systems where $^1O_2$ may be involved including erythropoietic protoporphyria[52] and hematoporphyrin photochemotherapy.[53-55]

The relatively precise distance and angle information for **4**–**7** provided by NMR studies coupled with the triplet energy transfer rate constants determined by flash photolysis provide correlations among structural, dynamical, and photophysical parameters which will be useful in developing or testing quantitative theories of energy transfer between chromophores within a single molecule. For example, it appears that a quantum mechanical calculation of orbital overlap would be necessary in order to correlate the above-mentioned electron transfer in polystyrene with structure. These molecular systems are also potentially useful for studying intramolecular electron transfer reactions; in fact, a carotenoporphyrin linked to a quinone has recently been found to form a long-lived charge-separated state upon excitation with visible light.[56]

Acknowledgment. This material is based upon results supported in part by the National Science Foundation under Grants CHE-8209348 and INT-8212583 (CNRS-NSF Exchange Program), CNRS Grant 3064, the North Atlantic Treaty Organization under Grant RG.083.81, the U.S. Department of Energy under Grant FG02-79ER10545 and the Cancer Research Campaign (UK). We thank Hoffmann-La Roche, Inc., for a gift of β-apo-8′-carotenal.

Registry No. 6, 95998-78-0; **7**, 95998-79-1; **8**, 95998-80-4; **9**, 95998-81-5; **10**, 95998-82-6; **11**, 95998-83-7; **12**, 95998-84-8; **13**, 95998-85-9; **14**, 95998-86-0; **15**, 95998-87-1; **16**, 95998-88-2; **17**, 1253-46-9; **18**, 90652-11-2; **19**, 90447-13-5; 5-(4-hydroxyphenyl)-10,15,20-tris(4-methylphenyl)porphyrin, 57412-08-5; 7′-apo-7′-(4-(iodomethyl)-phenyl)-β-carotene, 95998-89-3; 5-(3-hydroxyphenyl)-10,15,20-tris(4-methylphenyl)porphyrin, 57412-06-3; 5-(2-hydroxyphenyl)-10,15,20-tris(4-methylphenyl)porphyrin, 57412-07-4; 5-(4-(3-hydroxypropoxylphenyl)-10,15,20-tris(4-methylphenyl)porphyrin, 95998-90-6; α-bromo-*p*-toluoyl chloride, 52780-16-2; 2,3-dimethoxybenzaldehyde, 86-51-1; *p*-tolualdehyde, 104-87-0; pyrrole, 109-97-7; propionic acid, 79-09-4; 2,6-dimethoxybenzaldehyde, 3392-97-0; ethylene oxide, 75-21-8; methyl α-bromo-*p*-toluate, 2417-72-3; β-apo-8′-carotenal, 1107-26-2; oxygen, 7782-44-7.

---

(52) Mathews-Roth, M. M. *J. Natl. Cancer Inst.* (*U.S.*) **1982**, *69*, 279–285.

(53) Weishaupt, K. R.; Gomer, C. J.; Dougherty, T. J. *Cancer Res.* **1976**, *36*, 2326–2329.

(54) Poletti, A.; Murgia, S. M.; Cannistraro, S. *Photobiochem. Photobiophys.* **1981**, *2*, 167–172.

(55) Bensasson, R. V.; Moore, T. A.; Gust, D.; Moore, A. L.; Joy, A.; Tom, R.; Nemeth, G. A.; Land, E. J. "Proceedings of the International Symposium on Tumour Phototherapy"; Andreoni, A., Cubeddu, R. Eds.; Plenum Press: New York, 1984; pp 93–94.

(56) Moore, T. A.; Gust, D.; Mathis, P.; Mialocq, J. C.; Chachaty, C.; Bensasson, R. V.; Land, E. J.; Doizi, D.; Liddell, P. A.; Lehman, W. R.; Nemeth, G. A.; Moore, A. L. *Nature* (*London*) **1984**, *307*, 630–632.

Acid-Catalyzed Enolization and Aldol Condensation of Acetaldehyde

Lynn M. Baigrie,[1a] Robin A. Cox,[1b]* Henryka Slebocka-Tilk,[1a] Michal Tencer,[1a] and Thomas T. Tidwell*[1a]

Contribution from the Department of Chemistry and Scarborough College, University of Toronto, Toronto, Ontario, Canada M5S 1A1. *Received December 3, 1984*

Abstract: The condensation of acetaldehyde (**1**) to an equilibrium mixture of aldol (**2**) and crotonaldehyde (**3**) is second order in **1**. An excess acidity analysis reveals that a water molecule is also involved in the rate-limiting step; the reaction is actually the *base-assisted* addition of vinyl alcohol to protonated **1**, even in concentrated H_2SO_4. A previous report of a kinetically first-order conversion of **1** to **3** is shown to be due to the presence of a fast-reacting oligomer of **1**. The reaction of **1** in D_2SO_4 leads to partially deuterated **3**, a result ascribed to partial conversion of vinyl alcohol to deuterated **1**. Hydrogen isotope exchange of **3** was also observed, but at a slower rate. The rates of enolization of **1** were studied by iodination and are consistent with previous results and the proposed mechanism. The interconversion of **2** and **3** is shown to proceed via the enol of **2**; in this case the rate-limiting step is water attack on/water loss from protonated **3**/**2**, not proton transfer at carbon.

The acid-catalyzed condensation of acetaldehyde (**1**) to aldol (**2**) and the subsequent dehydration of **2** to crotonaldehyde (**3**) is the simplest example of this fundamental class of organic reactions (eq 1). This reaction sequence is of particular relevance to a study in our laboratory of the acid-catalyzed hydration of acetylene to acetaldehyde[2] because **1** is converted to **3** under these conditions. Surprisingly, however, although enolization is well studied,[3] and the mechanism of the acid-catalyzed aldol reaction is sometimes discussed,[4] the only thoroughly investigated example of the latter process involves ketones and aromatic aldehydes.[5] The transformation of **1** to the equilibrium mixture of **2** and **3** has only once been the object of quantitative study.[6] However, there was not only a discrepancy found between these results[6] and an examination of acetaldehyde enolization using bromination rates,[7] but also there was a puzzling indication[6] that the reaction shown in eq 1 was first order in acetaldehyde, contrary to expectation.[4]

$$\underset{\mathbf{1}}{2CH_3CH{=}O} + H^+ \xrightarrow{k_2}$$

$$\underset{\mathbf{2}}{CH_3CH(OH)CH_2CH{=}O} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{\mathbf{3}}{CH_3CH{=}CHCH{=}O} + H_2O \qquad (1)$$

Thus McTigue and Gruen[6] reported that **1** in H_2SO_4 gave first-order formation of the characteristic UV absorption of **3**,

---

(1) (a) Scarborough College and Department of Chemistry. (b) Department of Chemistry. Mechanistic Studies in Strong Acids. X. Part IX is ref 12a.

