Calcd for $C_{21}H_{28}O_4N_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.56; H, 7.09; N, 13.95.

Octalone 20d: IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 0.75 (d, 3, J = 7 Hz, Me), 0.89, 0.89, 1.04, 1.67 (s, 3 each, methyls), 5.10 (br s, 1, olefinic H). Anal. Calcd for $C_{15}H_{24}O$: C, 81.77; H, 10.98. Found: C, 81.41; H, 10.95.

Octalone 21a: IR 1697 (s, C=O) cm^{-1}; ^1H NMR δ 1.09, 1.12, 1.18, 1.65 (s, 3 each, methyls), 5.28 (m, 1, olefinic H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.77; H, 10.79.

Octalone 21b: IR 1697 (s, C=O) cm^{-1}; ^1H NMR δ 1.07, 1.09, 1.17, 1.64 (s, 3 each, methyls), 5.27 (br s, 1, olefinic H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.25; H, 10.85.

Octalone 21c: IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 1.00 (d, 3, J = 8 Hz, Me), 1.04, 1.18, 1.21, 1.68 (s, 3 each, methyls), 5.35 (br s, 1, olefinic H). Anal. Calcd for $C_{15}H_{24}O$: C, 81.77; H, 10.98. Found: C, 82.02; H, 10.91.

Octalone 21d: IR 1695 (s, C=O) cm^{-1}; ^1H NMR δ 0.78 (d, 3, J = 7 Hz, Me), 0.95, 1.08, 1.17, 1.66 (s, 3 each, methyls), 5.07 (br s, 1, olefinic H). Anal. Calcd for $C_{15}H_{24}O$: C, 81.77; H, 10.98. Found: C, 81.70; H, 11.05.

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Registry No. **6a**, 106-99-0; **6b**, 78-79-5; **6d**, 1118-58-7; **7a**, 1073-13-8; **7b**, 4694-17-1; **8**, 40122-96-1; **9a**, 13395-71-6; **9b**, 42747-41-1; **9c**, 20013-73-4; **10**, 104849-81-2; **11**, 70358-63-3; **12**, 104850-07-9; **13**, 104849-82-3; **14**, 70358-64-4; **15**, 104849-83-4; **15** (dinitrophenylhydrazone), 104849-97-0; **16a**, 104849-84-5; **16a** (dinitrophenylhydrazone), 104849-98-1; **16b**, 104849-90-3; **16b** (dinitrophenylhydrazone), 104849-99-2; **16c**, 104973-34-4; **16c** (dinitrophenylhydrazone), 104974-19-8; **17a**, 104874-80-8; **17a** (dinitrophenylhydrazone), 104850-00-2; **17b**, 104974-18-7; **17b** (dinitrophenylhydrazone), 104973-36-6; **17c**, 104973-35-5; **18**, 104849-80-1; **18** (dinitrophenylhydrazone), 104850-01-3; **19a**, 104849-85-6; **19a** (dinitrophenylhydrazone), 104850-02-4; **19b**, 104849-86-7; **19b** (dinitrophenylhydrazone), 104850-03-5; **19c**, 104849-91-4; **19c** (dinitrophenylhydrazone), 104850-04-6; **19d**, 104849-92-5; **19d** (dinitrophenylhydrazone), 104850-05-7; **20a**, 104849-87-8; **20a** (dinitrophenylhydrazone), 104875-16-3; **20c**, 104849-93-6; **20c** (dinitrophenylhydrazone), 104850-06-8; **20d**, 104849-94-7; **21a**, 104849-88-9; **21b**, 104849-89-0; **21c**, 104849-95-8; **21d**, 104849-96-9.

Reduction of α-Halo Ketones by Organotin Hydrides. An Electron-Transfer-Hydrogen Atom Abstraction Mechanism[1]

Dennis D. Tanner* and Haribansh Kumar Singh[2]

Department of Chemistry, The Univeristy of Alberta, Edmonton, Alberta, T6G 2G2 Canada

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The mechanism for the reduction of α-chloro- and α-bromoacetophenone with triphenyltin hydride was investigated. The reductions were found to follow the same reduction pathways as has previously been reported for the reduction of α-fluoroacetophenone. Both homolytic and heterolytic reactions could be recognized since the homolytic reactions yield acetophenone and the heterolytic reactions yield α-(halomethyl)benzyl alcohol. The homolytic reductions proceed by a free-radical chain process where the initiation step and one of the propagation steps involve SET reactions. The reduction apparently does not proceed by a direct halogen transfer since no secondary deuterium isotope effect was observed on reduction of α,α-dideuterio-α-haloacetophenone.

