Fragmentation of Substituted Acetophenone and Halobenzophenone Ketyls. Calibration of a Mechanistic Probe

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Abstract: Disubstituted acetophenones, $XC_4H_4COCH_2Y$, and benzophenones, $XC_4H_4COC_6H_4Y$, are used to measure the cleavage rate constants, k_{fY}, of a series of α-substituted acetophenone ketyls and ring-substituted benzophenone ketyls. The cleavage rate constants can be determined from the competitive rates of fragmentation, k_{fY}/k_{fX}, of a series of ketyls, $[XC_6H_4COCH_2Y]^{\bullet-}$ and $[XC_6H_4COC_6H_4Y]^{\bullet-}$, since the rate constants, k_{fX}, for a number of ketyl fragmentations have been electrochemically determined. Ring fragmentation is not significantly affected by substitution at the α-position of the acetophenone nor on the opposite ring of the benzophenone. The ketyls are formed by the reaction of 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) with the disubstituted ketones. Ketyl fragmentation can be used as a diagnostic chemical probe for reactions of ketones suspected of having ketyl intermediates.

Introduction

Electron-Transfer–Fragmentation Reactions of Substituted Acetophenones. α-Haloacetophenones have been used successfully as chemical probes to distinguish between electron transfer–hydrogen atom abstraction and hydride-transfer mechanisms in reductions by organotin hydrides,[3] organosilanes,[4] 1,4-dihydropyridines,[5] enzyme (HLADH) mediated NADH reductions,[6] and the reductions of ketones by 1,3-dimethyl-2-phenylbenzimidazoline (DMBI).[7] The mechanistic pathways for reduction by the reducing agent, ZH, can be distinguished on the basis of the products formed since acetophenone is the product of homolytic reduction and the halohydrin is the product of the heterolytic process.

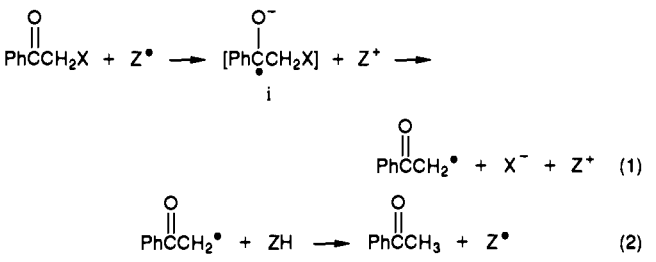
The mechanism used to rationalize the products formed from the homolytic pathway involves an electron transfer (ET) as one of the chain-propagation reactions, Scheme I.

Originally, the ketyl radical anion, i, was proposed as an intermediate in the reaction, eq 1.[3-5] Subsequently,[6,7] the ketyl was proposed to fragment by dissociative ET, since fast cyclic voltammetry (CV) at 10^3 V/s showed only one irreversible wave and a second reversible wave assigned to the reversible reduction of the enolyl radical to its anion.[6]

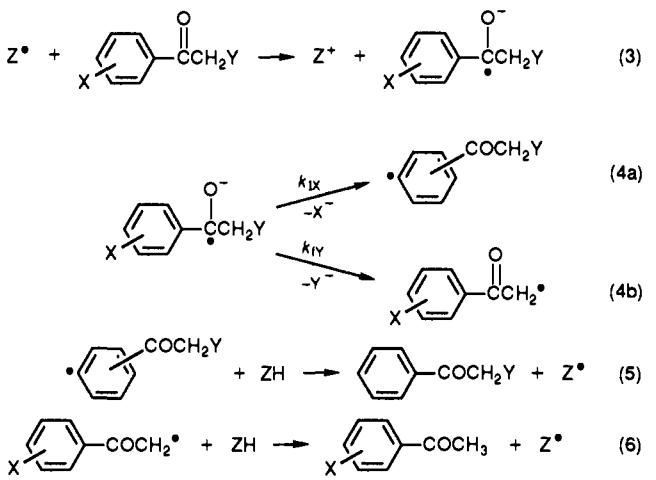
Enzymatic reduction reactions of the α-haloacetophenones by NADH produced only optically pure halohydrins (heterolytic reduction products).[6] However, in order to differentiate between ET followed by very fast hydrogen atom transfer between radical ion pairs, and a hydride-transfer process, it is important to establish whether ET to an α-haloketone is a dissociative process.

Recently the results of the electrochemical reduction of a number of ring-substituted acetophenones and benzophenones have been reported.[8,9,10] When the substituents were halogens, the rate constants for fragmentation of the halide anions from the intermediate ketyls, k_{fX}, were determined. The cleavage rates of α-substituted acetophenones, however, have not been determined.