(2) Baigrie, L. M.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T. T., manuscript in preparation.

(3) (a) Bell, R. P. "The Proton in Chemistry"; 2nd ed.; Chapman and Hall: London, 1973. (b) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1–77.

(4) (a) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1–444. (b) Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; 2nd ed.; Cornell: New York, 1969; pp 828–834 and 1003–1006. (c) Liler, M. "Reaction Mechanisms in Sulfuric Acid"; Academic Press: London, 1971; pp 231–232.

(5) Noyce, D. S.; Snyder, L. R. *J. Am. Chem. Soc.* **1959**, *81*, 620–624.

(6) McTigue, P. T.; Gruen, L. C. *Aust. J. Chem.* **1963**, *16*, 177–179.

(7) McTigue, P. T.; Sime, J. M. *Aust. J. Chem.* **1967**, *20*, 905–910.

Table I. Rate and Equilibrium Constants for the Interconversion of Aldol (**2**) and Crotonaldehyde (**3**) in H_2SO_4, 25 °C[a]

H_2SO_4, % w/w	X	log C_{H^+}	log a_{H_2O}	10^5k_{obsd}, s^{-1}	$K_{eq}{}^b$	10^5k_3, s^{-1}	10^5k_{-3}, s^{-1}
9.4	0.21	0.09	1.72	3.18	1.15	1.70	1.48
13.4	0.33	0.26	1.70	5.36	1.36	3.09	2.27
18.9	0.53	0.43	1.67	9.54	1.52	5.75	3.79
26.0	0.84	0.60	1.62	18.5	1.89	12.1	6.41
32.6	1.18	0.72	1.55	30.1	2.29	21.0	9.14
40.6	1.67	0.84	1.43	57.5	3.10	43.5	14.0
47.8	2.18	0.92	1.27	102	5.08	85.3	16.8
52.6	2.56	0.97	1.12	147	7.30	129	17.7
58.4	3.08	1.03	0.91	261	13.5	243	18.0
64.2	3.70	1.07	0.62	501	>99	501	

[a] Measured, both beginning with **3** and with **2** (derived from **5**), with agreement of ±5%. [b] Measured value, $K_{eq} = k_3/k_{-3}$.

with a linear dependence of log k on the acidity function H_0 of near unit slope for acid concentrations below 32%, and that above this concentration the rate became invariant with acidity. These results were interpreted in terms of rate-limiting enolization of **1** and were used to derive a pK_a of −2.7 for protonated acetaldehyde.[6]

Subsequently McTigue and Sime[7] measured the acid-catalyzed bromination of **1** and found that the rates were similar to those for the formation of **3** reported previously[6] at lower acidities but did not level off at higher acidities. The previously claimed pK_a value was withdrawn.

The iodination of acetaldehyde in acid was studied by Talvik and Hiidmaa,[8] who reported $k_{H^+} = 1.65 \times 10^{-5}$ M^{-1} s^{-1} for this reaction, as compared to the value of 1×10^{-5} M^{-1} s^{-1} calculated[9] from the graphical data given[7] for bromination. The iodination rate was, however, evidently statistically adjusted for the number of enolizable hydrogens and was also corrected for hydration of **1**, and it is not clear from the presentation if the two rate constants above are directly comparable.

In order to clarify the uncertain picture of the formation of **3** from **1** (eq 1) and to provide a consistent study of the enolization of **1**, a study of these reactions was undertaken. The excess acidity method,[10] already successfully applied to enolization processes,[11] several hydrolyses,[12] and aromatic nitrations,[13] is used to analyze the results and delineate the reaction mechanism.

Results

The rates of conversion of carefully purified acetaldehyde (**1**), in sulfuric acid, to an equilibrium mixture of **2** and **3** (eq 1) were measured by monitoring the increase of the characteristic UV absorption of **3**.[14,15] The essentially complete conversion of **1** to **3** at acid concentrations greater than 60% was established by direct observation of the ^{1}H NMR spectrum of **3** in the reaction medium. At lower acid concentrations ^{1}H NMR signals attributable to **2** were also observed, and thus it was necessary to study the interconversion of **2** and **3**.

Values of the constant for the equilibrium between **2** and **3**, $K_{eq} = k_3/k_{-3}$, in different acids were calculated from the final UV absorption beginning with **3** and are reported in Table I. Previous investigators reported K_{eq} values of 1.1[16] and 1.3[17] at 25 °C, but they did not observe a dependence of the equilibrium upon acidity. Our measurements extend to much higher acidities than theirs, however. As anticipated from the reported pK_{BH^+} of −4.32,[14a] **3** is completely protonated to **4**[15] in H_2SO_4 stronger than 64%, and there is no detectable **2** present above this acidity.

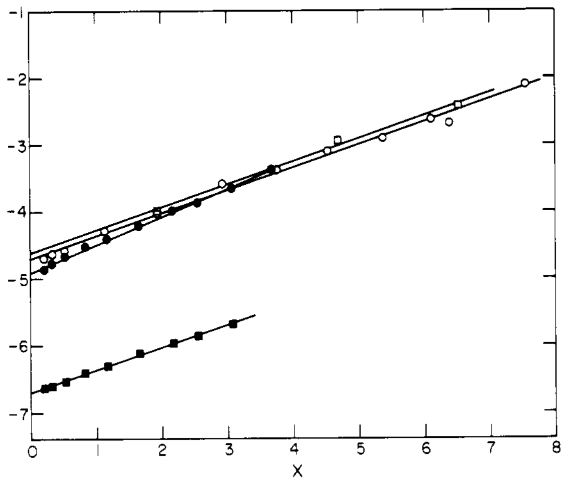


Figure 1. Excess acidity analysis of the interconversion of **2** and **3** and of the reaction of unpurified acetaldehyde in H_2SO_4 and D_2SO_4. Plots against X of (●) log k_3 − log C_{H^+} (**2** → **3**), (■) log k_{-3} − log C_{H^+} − log a_w (**3** → **2**), (○) log k − log C_{H^+} for the reaction of unpurified **1** in H_2SO_4, and (□) log k − log C_{H^+} for the reaction of unpurified **1** in D_2SO_4.