Introduction

Early work on the triorganotin hydride reduction of alkyl halides established that the reagents selectively reduce the carbon-halogen bond in the presence of a number of other functional groups which are themselves unaffected.[3] Two of the substrates used to demonstrate this selective reactivity were α-chloro- and α-bromoacetophenone (eq 1, X = Cl, Br). Recently[4] we have demonstrated that the

$$PhC(=O)CH_2X + n\text{-}Bu_3SnH \rightarrow PhC(=O)CH_3 + n\text{-}Bu_3SnX \quad (1)$$

triphenyltin hydride reduction of α-fluoroacetophenone (I) proceeds by homolytic and heterolytic pathways depending upon the conditions under which the reaction is carried out. The heterolytic reaction of I leads, after hydrolysis, to α-fluoromethylbenzyl alcohol (II) (see Scheme Ia), while the homolytic pathway yields acetophenone (see Scheme Ib), which under the reaction conditions is unreactive.

The defluorination was rationalized by a chain mechanism whose initiation step (eq 4) and one of its propagation steps (eq 5) both involved a single-electron-transfer (SET) reaction. The homolytic mechanism yielded acetophenone as the sole product.

Since the formation of dehalogenated ketone is indicative of a radical chain process which involves a SET-hydrogen atom transfer sequence, it was of interest to examine more closely the reduction of α-chloro- and α-bromoacetophenone.

Results

The reduction of both α-chloro- and α-bromoacetophenone was carried out in several solvents. The effect, on the product distribution and their relative rates of formation, of an added initiator, azobisisobutyronitrile (AIBN), or an inhibitor, p-dinitrobenzene (DNB), was examined. The results of the studies are listed in Tables I and II.

By analogy to the results previously reported for the reduction of α-fluoroacetophenone,[4] the reductions, at least in the less polar solvents, appear to follow the homolytic pathway. Qualitatively the reduction of these halo ketones appear to be faster than the reduction of the fluoride.

Electrolytic reduction at a dropping mercury electrode (DME) of the α-halosubstituted acetophenones were com-

(1) Presented in part at the Special International Symposium on Free-Radicals, Sept. 1985, Lanzhou, Peoples Republic of China.
(2) Postdoctoral Fellow, University of Alberta, 1984-1986.
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0022-3263/86/1951-5182$01.50/0

Table I. Reduction of α-Chloroacetophenone with Triphenyltin Hydride

reaction	solvent	conditions[a-c]	% product yield[d] $PhCOCH_3$	% product yield[d] $ClCH_2CHOHPh$	% product yield[d] $CH_3CHOHPh$	unreacted ketone
1	benzene	61 °C	49.0 ± 1.0	traces	–	51.5 ± 0.5
2		61 °C *m*-DNB (6%)	4.0 ± 0.0	–	–	96.0 ± 0.0
3		61 °C AIBN (3%)	78.0 ± 1.0	–	–	23.5 ± 0.5
4	tetrahydrofuran	61 °C	30.0 ± 0.7	–	–	70.0 ± 1.4
5		61 °C AIBN (14%)	83.4 ± 1.1	–	–	17.4 ± 0.8
6		61 °C	34.8 ± 3.9	–	–	64.6 ± 2.4
7		61 °C *m*-DNB (6%)	–	–	–	98.3 ± 2.4
8	acetonitrile	61 °C	38.5 ± 7.5	3.5 ± 1.5	–	61.0 ± 3.0
9		61 °C *m*-DNB (6%)	8.5 ± 0.5	2.0 ± 0.0	–	91.0 ± 4.0
10		61 °C AIBN (3%)	86.5 ± 0.5	–	–	15.0 ± 3.0
11	methanol	61 °C	18.0 ± 0.0	30.5 ± 1.5	–	52.5 ± 0.5
12		61 °C *m*-DNB (6%)	5.0 ± 0.0	32.4 ± 0.4	–	60.8 ± 2.3
13		61 °C AIBN (3%)	71.5 ± 1.5	1.0 ± 0.0	1.3 ± 0.3	21.5 ± 3.5

[a] A mole ratio of 1:1 of ketone to triphenyltin hydride was used. [b] Reaction times for all reactions in benzene, acetonitrile, and methanol were 4 days. [c] Reaction time in THF for reactions 4 and 5 were 41 h while for reactions 6 and 7 were 3 days. [d] Errors are the mean deviation from the average value obtained from two or more independent experiments.

