50.1 (d, C_5 or C_7), 52.8 (d, C_5 or C_7), 53.2 (t, C_1), 54.4 (d, C_2), 82.3 (d, C_6), 117.6 (t, C_{12}), 138.2 (s, C_{11}), 169.9 (s, C_{12}), 201.2 (s, C_3); MS (13.5 eV), *m/e* (relative intensity) 328 [M^+ (^{81}Br), 12] 327 [M^+ (^{81}Br) – 1, 43], 326 [M^+ (^{79}Br), 16], 325 [M^+ (^{79}Br) – 1, 33], 248 (24), 246 (54), 231 (57), 229 (100), 220 (39), 219 (36); $[\alpha]^{20}_D$ +26.4° (*c* 1.46, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.81. Found: C, 54.82; H, 5.95.

Tuberiferin (9). A mixture of **8** (450 mg, 1.38 mmol), Li_2CO_3 (270 mg, 3.65 mmol), and LiBr (205 mg, 2.36 mmol) in anhydrous DMF (15 mL) was stirred at 123–131 °C for 1.5 h, cooled to room temperature, poured into a saturated aqueous solution of NH_4Cl (15 mL), and extracted with ethyl acetate (5 × 20 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (3 × 50 mL), dried (Na_2SO_4), and concentrated to give a crystalline material, which was recrystallized from ethyl acetate to give spectroscopically pure **9** (289 mg, 85%). The analytical sample of **9** was obtained by further recrystallization from ethyl acetate as prisms: mp 179–181 °C;[12] IR (KBr)[12] 3085, 3025, 1763, 1665, 1625, 1410, 1250, 1235, 1142, 997, 965, 945, 830 cm^{-1}; ^1H NMR (90 MHz) δ 1.17 (3 H, s, C_{10}-CH_3), 1.39 (3 H, d, *J* = 6.8 Hz, C_4-CH_3), 2.08 (1 H, dd, *J* = 10.5, 12.0 Hz, C_5-H), 2.58 (1 H, dq, *J* = 12.0, 6.8 Hz, C_4-H), 3.96 (1 H, dd, *J* = 10.5, 10.5 Hz, C_6-H), 5.41 (1 H, d, *J* = 3.0 Hz, C_{12}-H_a), 5.85 (1 H, d, *J* = 10.0 Hz, C_2-H), 6.05 (1 H, d, *J* = 3.3 Hz, C_{12}-H_b), 6.68 (1 H, d, *J* = 10.0 Hz, C_1-H); ^{13}C NMR δ 14.6 (q, C_{15}), 19.2 (q, C_{14}), 21.1 (t, C_8), 37.1 (t, C_9), 38.4 (s, C_{10}), 41.9 (d, C_4), 50.1 (d, C_5 or C_7), 52.2 (d, C_5 or C_7), 81.9 (d, C_6), 117.2 (t, C_{12}), 126.4 (d, C_2), 138.3 (s, C_{11}), 158.0 (d, C_1), 170.0 (s, C_{13}), 200.2 (s, C_3); MS (13.5 eV), *m/e* (relative intensity) 246 (M^+, 100), 218 (74), 192 (27), 190 (20); $[\alpha]^{20}_D$ +12.2° (*c* 2.12, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.98; H, 7.33.

When the crude sample of **9** was chromatographed over silica gel and eluted successively with chloroform and ethyl acetate, the eluent with ethyl acetate gave a crystalline material, mp 155–157 °C.[13,14] Although the ^1H NMR spectrum in $CDCl_3$ and IR spectrum in chloroform were identical with those of prisms, mp 179–181 °C, above mentioned, the IR spectrum recorded as KBr disk was apparently different: IR (KBr)[13] 3100, 3040, 2950, 1765, 1680, 1622, 1412, 1255, 1240, 1150, 1140, 1000, 990, 950, 838 cm^{-1}; IR ($CHCl_3$) 3025, 2945, 1765, 1670, 1410, 1245, 1137, 998, 967, 823 cm^{-1}.

Synthesis of Tuberiferin (9) from 7 without Purification of 8. The solution of PTAB (255 mg, 0.677 mmol) in THF (3.0 mL) was added to the stirred solution of **7** (150 mg, 0.605 mmol) in THF (6 mL) at –2 °C over a period of 5 min. The mixture was stirred for 1 h at this temperature and worked up as usual to give 216 mg of crude **8**.