$$\underset{\mathbf{4}}{CH_3CH{=}CHCH{=}OH^+}$$

Values of $k_{obsd} = k_3 + k_{-3}$ were obtained both by measuring the rate of decrease of the UV absorption of **3** and also from the appearance of this absorption from **2**, generated in situ from reaction of 3-(trimethylsilyloxy)butanal (**5**), obtained by the sequence shown in eq 2. This method for preparation of **2** was adopted because, reports of the preparation of pure **2** notwithstanding,[18] in our hands this compound is unstable in a pure state due to facile dehydration and oligomerization.

$$CH_3CH(OSiMe_3)CH_2CO_2Et \xrightarrow[\text{(2) } H_2O]{\text{(1) DIBAL}} \underset{\mathbf{5}}{CH_3CH(OSiMe_3)CH_2CHO} \xrightarrow{H^+} \mathbf{2} \quad (2)$$

As required for the equilibration of eq 1, k_{obsd} measured beginning with either **2** or **3** was the same. The individual rate constants k_3 and k_{-3} were calculated from the measured values of k_{obsd} and K_{eq}, and all of these are reported in Table I.

These rate constants were subjected to an excess acidity analysis[10] by using available[19] values of X and log C_{H^+}. The excess acidity kinetic method has been described elsewhere,[10] and many

---

[8] Talvik, A.; Hiidmaa, S. *Org. React. (Tartu)* **1968**, *5*, 121–126.

[9] Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567–7572.

[10] Cox, R. A.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2944–2951.

[11] Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2952–2959.

[12] (a) Cox, R. A.; Yates, K. *Can. J. Chem.* **1984**, *62*, 1613–1617. (b) Cox, R. A.; Yates, K. *Ibid.* **1982**, *60*, 3061–3070. (c) Cox, R. A.; Yates, K. *Ibid.* **1981**, *59*, 2853–2863. (d) Cox, R. A.; Goldman, M. F.; Yates, K. *Ibid.* **1979**, *57*, 2960–2966.

[13] (a) Marziano, N. C.; Sampoli, M.; Pinna, F.; Passerini, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1163–1166. (b) Marziano, N. C.; Traverso, P. G.; Cimino, G. C. *Ibid.* **1980**, 574–578. (c) Marziano, N. C.; Sampoli, M. *Chem. Commun.* **1983**, 523–524.

[14] (a) Zalewski, R. I.; Dunn, G. E. *Can. J. Chem.* **1968**, *46*, 2468–2470. (b) Palmer, M. H.; Urch, D. S. *J. Chem. Soc.* **1963**, 174–178.

[15] Childs, R. F.; Lund, E. F.; Marshall, A. G.; Morrisey, W. J.; Rogerson, C. V. *J. Am. Chem. Soc.* **1976**, *98*, 5924–5931.

[16] Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1937**, *59*, 1461–1465.

[17] Bell, R. P.; Preston, J.; Whitney, R. B. *J. Chem. Soc.* **1962**, 1166–1170.

[18] (a) Späth, E.; Lorenz, R.; Freund, E. *Chem. Ber.* **1943**, *76*, 1196–1208. (b) Kyriakides, L. P. *J. Am. Chem. Soc.* **1914**, *36*, 530–537.

[19] Cox, R. A.; Yates, K. *J. Am. Chem. Soc.* **1978**, *100*, 3861–3867.

Table II. Rates of Conversion of Acetaldehyde (**1**) to the Equilibrium Mixture of Aldol (**2**) and Crotonaldehyde (**3**) in Sulfuric Acid, 25 °C

H_2SO_4, % w/w	X	log C_{H^+}	log a_{H_2O}[a]	$10^5 k_2$,[b] M^{-1} s^{-1}
47.8	2.18	0.92	1.27	2.01[c]
52.6	2.56	0.97	1.12	3.91[c]
58.4	3.08	1.03	0.91	10.9[c]
64.2	3.70	1.07	0.62	26.1
69.9	4.44	1.11	0.24	66.1
73.1	4.93	1.13	-0.02	113
78.4	5.85	1.15	-0.55	198
81.3	6.40	1.16	-0.91	285
88.2	7.67	1.06	-1.92	306

[a] In molarity units. [b] Method of initial rates. [c] k_2 was obtained from the observed rate by multiplying by the factor $(K_{eq}^{-1} + 1)$ (Table I).

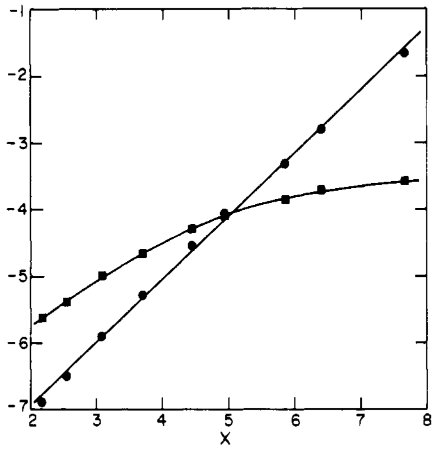


Figure 2. Excess acidity analysis of the condensation of pure **1** to **2** and **3**. Plots against X of (■) log k_2 – log C_{H^+} and (●) log k_2 – log C_{H^+} – log a_w.

examples of its use are available.[10-13] It can be briefly summarized as a combination of the Bunnett–Olsen kinetic method[20] with the improved r-parameter version[21] of the original Bunnett w-parameter treatment,[22] or alternatively as an extension of the Kresge α-coefficient method[23] to A-1 and A-2 reactions ($m^{\ddagger}$ and α are identical for A-S_E2 reactions[10]).