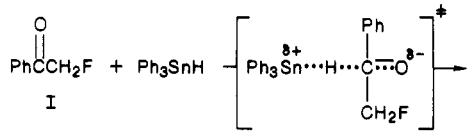
Table II. Reduction of α-Bromoacetophenone with Triphenyltin Hydride

reaction	solvent	conditions[a]	% product yield[b,c] $PhCOCH_3$	% product yield[b,c] unreacted ketone
1	benzene	61 °C, 30 min	70.6 ± 0.8	21.7 ± 2.4
2		61 °C, *m*-DNB (6%) 30 min	16.2 ± 3.2	82.3 ± 4.7
3	acetonitrile	61 °C, 30 min	82.3 ± 2.4	23.5 ± 3.5
4		61 °C, 30 min, *m*-DNB (6%)	42.6 ± 0.1	59.5 ± 3.5
5		61 °C, 60 min	73.6 ± 1.1	17.5 ± 0.7
6		61 °C, 60 min	88.0 ± 0.8	1.5 ± 0.7
7	methanol	61 °C, 30 min	93.0 ± 0.0	tr
8		61 °C, 30 min, DNB (6%)	92.6	2.2

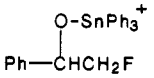
[a] A mole ratio of 1:1 of ketone to triphenyltin hydride was used except run 6 when ketone and tin hydride ratio was 1:1.5. [b] The errors reported are the mean deviation from the average value for two or more independent experiments. [c] Yields determined by GLPC.

Scheme I

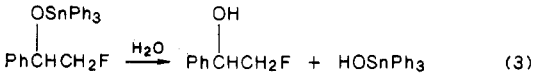
(a) Heterolytic Reduction



I

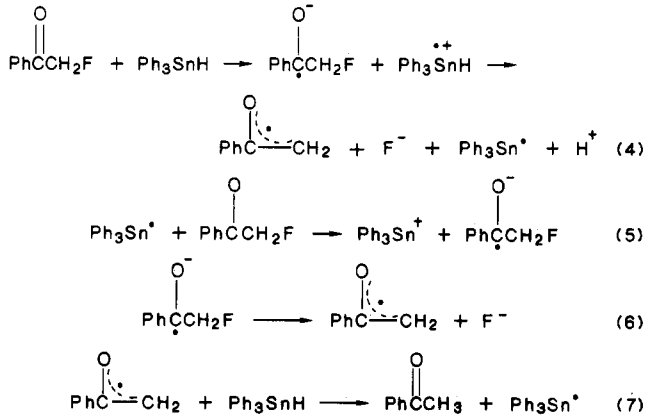


(2)



II (3)

(b) Homolytic Reduction



(4) (5) (6) (7)

pared to that of acetophenone itself. As expected halogenation lowered the $E_{1/2}$ for reduction, and the magnitude of the reduction potential, at mercury, suggests that in the heterogeneous media the α-bromo and α-chloroaceto-

Table III. Polarographic Half-Wave Potentials of a Series of Ketones in Acetonitrile, 23 °C

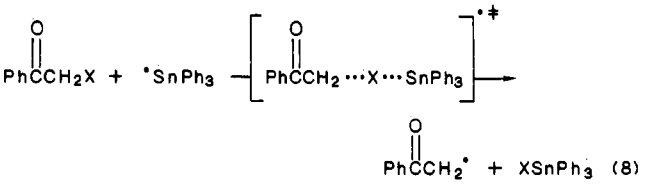
ketone	$E_{1/2}$, V[a]
α-bromoacetophenone	−0.78
α-chloroacetophenone	−1.48
α,α,α-trifluoroacetophenone	−1.52
α-fluoroacetophenone	−1.85
acetophenone	−2.18

[a] ($Ag/Ag^+ClO_4^-$, 0.1 M) electrode as reference.

phenones are both better electron acceptors than α-fluoroacetophenone; see Table III.