The mixture of this crude **8** (216 mg), Li_2CO_3 (131 mg, 1.77 mmol), and LiBr (98 mg, 1.13 mmol) in anhydrous DMF (6.5 mL) was stirred at 123–131 °C for 1.5 h and worked up as usual to give a crystalline material (183 mg), which was purified by column chromatography [Merck, silica gel, 70–250 mesh, 15 g, AcOEt–$CHCl_3$ (1:9)] to give spectroscopically pure **9** (130 mg, 87% overall yield from **7**).

Cell Growth Inhibitory Activity of Compounds to Murine Lymphocytic Cell (P388) in Vitro. Murine lymphocytic leukemia cells (P388) were incubated with compounds at 37 °C in humidified atmosphere of 5% CO_2 for 48 h. After incubation, the cell number was counted with a Coulter counter (Model ZBI, Coulter Electronics, Inc., Haialeah, FL), and the cell growth inhibition ratio (%) was calculated according to

$$\text{cell growth inhibn ratio (\%)} = \left(1 - \frac{T - C_0}{C - C_0}\right) \times 100$$

where T = cell count after culture with compound, C = cell count after culture without compound, and C_0 = cell count at the start of culture.

Plant Growth Regulation Activity of Compounds. The compounds (15 mg) dissolved in 0.3 mL of solvent (acetone–Tween 80, 10:1) were diluted with water to give test solutions. Three kinds of seeds, *E. frumentacea*, *B. juncea*, and *C. sativus*, were sown in a Petri dish (10 cm × 15 cm) containing 10 mL of the test solution and incubated under light (4000 lx) at 27 °C for 10 days. The germination of seeds and the growth of seedlings were observed and examined. Effects of compounds on plants were expressed as four rating scales (+++, serious or complete inhibition; ++, obvious effect; +, slight detectable effect; –, no effect).

Preventive or Curative Activity of Compounds in Controlling Crop Diseases. The diseases and the test methods are shown in Table IV. Test samples, which were formulated as emulsifiable in water, were applied by spraying to the plants or drenching to soil before or after inoculation. The plants were inoculated with spores or hypha of fungal pathogens. After incubation, disease severity of test plants was observed under desirable conditions for 4–15 days. The activity was expressed as a score from 0 through 5 (0, 0–29%; 1, 30–49%; 2, 50–69%; 3, 70–89%; 4, 90–99%; 5, 100%; controlled vs. untreated).

Acknowledgment. We express our thanks to Professor S. Yamaguchi for a loan of a polarimeter and for his help in the measurement of optical rotation.

Registry No. **1**, 481-06-1; **2**, 14804-46-7; **3**, 13902-54-0; **4**, 66767-50-8; **5**, 66726-14-5; **6**, 110193-06-1; **7**, 66726-13-4; **8**, 92214-65-8; **9**, 18375-00-3; **10**, 99297-23-1; **11**, 62326-48-1; **12**, 39813-41-7.

(12) Melting point and IR (KBr) data recorded here are in good accordance with those reported by K. Yamakawa et al.[4a]

(13) Melting point and IR (KBr) data recorded here are in good accordance with those reported by J. B. Barrera et al.[9]

(14) A possible explanation is that (+)-tuberiferin has two crystal forms whose melting points and IR spectra in KBr disk are different from each other.

Activation of Zinc by Trimethylchlorosilane: An Improved Procedure for the Preparation of β-Hydroxy Esters from Ethyl Bromoacetate and Aldehydes or Ketones (Reformatsky Reaction)

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Received March 11, 1987

The Reformatsky reaction is the Reformatsky generally applicable procedure for converting aldehydes and ketones to β-hydroxy esters (Scheme I).[1-5]

Scheme I

$$\text{RCOR}' + \text{BrCH}_2\text{COOC}_2\text{H}_5 \xrightarrow[(2)\text{H}_2\text{O}]{(1)\ \text{Zn}} \text{RC(OH)(R}')\text{CH}_2\text{COOC}_2\text{H}_5$$

Normally the reaction is carried out at reflux temperatures by adding carbonyl substrate and bromo ester simultaneously to a suspension of zinc in an appropriate solvent, generally benzene or an ether–benzene mixture. Numerous variations have been proposed in order to improve both the yield and the purity of the hydroxy esters formed.[6-11]

(1) Shriner, R. L. *Org. React.* (*N.Y.*) **1942**, *1*, 1.
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(3) Gaudemar, M. *Organomet. Chem. Rev. Sect. A* **1972**, *8*, 183.
(4) Henecka, H. In *Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1952; Vol. VIII, p 511.
(5) Nützel, K. In *Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1973, Vol. XIII/2a, p 809.
(6) Use of a trimethyl borate–tetrahydrofuran mixture as solvent: Rathke, M. W. *J. Org. Chem.* **1970**, *35*, 3966.
(7) Use of a zinc–copper couple: Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.