For k_3 a plot of log k_3 – log C_{H^+} against X was found to be linear, with slope 0.413 ± 0.007, intercept –4.90 ± 0.01, and correlation coefficient r 0.999 (see Figure 1). For k_{-3} the corresponding plot curved downward, indicating that water was involved in the reaction,[10] and indeed a plot of log k_{-3} – log C_{H^+} – log a_w against X was a good straight line (see Figure 1): slope 0.337 ± 0.004, intercept –6.70 ± 0.01,[25] r 0.999. The intercepts give standard-state (indicated by superscript zero) second-order rate constants of $(1.26 \pm 0.04) \times 10^{-5}$ M^{-1} s^{-1} for k_3^0 and $(1.09 \pm 0.02) \times 10^{-5}$ M^{-1} s^{-1} for k_{-3}^0, and these allow calculation of a standard-state extrapolated value of 1.15 ± 0.04 for K_{eq}^0, in good agreement with published values.[16,17]

Second-order rate constants k_2 for the conversion of **1** to the equilibrium mixture of **2** and **3** were calculated in most cases by the method of initial rates with eq 3,[6,26] and the same rate constant was obtained in one case by Tobey's method,[27] in which a plot of $A_1 - A_2$ vs. $t_2A_2 - t_1A_1$ has a slope of $k_2[\mathbf{1}]$. Values of k_2 were invariant with [**1**] and are listed in Table II. The first three values required correction with K_{eq}, as indicated.

$$k_2 = ([CH_3CHO]^2)^{-1}d[\mathbf{3}]/dt \qquad (3)$$

Table III. Rates of Crotonaldehyde Formation from Unpurified Acetaldehyde and Sulfuric Acid, 25 °C

H_2SO_4, %w/w	X	log C_{H^+}	$10^5 k$, s^{-1}
9.4	0.21	0.09	2.56
13.4	0.33	0.26	4.30
18.9	0.53	0.43	7.30
26.0	0.84	0.60	12.9
31.7	1.13	0.70	26.4
44.6	1.94	0.89	73.8
56.8	2.93	1.01	268
64.7	3.76	1.08	510
70.6	4.55	1.12	1030
75.7	5.37	1.14	1750
79.8	6.11	1.16	3490
81.3	6.40	1.16	3010
87.5	7.55	1.08	9570
42.7[a]	1.96	0.89	76.7
69.8[a]	4.69	1.12	1490
80.7[a]	6.53	1.16	5280

[a] % D_2SO_4 w/w.

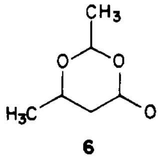
Table IV. Rates of Iodination of Acetaldehyde (**1**) in H_2SO_4 at 25 °C

H_2SO_4, % w/w	X	log C_{H^+}	log a_{H_2O}[a]	$10^5 k_1$,[b] s^{-1}
4.8	0.10	-0.22	1.73	0.739
9.4	0.21	0.09	1.72	1.88
13.4	0.33	0.26	1.70	3.25
18.9	0.53	0.43	1.67	6.77

[a] In molarity units. [b] Measured by using the method of direct iodine addition; at least two runs at each acidity, ±10%.

The excess acidity plot of log k_2 – log C_{H^+} against X curved downward, as shown in Figure 2, again indicating water involvement; the plot of log k_2 – log C_{H^+} – log a_w against X, also shown in Figure 2, has slope 0.95 ± 0.02, intercept –8.86 ± 0.08,[25] and r 0.999. Despite the good correlation coefficient slight downward curvature may still be present, however.

When the acetaldehyde used was not purified by distillation, the formation of crotonaldehyde (**3**) could be observed by UV as a first-order process at much lower acid strengths and shorter reaction times than required for the second-order process observed with purified acetaldehyde. However, the amount of **3** formed under the former conditions was less than 5% of the amount anticipated on the basis of the measured equilibrium constant for interconversion of **2** and **3**. These k values for the formation of **3** from unpurified **1** are presented in Table III, and comparison of k to the k_{obsd} values for interconversion of **2** and **3** (Table I) reveals a striking similarity, with the values of k_{obsd} exceeding those of k by about 30% at each acidity. A likely explanation of this behavior is that the source of **3** from unpurified **1** is some combination of oligomers of **1** in the sample. In addition to **2** several other oligomers are conceivable, for instance **6**, whose formation from acetaldehyde has been reported[28] and which would be expected to react in acid to form **3** at a rate similar to that of **2**.



6

This similarity is even more evident in the excess acidity plot, which is given in Figure 1; as can be seen, the lines for log k_3 – log C_{H^+} and log k – log C_{H^+} practically coincide. The parameters for the latter plot are slope 0.342 ± 0.008 and intercept –4.71 ± 0.03. The k values observed when unpurified **1** is used correspond

---

(20) Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* **1966**, *44*, 1917–1931.

(21) Yates, K. *Acc. Chem. Res.* **1971**, *4*, 136–144.

(22) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4956–4983.

(23) Kresge, A. J.; More O'Ferrall, R. A.; Hakka, L. E.; Vitullo, V. P. *J. Chem. Soc., Chem. Commun.* **1965**, 46–48.

(24) Cox, R. A.; Yates, K. *Can. J. Chem.* **1983**, *61*, 2225–2243.

(25) Water activities in molarity units were used,[12] giving true second-order rate constants, i.e., values in 1 M water. To obtain values in 55 M water it is necessary to add 1.74 to these intercepts (twice for two water molecules).

(26) Livingston, R. In "Investigation of Rates and Mechanisms of Reactions"; 2nd ed.; Friess, S. L., Lewis, E. S., Weissberger, A., Eds.; Interscience: New York, 1961; Vol. 8, Part 1, Chapter 5, pp 122–124.

(27) (a) Tobey, S. W. *J. Chem. Educ.* **1962**, *39*, 473–474. (b) Espenson, J. H. *Ibid.* **1980**, *57*, 160.

rather closely to those observed by McTigue and Gruen[6] under similar conditions, and we believe they were unquestionably observing the same reaction, namely formation of **3** from oligomers of **1** such as **2** or **6**. The quantitative resemblance of k to rates of bromination of acetaldehyde[7] is only accidental. The reaction in D_2SO_4 (see Table III) gave a parallel line with a slightly less negative intercept of −4.63 ± 0.05 (see Figure 1), indicating a small inverse solvent isotope effect of 0.83 ± 0.12.

Rates of enolization of **1**, k_1, were measured by iodination, with **1** in large excess over I_2, by monitoring the zero-order disappearance of the I_2 absorption at 461 nm.[29,30d] In most experiments I_2 was added directly,[30b] and in others it was generated from the reaction of KI and KIO_3.[29b,30d] The first-order dependence of the rates on acetaldehyde concentration was confirmed experimentally, and the measured rate constants are collected in Table IV.