The relative rates of reduction by a homogeneous solution of triphenyltin hydride showed the same order; see Table IV.

Although a direct atom-transfer mechanism had been ruled out in the reduction of α-fluoroacetophenone by triphenyltin hydride, it could not be argued that this process does not take place during the dehalogenation of the other haloacetophenones. Thus the details of the homolytic dehalogenation were investigated. A mechanism which invoked direct atom transfer should exhibit a significant secondary α-deuterium isotope effect upon breaking of the carbon–halogen bond (eq 8). The results



(8)

obtained from the competitive dehalogenation of 1/1 mixtures of the α,α-dideuterio-α-haloacetophenones and their protiated analogues are listed in Table V for both the α-chloro- and the α-bromoacetophenones.

Table IV. Relative Rates of Reduction of the α-Haloacetophenones with Triphenyltin Hydride[a,b]

solvent	$[PhCOCH_2F]^0$	$[PhCOCH_2Cl]^0$	$[PhCOCH_2Br]^0$	$[PhCOCH_2F]^f$	$[PhCOCH_2Cl]^f$	$[PhCOCH_2Br]^f$	k_{Cl}/k_F	k_{br}/k_{Cl}
acetonitrile	0.0200	0.0200		0.0134	0.00531		3.3	
	0.0200	0.0200		0.0188	0.0167		2.9	
		0.0200	0.0200		0.0171	0.00495		8.7
		0.0200	0.0200		0.0153	0.00461		5.4
benzene	0.0200	0.0200		0.0169	0.0139		2.1	
	0.0200	0.0200		0.0136	0.00596		3.1	
	0.0200	0.0200		0.0163	0.0126		2.3	
	0.0200	0.0200		0.0165	0.0119		2.7	
		0.0200	0.0200		0.0183	0.0036		19.3
		0.0200	0.0200		0.0183	0.0021		25.3

[a] Superscripts above concentrations denote initial concentrations (0) and final concentrations (f). [b] Relative rates of disappearance were calculated from the ratio $\log [(RX)^0/(RX)^f]/\log [(RF)^0/(RF)^f] = k_X/k_F$.

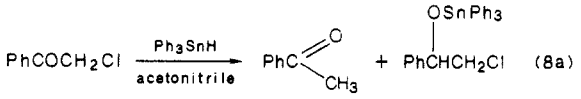
Table V. Mass Spectral Analysis, m/e, Ratios of the Reactants and Products for the Reactions of C_8H_7OX vs. $C_8H_5D_2OX$

substituent (X)	reactants $(m/e)/(m/e)^{a,b}$	reactants ratio[c,d]	reaction, %	product mixture $(m/e)/(m/e)$	product mixture ratio[c,d]	$(m/e)/(m/e)$	ratio[d]
bromo	(198/202)	1.07 ± 0.02	77	(198/202)	1.11 ± 0.02	(120/122)	1.12 ± 0.02
	(198/202)	1.07 ± 0.01	38	(198/202)	1.08 ± 0.02	(120/122)	1.02 ± 0.02
chloro	(154/158)	1.01 ± 0.04	40	(120/122)	1.05 ± 0.04		
	(154/158)	1.08 ± 0.04	42	(120/122)	1.03 ± 0.03		
	(154/158)	1.03 ± 0.03	35	(120/122)	1.09 ± 0.01		
	(154/158)	0.98 ± 0.04	25	(120/122)	1.07 ± 0.01		

[a] Nominal mass. [b] The high-resolution mass spectra of the α-haloacetophenones and their deuterated analogoues showed the both parent ions to be singlet. [c] Corrected for natural abundance. [d] Errors are the mean deviation from the average of >8 determinations.