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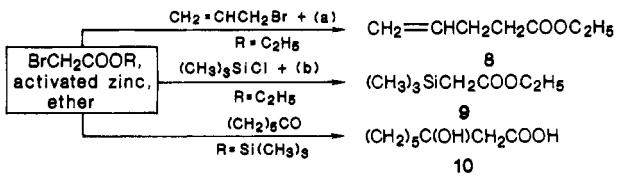
Table I. Reaction of Carbonyl Compounds with Activated Zinc and Alkyl Bromo Ester $BrCH_2COOR$

carbonyl compd	R	procedure	product	no.	yield,[a] %	bp, °C/mmHg	ref
butyraldehyde	C_2H_5	A	n-$C_3H_7CHOHCH_2COOC_2H_5$	1	70	94–95/12	8, 16
		C			63		
2-methylpropionaldehyde	C_2H_5	A	i-$C_3H_7CHOHCH_2COOC_2H_5$	2	72	88/10	
benzaldehyde	C_2H_5	A	$C_6H_5CHOHCH_2COOC_2H_5$	3	72	104/0.1	17
5-nonanone	C_2H_5	A	$(n$-$C_4H_9)_2C(OH)CH_2COOC_2H_5$	4	78	140/14	
		B			76		
cyclopentanone	C_2H_5	A	$(CH_2)_4C(OH)CH_2COOC_2H_5$	5	65	102/12	7, 10
		C			80		
cyclohexanone	C_2H_5	A	$(CH_2)_5C(OH)CH_2COOC_2H_5$	6	80	108/11	1
		B			73		
		C			78		
cyclopentanone	n-C_8H_{17}	C	$(CH_2)_4C(OH)CH_2COO(n$-$C_8H_{17})$	7	83[b]	108–110/0.07	

[a] All products gave analytical data and spectra in accordance with the assigned structure. The yields reported represent isolated materials of 98% or better GLPC purity. [b] As far as we know, this is the first example of the use of a bromo ester with a fairly long carbon chain; this reaction might be useful to prepare β-hydroxy esters with increased lipophilicity compared with β-hydroxy esters prepared from ethyl bromoacetate.

Scheme II[a]



[a] Catalysts: (a) copper(II) acetylacetonate; (b) copper(I) chloride.

We now report that the Reformatsky reaction proceeds most easily in diethyl ether provided a small amount (5–10 mol %) of trimethylchlorosilane has been prevously added to the suspension of zinc in ether.[12]

The reaction can be carried out in three different ways.

Procedure A: addition of the carbonyl compound–bromo ester mixture to a suspension of activated zinc in ether.

Procedure B: addition of the bromo ester to a mixture of carbonyl compound and activated zinc in ether.[13]

Procedure C: preparation of the zinc–bromo ester reagent by addition of the bromo ester to a suspension of activated zinc in ether and then introduction of the carbonyl compound.[14] During this two-step Reformatsky reaction the theoretical amount of zinc is used, and the β-hydroxy ester is obtained free from any ethyl acetoacetate that could have arisen from a self-condensation of the starting bromo ester.[15]

It appears from the results we obtained (Table I) that any of these three procedures provides the expected β-hydroxy esters in good yields. When an aldehyde was used, the mixture was carefully hydrolyzed with hydrochloric acid; otherwise, the secondary alcohol ester is obtained together with some of the corresponding trimethylsilyl ether ester $RCH[OSi(CH_3)_3]CH_2COOC_2H_5$.

In agreement with previous work, the zinc derivative of ethyl bromoacetate prepared from activated zinc can be coupled with 3-bromo-1-propene by using copper(II) acetylacetonate as a catalyst (yield 69%),[14c] and it can be reacted with trimethylchlorosilane in the presence of copper(I) chloride (yield 65%;[18,19] Scheme II). In the same way, the zinc derivative of trimethylsilyl bromoacetate reacts with cyclohexanone to give the expected β-hydroxy acid but with a rather low yield (35%; Scheme II); such a reaction had already been carried out in a benzene–ether mixture or in dimethoxymethane.[20]

In conclusion, it appears that ethyl bromoacetate reacts very easily with zinc in diethyl ether when the metal has been previously activated by the addition of some trimethylchlorosilane; the mechanism of this activation is still unclear.[22]

Experimental Section

Reactions are carried out under an atmosphere of nitrogen. ^1H NMR spectra are recorded on a Perkin-Elmer R24A (60 MHz).