The stoichiometry of the iodination and bromination of **1** was not established by previous workers,[7,8] and ICH_2CHO is not a well-characterized compound. Our attempt to observe the product of reaction of equimolar amounts of **1** and I_2 directly by ^1H NMR was not successful, as no interpretable signals were observed. There is, however, evidence that iodoacetone,[30a,b] bromoacetone,[30c] and iodoacetophenone[30d] are not more reactive than their parents in acid, and the large excess of **1** used in our experiments suggests that the reaction being observed is formation of ICH_2CHO, and that diiodination does not interfere. This conclusion was also reached by previous workers.[8] It has been observed[30] that the iodination of ketones is reversible and that free I_2 is sometimes present at equilibrium. However, this did not occur for acetone,[30b] and in our experiments the absorption ascribable to iodine decreased to zero, so there is no evidence for reversibility under our conditions. The excess of **1** present and the absence of added iodide would tend to favor complete iodination.

Enolization of ketones is known to involve two water molecules acting together as a base,[11] and the corresponding excess acidity plot for **1**, $\log k_1 - \log C_{H^+} - 2 \log a_w$ against X, was found to be linear as before,[11] with slope 0.96 ± 0.03, intercept −8.46 ± 0.01,[25] and r 0.999, giving a k_{H^+} value of $(1.06 \pm 0.03) \times 10^{-5}$ M^{-1} s^{-1} in water. This is in reasonable agreement with rate constants previously obtained by bromination[7] and by iodination.[8] Another recent measurement by Kresge and co-workers,[31] involving iodination of **1** at an ionic strength of 0.1 and perchloric acid solutions less acidic that ours, gave $k_{H^+} = 0.858 \times 10^{-5}$ M^{-1} s^{-1}. This number is not corrected for acetaldehyde hydration (see below).[31] These rate constants are in satisfactory agreement, but the slightly greater rate observed in H_2SO_4 may indicate base catalysis by SO_4^{2-} (or possibly HSO_4^-) in the latter system. Recent measurements indicate that this may lead to rate differences of 20–30% between the two systems.[31]

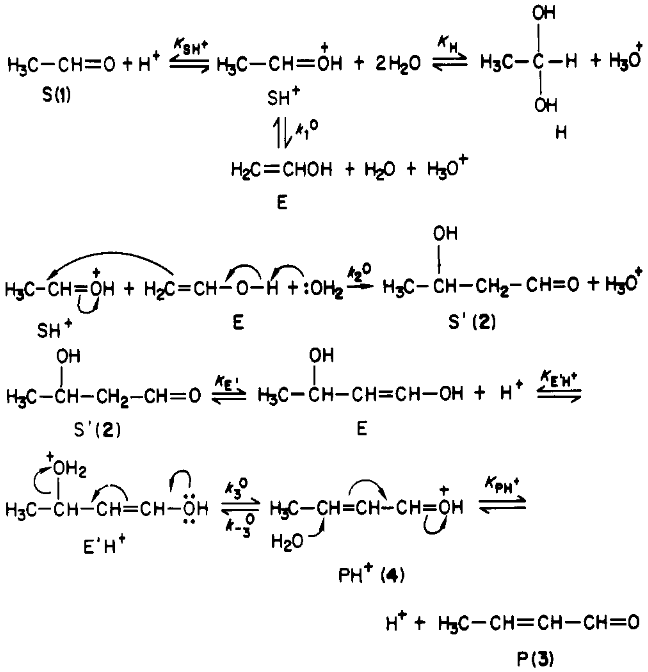
The conversion of **1** to **3** and the exchange of hydrogen for deuterium in **3** were both examined by ^1H NMR in 80% D_2SO_4, in which medium **3** is completely in the conjugate acid form **4** and no **2** is visible. The ^1H NMR spectrum of **4** initially agreed with that reported for this species,[15] but on standing the signal for H-4 diminished in intensity relative to those of H-1 and H-3 and broadened; that for H-3 maintained its intensity relative to H-1, but the large couplings disappeared, while a very broad singlet centered on the previous quartet appeared. H-2 remained sharp but lost its intensity relative to H-1 and H-3, and H-1 maintained its intensity relative to H-3 but changed to a slightly broadened singlet. These changes are consistent with the formation of **7**, with a half-life of about 1 day. In other studies[15,32] of the reaction of **3** in strong deuterated acids no carbon deuteration was observed, a result attributable to a combination of insufficient reaction time for exchange and low basicity of the media used.

$$CD_3CH{=}CDCH{=}OD^+$$

7

In the conversion of **1** to the conjugate acid of crotonaldehyde in 80% D_2SO_4, the ^1H NMR spectrum of the product indicated that about 50% deuterium incorporation at H-2 and H-4 had occurred, as indicated by the decrease in the integrals for these positions. Under these conditions the formation of **3** from **1** is faster than the exchange of **3**, so the deuterium exchange must occur in **1** prior to the formation of **3**.

Scheme I



Discussion

The discussion will be based upon Scheme I, which delineates the proposed mechanisms for the processes involved in the acetaldehyde condensation. Four of the reactions in this scheme have been studied in detail: acetaldehyde enolization (k_1^0), the condensation process (k_2^0), the dehydration of aldol (k_3^0), and the hydration of crotonaldehyde (k_{-3}^0).

Beginning with the enolization, the results presented here as well as the previous studies of acetaldehyde bromination[7] and iodination[8] all indicate that the accepted[3,11] mechanism for acid-catalyzed enolization of ketones applies to acetaldehyde as well (Scheme I, upper). Interestingly our measured rate constant for this process, k_{H^+} $(=k_1^0/K_{SH^+})$,[11] of $(1.06 \pm 0.03) \times 10^{-5}$ M s^{-1} is very similar to that found for acetone under the same conditions, i.e., extrapolated from sulfuric acid solutions, of $(1.04 \pm 0.12) \times 10^{-5}$ M^{-1} s^{-1}.[11] However, this agreement is accidental, because the pK_{SH^+} values are different. That for acetone is −5.37, with an m^* value of 0.85.[11] The reported H_0 at half-protonation for **1** is −10.2;[33] the acidity dependence is unknown, but assuming it is the same as that for acetone, multiplying by 0.85[34] gives a pK_{SH^+} estimate of −8.67. This estimate is reasonable; the resulting ΔpK between **1** and acetone is 3.3 pK units, compared to Levy's reported 2.7 H_0 units.[33] Gas-phase measurements are also in reasonable agreement. The observed proton affinity difference of 8.3 kcal/mol[35] converts to a ΔpK of 6.1 units, of which 3.3 units

---

[28] (a) Saunders, R. H.; Murray, M. J.; Cleveland, F. F.; Komarewsky, V. I. *J. Am. Chem. Soc.* **1943**, *65*, 1309–1311. (b) Späth, E.; Lorenz, R.; Freund, E. *Chem. Ber.* **1943**, *76*, 57–68. (c) Gruen, L. C.; McTigue, P. T. *Aust. J. Chem.* **1964**, *17*, 953–960.