Discussion

The triphenyltin hydride reduction of α-chloroacetophenone proceeds by both homolytic and heterolytic mechanisms (see Table I). As was found in the study of the reduction of α-fluoroacetophenone[4] the reaction yields two products, acetophenone and α-(chloromethyl)benzyl alcohol. In the less polar solvents, benzene and tetrahydrofuran (THF), only the product of homolytic reduction is formed. An NMR spectrum of the reaction mixture, before the product was isolated, showed only acetophenone. The homolytic product is formed by a chain reaction which can be inhibited by small amounts of DNB and can be initiated by AIBN. Minor amounts (2–4%) of the heterolytic product, the chlorohydrin, as its derivative stannyl ether, was formed in the more polar solvent, acetonitrile (eq 8a). Upon hydrolysis the stannoxide yields



(8a)

the chlorohydrin. The formation of the homolytic product was inhibited by DNB while the heterolytic product was not significantly affected. The formation of the product of radical reduction, acetophenone, is promoted by the addition of AIBN; the rate of the radical chain reduction pathway increases so that the slower heterolytic reaction does not compete—no chlorohydrin could be detected. In solvent methanol, the most polar solvent used, the product resulting from hydride transfer is the major product. The addition of DNB inhibits the formation of acetophenone but does not affect the formation of chlorohydrin. As in the reactions carried out in acetonitrile, AIBN promotes the formation of acetophenone. Even in the polar solvent which favors hydride transfer, the faster radical chain reduction is the dominant reaction pathway and acetophenone is the almost exclusive product.

The reduction of α-bromoacetophenone in all three of the solvents used, benzene, acetonitrile and, methanol, yields only acetophenone, see Table II. As in the case of the other haloacetophenone, the uninitiated reduction can be inhibited by DNB in benzene and in acetonitrile. In methanol the formation of acetophenone does not appear to be affected by DNB. Both the bromohydrin and the starting material were stable in methanol under the reaction conditions, and a satisfactory material balance could be obtained for bromoacetophenone and its reduction product. Traces of the methanolysis product, α-methoxyacetophenone, were formed. The uninitiated rate of reduction does not appear to be sensitive to solvent polarity, and SET initiation is apparently extremely favorable even in nonpolar solvents.

Qualitatively the ease of reduction appears to indicate that the bromide is reduced homolytically faster than the chloride or the fluoride. The competitive rates of reduction were determined. As predicted the relative rates of tin hydride reduction are F/Cl/Br 1/3/21 in acetonitrile and 1/2.5/54 in benzene: see Table IV. Since the gas-phase electron affinity of acceptor molecules has been found, with few exceptions, to have the same order as the nonohomogeneous irreversible polarographic half-wave potentials for reduction at mercury,[5] the polarographic $E_{1/2}$ values were determined for the haloacetophenones, see Table III. As expected the reduction potentials followed the same order as the relative rates of tin hydride reduction: Br > Cl > F > H.

Since the homolytic reduction of the three α-haloketones with triphenyltin hydride yields acetophenone, a detailed mechanism for the dehalogenation was considered. The formation of acetophenone from the reduction of α-fluoroacetophenone was rationalized as proceeding via a ketal intermediate formed by electron transfer from the stannyl radical (eq 5). Acetophenone is subsequently formed from the transfer of the enolyl radical with triphenyltin hydride (eq 7). An alternative pathway to the formation of the enolyl radical, direct atom transfer, was rejected[4] since it has been shown[6] that even benzyl fluoride is not reduced by organotin hydride. However, this mechanism could not, a priori, be eliminated as a possible pathway for the reduction of α-chloro- or α-bromoacetophenone. A probe

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for this mechanism involved the competitive reduction of an α,α-dideuterio-α-haloacetophenone vs. its protiated analogue. The extent of reorganization, in the transition state, of the carbon–halogen bond should be expressed as a secondary deuterium isotope effect. Although the magnitude of the secondary deuterium isotope effect for abstraction of halogen α- to a carbonyl is not known, typical values for hydrogen atom abstraction[7] or azo decompositions[8] show secondary deuterium isotope effects of 13–22%/deuterium atom. The results of the competitive reductions for the haloacetophenones are listed in Table V. The protium to deuterium ratio of the initial mixture was compared with that of the mixture of the product acetophenones, deuterated and undeuterated, and the mixture of recovered starting material (eq 9). The

$$\mathrm{PhCOCD_2X + PhCOCH_2X \xrightarrow{Ph_3SnH} PhCOCD_2H + PhCOCH_2H + PhCOCD_2X + PhCOCH_2X} \quad (9)$$

bromoacetophenone, both at high and at low conversion, showed the same deuterium to protium ratio before reaction and after reaction for both the product acetophenones and the recovered starting material (see Table V); no deuterium isotope effect is observed. The same experiments were performed on the mixture of α-chloroacetophenones. Although there was more experimental scatter, and the recovered starting material could not be analyzed, the mixture of product acetophenones and the starting material gives results which were consistent with the absence of a significant secondary deuterium isotope effect. These results are clearly consistent with an electron-transfer process which does not involve a significant change in hybridization of the carbon–halogen bond and is in opposition to the direct atom-transfer mechanism.