Zinc Activation. Trimethylchlorosilane (0.3 mL, 0.0024 mol) is added from a syringe to a suspension of zinc powder (2.1 g, 0.032 mol) in anhydrous ether (50 mL). The mixture is stirred for 15 min at room temperature.

Ethyl 3-Phenyl-3-hydroxypropanoate (3),[17] Procedure A. After the suspension of activated zinc is heated to reflux, the heating is stopped, and a mixture of ethyl bromoacetate (4 g, 0.024 mol) and benzaldehyde (2.1 g, 0.02 mol) is added at such a rate that a gentle reflux is observed (20 min). After being heated to reflux for 1 h, the mixture is cooled and magnetically stirred for 15 min with 2 M hydrochloric acid (100 mL). The aqueous phase is extracted with ether (2 × 50 mL) and the combined organic phases are washed with a 5% $NaHCO_3$ solution (2 × 50 mL). After

(8) Use of acid-washed zinc: Frankenfeld, J. W.; Werner, J. J. *J. Org. Chem.* **1969**, *34*, 3689.
(9) Use of highly activated zinc: (a) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452. (b) Csuk, R.; Furstner, A.; Weidman, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775. (c) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1983**, *48*, 4108. (d) Rieke, R. D.; Tzu-Jung Li, P.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323.
(10) Use of a continuous-flow apparatus: Ruppert, J. F.; White, J. D. *J. Org. Chem.* **1974**, *39*, 269.
(11) Sonic acceleration in 1,4-dioxane: Boudjouk, P.; Han, B. H. *J. Org. Chem.* **1982**, *47*, 5030.
(12) A similar activation was used to carry out a Reformatsky reaction between ethyl 2-bromopropionate and ethyl formate: Gawronsky, J. K. *Tetrahedron Lett.* 1984, *25*, 2605.
(13) This rather unusual order of mixing the reagents is not without precedent: (a) Stoll, M. *Helv. Chim. Acta* **1951**, *34*, 678. (b) Klemm, L. H.; Bower, G. M. *J. Org. Chem.* **1958**, *23*, 344. (c) Inhoffen, H. H.; Raspe, G. *Justus Liebigs Ann. Chem.* **1953**, *592*, 214. (d) Inhoffen, H. H. *Justus Liebigs Ann. Chem.* **1950**, *568*, 47.
(14) The preparation of the zinc bromo ester in an initial step of the Reformatsky reaction has already been described. In diethyl ether: (a) Siegel, A.; Keckeis, H. *Monatsh. Chem.* **1953**, *84*, 910; *Chem. Abstr.* **1954**, *48*, 10545. (b) Vinograd, L. K.; Vulfson, N. S. *Dokl. Akad. Nauk SSSR* **1958**, *123*, 97; *Chem. Abstr.* **1959**, *53*, 5179. (c) Gaudemar, M. *Tetrahedron Lett.* **1983**, *24*, 2749. In an ether–benzene mixture: (d) Grob, C. A.; Brenneisen, P. *Helv. Chim. Acta* **1958**, *41*, 1184. (e) Vaugham, W. R.; Bernstein, S. C.; Lorber, M. E. *J. Org. Chem.* **1965**, *30*, 1790. In dimethoxymethane: (f) Gaudemar, M.; Cure, J. *C. R. Acad. Sci. Paris, Ser. C.* **1966**, *262*, 213. (g) Cure, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1968**, 3244. (h) Gaudemar-Bardone, F.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1969**, 2088. (i) Cure, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1969**, 2471.
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(16) Henbest, H. A.; Nicholls, B. *J. Chem. Soc.* **1959**, 227.
(17) Hauser, C. R.; Breslow, D. S. In *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 408.
(18) Fessenden, R. J.; Fessenden, J. S. *J. Org. Chem.* **1967**, *32*, 3535.
(19) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Org. Synth.* **1983**, *61*, 122.
(20) Horeau, A. *Tetrahedron Lett.* **1971**, 3227.

drying (K_2CO_3), the hydroxy ester is distilled: ^1H NMR (CCl_4) 1.1 (t, J = 7 Hz, 3 H, CH_3), 2.5 (d, J = 7 Hz, 2 H, CH_2CO), 3.95 (q, J = 7 Hz, 2 H, $COOCH_2$), 4.7–3.2 (m, 1 H, CHOH), 3.35 (s, 1 H, OH), 7.1–7.3 (m, 5 H, C_6H_5).