[29] (a) Lienhard, G. E.; Wang, T.-C. *J. Am. Chem. Soc.* **1969**, *91*, 1146–1153. (b) Harper, E. T.; Bender, M. L. *Ibid.* **1965**, *87*, 5625–5632.

[30] (a) Dawson, H. M.; Ark, H. *J. Chem. Soc.* **1911**, 1740–1745. (b) Satchell, D. P. N. *Ibid.* **1957**, 2878–2882. (c) Archer, G.; Bell, R. P. *Ibid.* **1959**, 3228–3230. (d) Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2779–2784, 2785–2791, 2791–2798.

[31] Kresge, A. J.; Keeffe, J. R., unpublished results privately communicated, 1984.

[32] Olah, G. A.; Halpern, Y.; Mo, Y. K.; Liang, G. *J. Am. Chem. Soc.* **1972**, *94*, 3554–3561.

[33] Levy, G. C.; Cargioli, J. D.; Racela, W. *J. Am. Chem. Soc.* **1970**, *92*, 6238–6246.

[34] The Yates-McClelland method; see ref 24.

[35] Aue, D. H.; Bowers, M. T. In "Gas Phase Ion Chemistry"; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2, p 26.

is 54%, which seems a reasonable gas-phase/solution-phase difference at these acidities.[35] Thus k_1^0 is some 2000 times greater for protonated **1** than it is for protonated acetone before taking any possible statistical corrections into account. In the comparison with acetone, the higher k_1^0 for **1** is essentially cancelled out by its decreased basicity, leading to the similarity in observed rates, as discussed previously for acetophenone enolizations.[11]

One possible statistical correction arises from the fact that acetaldehyde is hydrated in water[36] (see Scheme I); K_H is 1.4 in water at 25 °C according to ^{1}H NMR measurements[36d] and 1.06 based on UV spectroscopy.[36e] Accordingly, only half of the acetaldehyde present in water is in the form of **1**, and correcting the rate constants for this would make **1** more reactive by another factor of 2. The hydration of **1** is acid catalyzed, with $k_{H^+} = 750$ M^{-1} s^{-1},[36b,d] but the acidity dependence of K_H is not known. A decrease with acidity is expected, just as $k_{-3}/k_3 = 1/K_{eq}$ decreases (Table I). Because this acidity dependence is not known, we have not attempted to adjust the rates to account for the hydration of **1**. As shown in Scheme I, protonated **1** can be formed directly from the hydrate, which could therefore serve as an intermediate in the enolization. However, a simple steady-state treatment (see Appendix 1) reveals that this pathway does not affect the kinetic analysis.

The condensation of **1** to **2** and **3** (Scheme I, middle) was found to be second order in substrate, and so enolization of **1** is not the rate-determining step but a prior equilibrium process. This is supported by the prior deuterium incorporation into **1** found when the reaction is performed in 80% D_2SO_4. The excess acidity analysis reveals that a water molecule as well as a proton and two substrate molecules are involved in the transition state; the appropriate rate expression, eq 4, is derived in Appendix 2, which is the first application of the excess acidity method to a pseudo-second-order reaction.

$$\log k_2 - \log C_{H^+} - \log a_w = \log(k_2^0 K_E / K_{SH^+}) + m^{\ddagger} m^{*} X \qquad (4)$$

The mechanism most probably involves base assistance by a water molecule of attack of acetaldehyde enol upon protonated acetaldehyde, as shown in Scheme I. This is probably not a true termolecular process, as the water molecule would already be present in the solvation sheath. It is in fact closely analogous to the base-assisted attack of a water molecule upon a protonated ester found in ester hydrolyses in sulfuric acid, in which a neutral tetrahedral intermediate is formed in a process involving the attack of two water molecules.[12d] The reaction of **1** may be compared to the condensation of benzaldehyde and methyl ethyl ketone in acetic acid, which was reported[5] to be bimolecular and catalyzed by sulfuric acid, and was proposed to involve attack of protonated benzaldehyde on the enol.[5]

Examination of eq 4 reveals that the intercept of the linear plot in Figure 2 contains K_E and K_{SH^+}: $\log(k_2^0 K_E / K_{SH^+}) = -8.86$. For acetaldehyde pK_{SH^+} is estimated at -8.67 (see above), and K_E, the equilibrium constant for enol formation from acetaldehyde in water, has recently been measured directly by Kresge et al.[31,37] as 5.2×10^{-7}. Thus we have $\log k_2^0 = -8.86 - \log (5.2 \times 10^{-7}) + 8.67$, which gives 1.2×10^6 M^{-2} s^{-1} for k_2^0, the acetaldehyde condensation rate in the standard state and 1 M water (6.8×10^7 in 55 M water[25]), a fast reaction, but not fast enough to be diffusion controlled.

The slope of eq 4 is $m^{\ddagger}m^{*}$; m^{*} measures the equilibrium protonation behavior[19] of **1**, estimated at 0.85 (see above). Combining this with the observed slope gives a value for $m^{\ddagger}$, which is a measure of transition-state behavior,[10] of 1.12, quite a normal value for reactions which are not unimolecular and do not involve slow proton transfer.[10-12] However, $m^{\ddagger}$ contains an extra f_S term (see Appendix 2), which may affect the linearity. In fact f_S for most substrates decreases slowly with acidity,[38] which probably accounts for the slight downward curvature of the Figure 2 plot.

The conversion of **3** to **2** (k_{-3}) is the hydration of an alkene. For simple alkenes, e.g., styrenes, the rate-determining step is carbon protonation;[39] this has also been proposed for 3-buten-2-one hydration in perchloric acid.[40] For β-oxy-α,β-unsaturated carbonyl compounds the slow step in acid media is attack of water upon the carbonyl-protonated substrate.[41] The latter mechanism is followed here; the excess acidity analysis reveals the presence of a water molecule at the transition state, which would not be the case if protonation were rate determining. The mechanism is undoubtedly that shown at the bottom of Scheme I.