The absence of a deuterium isotope effect does not define a particular radical step other than one which sorts products, since each radical intermediate, be it deuterated or protiated, must eventually lead to product and would not show any selectivity.

Conclusions. The α-haloacetophenones, X = F, Cl, Br, undergo homolytic reduction with triphenyltin hydride to yield acetophenone by a chain reaction. The initiation step in the reduction of all three substrates proceeds by an SET from the tin hydride to the halo ketone. One of the steps in the propagation sequence also involves an electron-transfer reaction from the stannyl radical to the carbonyl to form the ketyl radical intermediate.

In polar solvents a competitive hydride-transfer mechanism operates for the reaction of the fluoro- and chloro ketone but during the reduction of bromoacetophenone, the strongest electron acceptor, only the homolytic pathway is followed, irrespective of the solvent polarity.

The apparent rates, judged from product yields, appeared to be insensitive to solvent polarity. Although an increase in polarity is predicted to increase the rate of electron-transfer initiation, the overall effect on the kinetics of a free-radical chain process will be difficult to predict, since the ratio of propagation to termination rate constants (nonpolar processes), the largest rate constants involved, would not be expected to be completely independent of solvent polarity.

Experimental Section

Materials. The internal and external standards, *p*-di-*tert*-butylbenzene (Aldrich), mp 78–79 °C (lit.[9] 80 °C), benzophenone (Fisher Chemical Co.), mp 48 °C (lit.[9] 48.1 °C), fluorene (Matheson, Coleman and Bell, mp 115–16 °C (lit.[9] 116–17 °C), were recrystallized from ethanol and dried under vacuum (55 °C).

Triphenyltin hydride (Alfa) was used as supplied.

α,α′-Azoisobutyronitrile (Aldrich) was recrystallized from ethanol–water and dried over P_2O_5 under vacuum, mp 101–102 °C (lit.[10] 103 °C).

Acetophenone (Fisher Chemical Co.) was distilled at 93–95 °C (10 mm) (lit.[9] 202.6 °C (760 mm)).

α-Fluoroacetophenone was prepared by treating fluoroacetyl chloride with benzene in the presence of aluminum trichloride.[11] Fractional distillation, 70–72 °C (1.5 mm) (lit. 65–70 °C (1 mm), gave the product in 81% yield: mp 26–27 °C (lit.[11] mp 27–28 °C); NMR ($CDCl_3$) δ 5.57 (d, 2 H, J = 47.5 Hz), 7.36–8.10 (m, 5 H); IR (neat) 5.86 μm (CO); MS, m/e 138, 105.

α,α,α-Trifluoroacetophenone was prepared by treating trifluoroacetic acid with an ether solution of phenylmagnesium bromide.[12] Fractional distillation, 69–70 °C (30 mm) (lit.[13] bp 75 °C (37 mm)) gave the product in 58% yield: IR (neat) 5.78 μm (CO); MS, m/e 176, 105.

α-Chloroacetophenone (Aldrich) was recrystallized from methanol, mp 53–54.5 °C (lit.[10] mp 54–56 °C).

α-Chloromethylbenzyl alcohol was prepared by the reaction of styrene with hypochloronous acid.[14] Fractional distillation, 130–35 °C (20 mm) (lit.[14] 118–26 °C (14 mm)), yielded the chlorohydrin as a colorless liquid: NMR ($CDCl_3$) δ 2.75 (s, 1 H) 3.5–3.80 (m, 2 H), 4.80–5.0 (dd, 1 H). Anal. Calcd for C_8H_9ClO: C, 61.36; H, 5.79; Cl, 22.63. Found: C, 61.34; H, 5.87; Cl, 22.88.

