3 + R'OH \rightleftarrows OAs(OR)_3(OHR') \\ \qquad\qquad\qquad\qquad \updownarrow \\ OAs(OR)_2(OR') + ROH \rightleftarrows OAs(OR)_2(OR')(OHR) \end{array} \quad (18)$$

anism requires that proton transfer between alkoxyl groups of the trigonal-bipyramidal intermediate, probably accompanied by pseudorotation,[21] be fast compared with dissociation of the intermediate. Such a postulate is consistent with the activation parameters which suggest essentially no bond breaking in the transition state. The intermediate is not a significant equilibrium species, however; NMR spectra showed no extra resonances and careful measurements showed that the α- and β-proton chemical shifts of isopropyl alcohol and triisopropyl arsenate were independent, respectively, or ester and alcohol concentrations.

The mechanism of the acid-catalyzed exchange process presents an interesting problem. A catalyst which operates by lowering the entropic contribution to the free energy of activation while increasing the enthalpic contribution is at least unusual. The exchange kinetics are cleanly first order in *p*-toluenesulfonic acid in the concentration range studied, 0.02–0.37 M. Measurement of the conductance of solutions of the acid in acetonitrile showed that the molar conductivity is small and very nonlinear in this concentration range.[3] Thus we conclude that the observed catalysis involves the undissociated acid.

Chemical shift experiments described above suggest that the catalyst is largely hydrogen bonded to the ester in the concentration range used in the kinetic experiments. It seems reasonable to suppose, therefore, that alcohol exchange with the ester–catalyst hydrogen-bonded complexes E·C, E·2C, and E·A·C proceeds faster than when the ester is free of hydrogen bonds or is associated only with alcohol molecules. The acid is expected to be a better hydrogen-bond donor, and this is reflected in the larger formation constant obtained from the chemical shift data. Hydrogen bonding to the unique ester oxygen might be expected to weaken the As=O bond, thereby facilitating the formation of a 5-coordinate intermediate. However, this cannot be the major catalytic effect since one would then expect the reaction to be catalyzed by alcohol as well. This inductive effect in either case would be partially compensated by increased steric crowding in formation of a 5-coordinate transition state or intermediate. The difference in behavior of the ester–acid and ester–alcohol hydrogen-bonded complexes must be due to the ability of the sulfonic acid to facilitate proton transfer.

The kinetic isotope effect found for the acid-catalyzed-exchange process suggests that proton transfer occurs in this case prior to the transition state. If formation of the 5-coordinate transition state is accompanied by at least partial transfer of the alcohol proton to one of the sulfonate oxygens, the system is set up for pseudo-rotation accompanied by shift of the proton to another alkoxyl group. Indeed, there seems to be nothing to prevent the entire process from being concerted. Such a mechanism is consistent with the activation parameters which suggest a looser transition state with relatively less As-O bond formation (and more As-O bond breaking) than in the uncatalyzed pathway. The effect of the catalyst apparently is to merge the proton-transfer step into the formation of the 5-coordinate species, thus destabilizing the intermediate and speeding the exchange process.

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Supplementary Material Available: Observed lifetimes for arsenate triester–alcohol exchange from NMR data for methyl, ethyl, *n*-propyl, *n*-butyl, and *n*-pentyl alcohols (5 pages). Ordering information is given on any current masthead page.

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A Semiclassical Treatment of Electron-Exchange Reactions. Application to the Hexaaquoiron(II)–Hexaaquoiron(III) System

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Abstract: A semiclassical description of electron-exchange reactions, in which a classical treatment of the solvent motion is combined with a quantum-mechanical description of the inner-sphere modes, is developed. This approach, which assumes that the solvent and inner-sphere reorganizations can be treated independently, yields relatively simple expressions for the variation of the electron-exchange rate constant and activation parameters with temperature. The semiclassical description is compared with the classical Marcus–Hush theory and with the quantum-mechanical theory of Kestner, Logan, and Jortner. The semiclassical formalism is remarkably successful in reproducing the results of the full quantum-mechanical theory at all temperatures. Both theories yield activation parameters that approach the classical values at high temperature. The activation parameters for the $Fe(H_2O)_6^{2+}$–$Fe(H_2O)_6^{3+}$ exchange reaction predicted by the various theories are compared with the experimental results. The calculations show that at 300 K the free energy of activation is close to the value predicted by the classical model despite the fact that the average energy of the reacting species is significantly less than the classical barrier.

Introduction

Electron transfer is of importance in a variety of physical, chemical, and biological systems, ranging from semiconductors to cytochromes.[1,2] Rates of electron transfer in these systems span some 20 orders of magnitude. There is a continuing interest in the origins of this large rate variation and both classical[3,4] and

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