The reverse process (k_3) then has to be unimolecular water loss from the hydroxyl-protonated enol of **2** (Scheme I), and the excess acidity analysis bears this out (Figure 1). The enolization of **2** cannot be rate-determining as this process would require two water molecules, as does the enolization of **1**, and no water activity dependence was observed. The reaction occurring with unpurified acetaldehyde is the same one, or at least a very similar reaction from another oligomer of **1**; this reaction shows an inverse solvent isotope effect, as would be expected for an alcohol dehydration.[42]

The slow deuterium exchange found in **3** (i.e., the slow formation of **7**) is probably the result of enolization processes. Deuterium incorporation at C-2 would result from the equilibration shown at the bottom of Scheme I, and it is not difficult to visualize slow D exchange at C-4 as resulting from vinylogous enolization of unexchanged **7**, i.e., **4**.

In summary, the mechanism of the acid-catalyzed aldol condensation has been elucidated for the first time and provides a unique example of base-assisted condensation in an acidic medium. The rates of acetaldehyde enolization, aldol dehydration, and crotonaldehyde hydration are all consistent with the overall mechanistic scheme proposed.

Experimental Section

3-(Trimethylsilyloxy)butanal (5). To ethyl 3-(trimethylsilyloxy)-butyrate[43] (6.0 g, 0.029 mol) in 80 mL of hexane at −80 °C was added 38 mL (0.038 mol) of 1 N diisobutylaluminum hydride (Aldrich) in hexane over 30 min. The mixture was stirred another 2 h and then water was added, and the solution was filtered through Celite and extracted with ether which was dried and evaporated. Purification by VPC (OV-17, 110 °C) gave **5**: ^{1}H NMR (CCl_4) δ 0.15 (s, 9, Me_3SiO), 1.22 (d, 3, $J = 6$ Hz, Me), 2.44 (double triplet, 2, $J_{2,3} = 6$ Hz, $J_{1,2} = 2$ Hz, CH_2CHO), 4.20 (sextet, 1, $J = 6$ Hz, $CH(OSiMe_3)$), and 10.06 (t, 1, $J = 2$ Hz, HC═O). This material was rather unstable, and so it was used directly in the kinetics experiments.

Reagent acetaldehyde was purified by distilling twice at atmospheric pressure prior to use, and crotonaldehyde was distilled once. Stock solutions of these were prepared in water or ethanol. Sulfuric acid solutions of known weight were titrated to obtain weight percentages. Kinetic measurements were carried out using a Cary 210 spectrophotometer and 1-cm cells, with the cell compartment thermostated at 25 °C. Reactions involving **3** were monitored at the λ_{max} of **3** for the particular acid used.

For the interconversion of **2** and **3** stock solutions of **3**, or of **5** to serve as a precursor of **2**, were injected into the thermostated solutions of acid and the change in absorption (A) with time was recorded. First-order rate constants were calculated from least-squares correlations of log A vs. t.

For the conversion of purified **1** to **3** by the method of initial rates a stock solution of **1** of accurately known concentration was weighed into acid to give an initial concentration of $1-8 \times 10^{-3}$ M, the solution was quickly mixed by shaking, and the absorbance was monitored. The

---

(36) (a) Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749–756. (b) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1–29. (c) Buschmann, H.-J.; Fuldner, H.-H.; Knoche, W. *Ber. Bunsenges. Phys. Chem.* **1980**, *84*, 41–44. (d) Buschmann, H.-J.; Dutkiewicz, E.; Knoche, W. *Ibid.* **1982**, *86*, 129–134. (e) Kurz, J. L. *J. Am. Chem. Soc.* **1967**, *89*, 3524–3528.

(37) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.

(38) Yates, K.; McClelland, R. A. *Prog. Phys. Org. Chem.* **1974**, *11*, 323–420.

(39) (a) Durand, J.-P.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1966**, 43–51. (b) Simandoux, J.-C.; Torck, B.; Hellin, M.; Coussemant, F. *Ibid.* **1972**, 4402–4409. (c) Ellis, G. W. L.; Johnson, C. D. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1025–1027. (d) Allen, A. D.; Rosenbaum, M.; Seto, N. O. L.; Tidwell, T. T. *J. Org. Chem.* **1982**, *47*, 4234–4239.

(40) Jensen, J. L.; Carre, D. J. *J. Org. Chem.* **1974**, *39*, 2103–2107.

(41) Fedor, L. R.; De, N. C.; Gurwara, S. K. *J. Am. Chem. Soc.* **1973**, *95*, 2905–2911.

(42) Noyce, D. S.; Hartter, D. R.; Pollack, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 3791–3794.

(43) Costa, D. J.; Boutin, N. E.; Riess, J. G. *Tetrahedron* **1974**, *30*, 3793–3797.

reactions were followed for changes of 0.5–2.0 A units (times of 1–36 h) and gave essentially linear changes in A with time for these periods. Second-order rate constants were obtained with eq 3 by substituting ϵ^{-1} dA for d[**3**] with the extinction coefficient ϵ for the particular acid.

For the conversion of **1** to **3** using Tobey's method[27] the initial concentration of **1** was 1–6 × 10^{-2} M. The reaction was carried out in 78.4% H_2SO_4. After 2–3 half-lives the absorbance readings were divided into two sets, A_1 and A_2, separated by a constant time interval. The plot of $A_1 - A_2$ vs. $t_2A_2 - t_1A_1$ was linear with slope k_2[**1**]. The rates agreed with those from the initial rates method to within ±5%.

For measurements of iodination rates stock solutions of **1** were added to sulfuric acid in the UV cell to give initial concentrations of 3–12.5 × 10^{-3} M. A solution of I_2 in ethanol was injected so that the initial I_2 concentration was no more than 10% of that of **1**. Addition of iodide gave a less stable absorption, so this was omitted. The decrease of the I_2 absorption with time was followed at 461 nm and gave linear plots for at least 95% reaction (r = 0.9999). The rates were calculated from the expression $-\mathrm{d}[I_2]/\mathrm{d}t = k_1[\mathbf{1}]$ or $k_1 = -(\epsilon[\mathbf{1}])^{-1}\,\mathrm{d}A/\mathrm{d}t$ where ϵ is the extinction coefficient measured for I_2 in the solution and dA/dt is the slope of the plot. Alternatively, **1** was added to I_2 generated from NaI and excess KIO_3. In this system,[29b,30d] each mol of **1** consumes 2.5 mol of I_2, so the rate expression is $k_1 = -(2.5\epsilon[\mathbf{1}])^{-1}\,\mathrm{d}A/\mathrm{d}t$. There was good agreement between the two methods.