Ethyl 1-Hydroxycyclohexylacetate (6),[1] Procedure B. Cyclohexanone (2 g, 0.02 mol) is rapidly added at room temperature to the suspension of activated zinc. After the mixture is heated to reflux, the heating is stopped, and pure ethyl bromoacetate (4 g, 0.024 mol) is slowly added at such a rate that ether gently refluxes (20 min). After being heated to reflux for 1 h, the mixture is cooled and poured into iced 12 M ammonia (100 mL). The aqueous phase is extracted with ether (2 × 50 mL), the combined phases are dried (K_2CO_3) and the hydroxy ester is distilled: ^1H NMR (CCl_4) 1.1–1.8 (m, 13 H, $(CH_2)_5/CH_3$), 2.3 (s, 2 H, CH_2CO), 3.2 (s, 1 H, OH), 4.0 (q, J = 7 Hz, 2 H, $COOCH_2$).

Ethyl 1-Hydroxycyclopentylacetate (5),[7,10] Procedure C. After the suspension of activated zinc is heated to reflux, the heating is stopped, and pure ethyl bromoacetate (4 g, 0.024 mol) is added at such a rate that ether gently boils (20 min). After being heated to reflux for 1 h, the mixture is stirred for 1 h at room temperature. (The solution thus obtained can be decanted off the excess zinc: the mass of the residual zinc shows that the reaction of the bromo ester is practically quantitative.) A solution of cyclopentanone (1.7 g, 0.02 mol) in ether (5 mL) is added while the temperature of the mixture is maintained at 18–20 °C by intermittent cooling (when an aldehyde is used, the mixture should be cooled at −10 °C). After being stirred for 1 h at room temperature, the mixture is poured into iced 12 M ammonia (100 mL). Treatment as above gives the hydroxy ester: ^1H NMR (CCl_4) 1.1–2.0 (m, 11 H, $(CH_2)_4/CH_3$), 2.5 (s, 2 H, CH_2CO), 3.2 (s, 1 H, OH), 4.0 (q, J = 7 Hz, 2 H, $COOCH_2$).

Ethyl 4-Pentenoate (8).[14c] The zinc derivative prepared (procedure C) from zinc (4.4 g, 0.067 mol), trimethylchlorosilane (0.55 mL, 0.0043 mol), ethyl bromoacetate (8.4 g, 0.05 mol), and ether (60 mL) is decanted off the excess zinc. After addition of copper(II) acetylacetonate (0.3 g, 0.0012 mol), a solution of 3-bromo-1-propene (3.6 g, 0.03 mol) in ether (5 mL) is added within 10 min while the mixture is maintained at 25 °C (intermittent external cooling). When the addition is over, fresh catalyst (0.3 g, 0.0012 mol) is added, and the mixture is stirred at room temperature for 1 h. After being poured into an iced saturated ammonium chloride solution (100 mL) and extracted with ether (3 × 50 mL), the combined organic phases are washed with a 5% $NaHCO_3$ solution (2 × 50 mL), dried (K_2CO_3), and distilled: bp (°C/mmHg) 59–60/53; ^1H NMR (CCl_4) 1.2 (t, J = 7 Hz, 3 H, CH_3), 2.0–2.5 (m, 4 H, CH_2CH_2), 4.0 (q, J = 7 Hz, 2 H, $COOCH_2$), 4.7–5.2 (m, 2 H, $=CH_2$), 5.3–6.1 (m, 1 H, =CH).

Ethyl (Trimethylsilyl)acetate (9).[18,19] The zinc derivative of ethyl bromoacetate is prepared exactly as described in the preparation of ethyl 4-pentenoate. The excess zinc is decanted off and, after adding copper(I) chloride (0.7 g, 0.0067 mol), trimethylchlorosilane (3.3 g, 0.03 mol) is added (5 min) to the mixture heated to reflux. Reflux is next maintained for 2 h. After being cooled, the mixture is poured into iced 2 M hydrochloric acid (100 mL). After extraction with ether (3 × 50 mL) washing of the organic phases with a 5% $NaHCO_3$ solution (3 × 50 mL), and drying (K_2CO_3), the ester is distilled: bp (°C/mmHg) 86–87/92; ^1H NMR (CCl_4) 0.12 (s, 9 H, $Si(CH_3)_3$), 1.2 (t, J = 7 Hz, 3 H, CH_3), 1.8 (s, 2 H, CH_2CO), 3.95 (q, J = 7 Hz, 2 H, $COOCH_2$).