α-Bromoacetophenone (Aldrich) was recrystallized from methanol; mp 49–51 °C (lit.[10] 48–51 °C).

α-Bromo-α,α-dideuterioacetophenone was synthesized by the reaction of bromine with α,α,α-trideuterioacetophenone in presence of aluminum trichloride in anhydrous ether.[15] During the purification it was washed with a D_2O–hexane mixture and then recrystallized from methanol, mp 47–49 °C. NMR ($CDCl_3$) showed <2.4% protium in the α-position. Anal. Calcd for $C_8H_9D_2BrO$: C, 47.78; Br, 39.80. Found: C, 47.69; Br, 39.99.

α-Chloro-α,α-dideuterioacetophenone was synthesized by the reaction of a calculated amount of chlorine with α,α,α-trideuterioacetophenone[15] in solvent carbon tetrachloride. The fractional distillation at 120–25 °C (4 mm) gave a colorless liquid, which after solidifying, was recrystallized from methanol, mp 52–54 °C. NMR ($CDCl_3$) showed <2.0% protium in the α-protium. Anal. Calcd for $C_8H_7D_2ClO$: C, 61.35; Cl, 22.68. Found: C, 61.43; Cl, 22.91.

Solvents benzene,[16] acetonitrile,[17] and methanol[16] were purified by standard procedures. Tetrahydrofuran was purified by letting it stand (12 h) over KOH followed by distillation from potassium metal.

General Procedure for the Reduction of the α-Halo Ketones. A solution, 0.05 M in ketone, 0.02 M in an internal standard, and 0.05 M in tin hydride, was placed in a reaction ampoule, the mixture was degassed by three freeze–thaw cycles, and the ampoule was sealed under vacuum. The reaction mixture was thermostated at 61 °C for a standard time (4 days for chloro ketone and 30 min for bromo ketone) in the absence of light. The ampoule was then opened and the product mixture analyzed by GLPC using a 4 ft. × $^1/_4$ in. glass column packed with 10% FFAP on chromosorb WAW DMCS 60/80 mesh or by HPLC using a 26 × 0.26 cm silica gel column, which was eluted with a mixture of hexane and chloroform. Products were identified by a comparison of their GLPC retention times, GLPC–mass spectra, GLPC–IR, and ^{1}H NMR with those of authentic samples. Duplicate experiments were run with each ketone to test the effects

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of inhibition by m-dinitrobenzene, initiation by AIBN, and polarity of the solvents.

GLPC analyses were carried out with a HP 402 gas chromatograph coupled to an HP 3388A integrator and the HPLC with a Varian 5000 liquid chromatograph coupled to a Vista 402 data handling system. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves. ^{1}H NMR high-resolution spectra were obtained with a Brucker WH 200 high-field spectrometer. GLPC/IR data obtained by using a Nicolet 7199 FT/IR spectrometer interfaced to a Varian 3700 gas chromatograph. GLPC/MS data were obtained by using a low-resolution, KRATOS MS 12, mass spectrometer coupled to a Varian 400 gas chromatograph.

Competitive Reduction between α-Halo Ketones. An aliquot solution of two of the α-halo ketones (0.02 M in each of the ketones), 0.02 M tin hydride, and the internal standard (0.02 M) was placed in a NMR tube, degassed, sealed, thermostated (61 °C), and allowed to react for 18 h. The relative reactivity determined as 1:3.2:21 for the reaction of the fluoro- to chloro- to bromoacetophenones reduced in solvent acetonitrile and 1:2.5:54 when the reductions were carried out in benzene. The ratio of k_{Br}/k_F was determined indirectly. The indirect value was obtained from the direct measurement of k_{Cl}/k_F and k_{Br}/k_{Cl}. All the relative reactivities are the mean values of two sets of individual experiments (see Table IV).

Secondary Deuterium Isotope Effects. An examination of the secondary deuterium isotope effect for the reduction of the α-halo ketones was carried out by investigating the competitive reduction of an acetonitrile solution of α-halo-α,α-dideuterioacetophenone (0.05 M) and undeuterated α-haloacetophenone (0.05 M) with triphenyltin hydride (0.1 M). Aliquot samples of the reaction mixtures were placed in reaction ampoules, degassed, sealed, thermostated (61 °C) and allowed to react for 1 h (bromo ketones) or 48 hr (chloro ketones).