In the reaction of unpurified **1** about 2 μL of the acetaldehyde was injected into the cuvette to give a 5 × 10^{-2} M solution, and the final A values indicated the formation of about 10^{-4} M **3**. In 87.5% H_2SO_4 the half-life for formation of **3** from unpurified **1** was 6 s (Table III), and in a 5 × 10^{-2} M solution of pure **1** the initial pseudo-first-order rate constant for formation of **3** from **1** in 88.2% acid would be 1.5 × 10^{-4} s^{-1} (Table II), or a half-life of 1 h. Thus the latter process would not interfere with measurement of the former.

Equilibrium constants for the interconversion of **2** and **3** (Table I) were calculated from the decrease in the absorption of **3** injected into the particular acid. There was no significant absorption due to **2**, and the rate of conversion was slow enough so that the fraction of **3** converted to **2** could be taken as $(A_0 - A)/A_0$, where A_0 and A are the initial and final absorbances.

In the stronger acids (88–96%) it was observed that the 256 nm λ_{max} of **3** shifted to a 254 nm maximum in a process whose first-order rate could be readily monitored. The rate of this process was lower in the stronger acids. This is probably due to a physical phenomenon of some sort, as no concomitant change in the ^{1}H NMR spectrum could be detected, but no specific assignment of this process has been made.

Acknowledgment. Valuable discussions with Professors A. Jerry Kresge and J. Peter Guthrie are gratefully acknowledged, as is the financial support of the Natural Sciences and Engineering Research Council of Canada.

Appendix 1. Steady-State Analysis of Enol Formation

In Scheme I, let $K_{SH^+} = k_{-4}/k_4$ and $K_H = k_{-5}/k_5$. Then

$$\mathrm{d}[SH^+]/\mathrm{d}t = k_4[S][H^+] + k_5[H][H_3O^+] - k_1[SH^+][H_2O]^2 - k_{-4}[SH^+] - k_{-5}[SH^+][H_2O]^2 = 0$$

$$\begin{aligned}\mathrm{d}[E]/\mathrm{d}t &= k_1[SH^+][H_2O]^2 \\ &= k_1[H_2O]^2(k_4[S][H^+] + k_5[H] \times [H_3O^+])/(k_1[H_2O]^2 + k_{-4} + k_{-5}[H_2O]^2)\end{aligned}$$

Now $k_4 \gg k_5$[36e] and $k_{-4} \gg k_{-5}$ and k_1, so this becomes

$$\begin{aligned}\mathrm{d}[E]/\mathrm{d}t &= k_1[H_2O]^2k_4[S][H^+]/k_{-4} \\ &= (k_1/K_{SH^+})[S][H^+][H_2O]^2\end{aligned}$$

which is the same equation previously obtained for enolization processes.[11] The rate depends on the actual concentration of free **1** present. This analysis applies to the aqueous standard state (for clarity the superscript zeroes are omitted here) and thus uses concentrations rather than activities. Since k_1 is the rate-determining step for enolization, it is assumed to be irreversible; enol is captured by iodine as soon as it is formed.

Appendix 2. Derivation of Rate Equation for Acetaldehyde Condensation

Using Scheme I, the observed second-order rate constants k_2 for the formation of **2** are given by

$$k_2C_S^{\,2} = k_2^{\,0}a_{SH^+}a_Ea_w/f_{\ddagger}$$

Writing $K_E = a_S/a_E$ and $K_{SH^+} = a_Sa_{H^+}/a_{SH^+}$, this becomes

$$k_2C_S^{\,2} = (k_2^{\,0}K_E/K_{SH^+})a_wC_S^{\,2}C_{H^+}(f_S^{\,2}f_{H^+}f_{\ddagger})$$

We have[10]

$$\begin{aligned}\log(f_Sf_{H^+}/f_{\ddagger}) &= m^{\ddagger}\log(f_Sf_{H^+}/f_{SH^+}) \\ &= m^{\ddagger}m^*\log(f_{B^*}f_{H^+}/f_{B^*H^+}) = m^{\ddagger}m^*X\end{aligned}$$

Thus if the variation of f_S with acidity is small, the activity coefficient ratio should still be linear in X. On taking logs eq 4 results.

Registry No. 1, 75-07-0; **2**, 107-89-1; **3**, 4170-30-3; **5**, 95764-57-1; vinyl alcohol, 557-75-5; hydrogen, 1333-74-0; ethyl 3-(trimethylsilyloxy)butyrate, 55816-59-6.

Host–Guest Complexation. 35. Spherands, the First Completely Preorganized Ligand Systems[1,2]

Donald J. Cram,* Takahiro Kaneda, Roger C. Helgeson, S. Bruce Brown, Carolyn B. Knobler, Emily Maverick, and Kenneth N. Trueblood

Contribution from the Department of Chemistry and Biochemistry, University of California at Los Angeles, Los Angeles, California 90024. *Received July 30, 1984*

Abstract: Spherands **1–5** and the related macrocycle **6** which are described in this paper are composed mainly of four to six aryloxy units attached to one another in such a way that the orbitals of the unshared electron pairs of their oxygens line an enforced cavity. These ligand systems strongly complex only Li^+ and Na^+ ions and reject K^+, Ca^{2+}, and Mg^{2+} ions. Their syntheses, representative crystal structures, and a qualitative survey of their binding properties are reported. The critical ring closures of these 18-membered-ring systems involved oxidations of appropriate bisaryllithiums with $Fe(acac)_3$ in refluxing benzene or THF to aryl radicals which coupled with one another—a reaction invented for construction of these hosts. The crystal structure of **1** clearly shows its unoccupied cavity lined with electron pairs. The crystal structures of **1**·LiCl and **1**·$NaCH_3SO_4$ indicate that no conformational reorganization of the host was involved in complexation. The crystal structures of the complexes of the polycyclic hosts **4**·$LiFeCl_4$ and **5**·LiCl show the ligating systems to be highly strained and to contain severe oxygen–oxygen compression.

Spherands are systems of ligands *organized prior to complexation* so that the orbitals of unshared electron pairs of the binding sites line a roughly spherical cavity enforced by a support structure of covalent bonds. Thus a spherand must be organized

0002-7863/85/1507-3645$01.50/0 © 1985 American Chemical Society