1-Hydroxycyclohexylacetic Acid (10). The zinc derivative prepared (procedure C) from zinc (4.4 g, 0.067 mol), trimethylchlorosilane (0.55 mL, 0.0043 mol), trimethylsilyl bromoacetate[21] (10.5 g, 0.05 mol), and ether (60 mL) is decanted off the excess zinc. The mass of the residual zinc shows that the reaction of the bromo ester is practically quantitative. To the green solution thus obtained is added a solution of cyclohexanone (4.1 g, 0.042 mol) in ether (5 mL), while the temperature is maintained at 18–20 °C. After being stirred for 1 h at room temperature, the mixture is added to iced 2 M hydrochloric acid (80 mL). After extraction with ether (50 mL), the organic phase is treated with 2 M sodium hydroxide (55 mL). After being washed with ether (2 × 30 mL), the aqueous phase is mixed with 2 M hydrochloric acid (70 mL) and extracted with ether (2 × 50 mL). The organic phase is washed with water (10 mL), dried ($MgSO_4$), and evaporated, leaving a yellow solid: mp 59 °C; ^1H NMR (CCl_4) 1.1–1.8 (m, 10 H, $(CH_2)_5$), 2.4 (s, 2 H, CH_2), 7.2–7.6 (m, 2 H, OH, COOH).

Registry No. 1, 2305-25-1; 2, 40309-42-0; 3, 5764-85-2; 4, 80256-55-9; 5, 3197-76-0; 6, 5326-50-1; 7, 110027-23-1; 8, 1968-40-7; 9, 4071-88-9; 10, 14399-63-4; CuC, 7758-89-6; ethyl bromoacetate, 105-36-2; butyraldehyde, 123-72-8; 2-methylpropionaldehyde, 78-84-2; benzaldehyde, 100-52-7; 5-nonanone, 502-56-7; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; octyl bromoacetate, 38674-98-5; copper(II) acetylacetonate, 13395-16-9; 3-bromo-1-pentene, 106-95-6; trimethylsilyl bromoacetate, 18291-80-0.

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A Comparison of the Hammett Acidity Function Method for Determination of pK_a Values with the Bunnett–Olsen and Excess Acidity Function Methods

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Received March 11, 1987

In a previous paper,[1] we noted that estimates of pK_a values derived by the Hammett acidity function method (HAFM) differed, in many cases by considerable amounts, from those derived by the Marziano–Cox–Yates excess acidity function method (EAM). This was particularly true for strong conjugate acids whose experimentally observable ionization region was in concentrated aqueous acid. We posed the question of which method gave the more accurate estimate of the real thermodynamic quantity and suggested that an appraisal could be based on the proposal: do the pK_a values obtained by any given procedure correlate in the "expected"[2] manner with other physicochemical properties of the substrates not dependent on acidity function theory in any way for their definition? By comparing HAFM and EAM in a manner conforming to this suggestion, the tentative conclusion was drawn that, at the present stage of development, HAFM performs as well as, and in some cases better than, EAM.

No comparison with the Bunnett–Olsen method (BOM)[3] was described because a close correspondence between EAM and BOM had been noted.[4] The relationship between these two approaches can be seen by comparing eq 1, for BOM, with eq 2, for EAM.

$$\log [BH^+]/[B] - \log [H^+] = (\phi_e - 1)(H_0 + \log[H^+]) + pK_a \quad (1)$$

$$\log [BH^+]/[B] - \log [H^+] = m^*X + pK_a \quad (2)$$

Correspondence between $-(H_0 + \log [H^+])$ and X, and therefore between $(1 - \phi_e)$ and m^*, apparently makes the

(1) Johnson, C. D.; Stratton, B. *J. Org. Chem.* **1986**, *51*, 4100.

(2) The quotes arise from the fact that the manner in which pK_a values might correlate in the way described, although established to a reasonable extent by precedent, may also involve subjective expectations arising from individual experience and thus opinion.

(3) Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* **1966**, *44*, 1899. It is interesting to note that these workers elaborated, in this paper, sources of errors in both the HAFM and BOM that are echoed by the views of R. Cox given in ref 1. We thank Professor Bunnett for discussion of this and other relevant points.

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