The product mixtures of the bromo ketones were isolated by removing the acetonitrile by rotary evaporation. The resultant residue was dissolved in ether. The ethereal solution was treated with excess KF in water (10 g in 100 mL).[18] The precipitated triphenyltin fluoride was removed by filtration, and the ether layer of the filtrate was separated and dried (anhydrous $MgSO_4$). Removal of the solvent yielded a solid which was analyzed by using a KRATOS MS 12 mass spectrometer. The intensity of the ratio of mass peaks m/e 198 (C_8H, OBr^{79}) and 202 ($C_8H_5D_2OBr^{81}$) in the starting material was compared with the same ratio in the unreacted starting material after the reduction had been partially completed. The products acetophenone and α,α-dideuterioacetophenone, m/e 120 (C_8H_8O) and 122 ($C_8H_6D_2O$) were also compared to the starting material for the ratio of protium to deuterium.

In the case of the α-chloroaceophenones the reaction mixture was concentrated, and the mixture of products was collected by preparative GLPC. The protium to deuterium ratio was determined using an AEI MS-50 mass spectrometer at high resolution. The ratio was determined by examining the mass peaks at m/e 158.0289 ($C_8H_5D_2O^{37}Cl$) and 154.0185 ($C_8H_7O^{35}Cl$) in the starting material and m/e 120.0579 (C_8H_8O) and 122.0701 ($C_8H_6D_2O$) in the products. The ratio of m/e mass peaks containing chlorine were corrected for natural abundance $^{35}Cl/^{37}Cl$ = 75.53/24.47.

The percentage reaction for the α-bromoacetophenones acetophenone reaction was determined by NMR.

Polarographic Reduction of Ketones. The current–voltage curves for the polarographic reductions of acetophenone, α-chloroacetophenone, α-fluoroacetophenone, α-bromoacetophenone, and α,α,α-trifluoroacetophenone were obtained on a Princeton Applied Research (PAR) Model 174A polarograph interfaced with a PAR 303 DME.

The solutions were anhydrous acetonitrile containing $(Bu)_4N^+ClO_4^-$ (0.1 M) and the appropriate ketone (0.005 M). The $E_{1/2}$ values relative to $Ag/AgClO_4$ (0.1 M) are listed in Table IV.

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Effects of Solvents and Additives on the Reaction of *N*-Benzyloxycarbonyl-L-aspartic Anhydride with L-Phenylalanine Methyl Ester (Synthesis of Aspartame)

Chin-Ping Yang* and Chein-Shyong Su

Department of Chemical Engineering, Tatung Institute of Technology, Taipei, Taiwan, Republic of China

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N-Benzyloxycarbonyl-L-aspartic anhydride (Z-L-aspartic anhydride) was reacted with L-phenylalanine methyl ester. The nature of the ring-opening reaction was affected by the organic solvent. In Me_2SO, DMF, and dimethylacetamide the β-isomer of Z-L-aspartyl-L-phenylalanine methyl ester (ZAPM) was predominant while in glacial acetic acid, esters, ketones, ethers, chlorohydrocarbons, acetonitrile, toluene, etc. the α-isomer of ZAPM prevailed. Especially in glacial acetic acid, the yield of α-form ZAPM reached more than 85%. The results of reactions in mixed solvents like acetonitrile–Me_2SO and ethyl acetate–acetonitrile showed that the yield of α-ZAPM changed linearly with a change in the composition of the mixed two solvents. The reaction in acetonitrile–acetic acid and Me_2SO–acetic acid showed that the addition of acetic acid not only caused a solvent effect by itself, but that the acid also affected the reaction. Therefore, the yield of α-ZAPM was increased by use of a mixed solvent containing only a small amount of glacial acetic acid. A mechanism to explain these experimental phenomena is presented.

Introduction

The reaction of N-protected L-aspartic anhydride with L-phenylalanine methyl ester has long been regarded as an important method for producing aspartame—α-L-aspartyl-L-phenylalanine methyl ester—discovered by Mazur et al.[1] Due to different modes of ring-opening, two isomers, the α-form and the β-form, are produced; however, only the α-form has a sweet taste. There are essentially three different chemical methods for production of aspartame.[2-19] In the first method, the α-carbonyl group

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