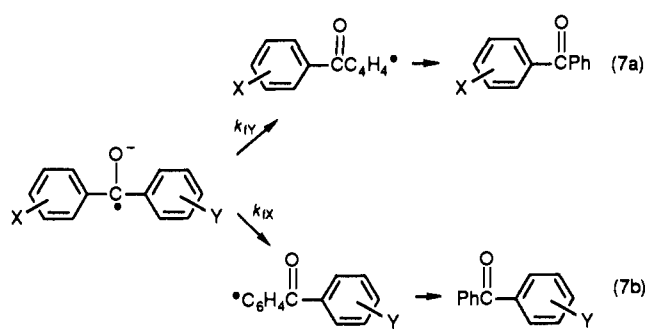
Scheme I



Scheme II



Scheme III



If one assumes that substitution at the α-position will not appreciably affect the rates of cleavage of a ring-halogenated substrate or vice versa, then the determination of the relative rates of competitive intramolecular fragmentation allows the calculation

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Table I. DMBI Reduction of α-Substituted Acetophenones **Ia–e**[a]

reaction	substrate $PhCOCH_2Y$ **Ia–e**	conditions	product (%)[b] $PhCOCH_3$	product (%)[b] $PhCOCH_2Y$
1	**Ia**. Y = OCOPh	60 h. C_6H_6	90.0 ± 0.1	3.2 ± 2.0
2	**Ib**. Y = $OCOCH_3$	60 h. C_6H_6	55.1 ± 1.0	45.3 ± 1.0
3	**Ic**. Y = OPh	48 h. AN	75.6 ± 0.3	2.6 ± 1.0
4	**Id**. Y = *p*-$TolSO_2$	48 h. THF	94.8 ± 0.7	
5	**Ie**. Y = SPh	48 h. THF	86.1 ± 0.7	12.3 ± 4.0

[a] All reactions were carried out at 61 °C in the dark with [**Ia–e**]/[DMBI] = 0.05–0.06 M. In the absence of AIBN (5%), almost no reaction occurred (yield <5%). [b] Average of two runs.

of the rates of cleavage of these α-substituents. Furthermore, a determination of the product ratios resulting from these competitive fragmentations allows a series of rate constants to be determined for ring-substituted acetophenones that were not previously determined electrochemically; see Scheme II.

Electron-Transfer–Fragmentation Reactions of Halobenzophenones. Since benzophenone and substituted benzophenones have been used as substrates to probe the mechanism of the reaction of ketones with a number of nucleophilic reagents,[11-15] it has been argued that the observation of EPR active intermediates are diagnostic of an electron-transfer process.[11-12] In several cases, the ketyl formation has been attributed to secondary electron-transfer reactions that do not follow the main mechanistic pathway.[14,15] The sensitivity of the EPR method detracts from its usefulness.

Since α-haloacetophenones are useful chemical probes for ET reductions, and since the key step in the mechanism is the ketyl cleavage to yield the enolyl radical $PhCO^{\bullet}CH_2$ (eq 1), a similar chemical probe can be established using the fragmentation reactions of dihalogenated benzophenone ketyls, where the homolytic pathway yields dehalogenated ketones; see Scheme III. The assumption that substitution on the two different rings does not appreciably effect the rate of the cleavage reaction of the substituent on the other ring has some experimental support since the fragmentation rate of 4,4′-dibromobenzophenone is only slightly less than the fragmentation rate of 4-bromobenzophenone and 4,4′-dichlorobenzophenone is deactivated by <6 times compared to its monochlorinated analogue.[10b] A determination of the product ratios resulting from the competitive reductive fragmentation of the dihalobenzophenone ketyls allows the calculation of the cleavage rate constants, k_{fY}, using the electrochemically established rates of fragmentation reported for the monohalobenzophenone ketyls, k_{fX}.[8-10] The use of competitive fragmentation rates assumes that the cleavage reactions are irreversible. No indication of reversible ion radical fragmentation has been reported[16] with the exception of the reduction of the nitroiodobenzenes (ortho, meta, and para) and *p*-nitrobenzyl iodide, where cleavage rates were affected by the addition of iodide ion. These observations were found to be true when the reductions were carried out in the absence of an adequate hydrogen atom donor and in the presence of high concentrations of added iodide ion.[17] Reductions carried out to low and high conversion did not show observable changes in their competitive rates (vide supra).

DMBI was used as the reducing agent, ZH (Schemes I and II). Its reactions with α-haloacetophenones have been shown to proceed by an ET chain mechanism.[7] A free radical chain mechanism was confirmed by initiation (AIBN) and inhibition (*p*-dinitrobenzene, DNB).[7] Similar results have now been obtained with the α-substituted acetophenones, and ring-halogenated acetophenones and benzophenones. The reduction reactions of both systems can be used as calibrated electron-transfer clocks. The usefulness of these clock reactions is apparent since the range of fragmentation rates, 10^1–10^{10} s^{-1}, is large and the relative rate constants are easily obtained.

Table II. DMBI Reduction of the Ring-Halogenated Acetophenones **IIa–g** and DMBI[a]

reaction	$XC_6H_4COCH_3$ **IIa–g**	product (%)[b] $PhCOCH_3$	product (%)[b] **IIa–g**	k_X (s^{-1})[c]
6	**IIa**. X = *o*-Br	80.6 ± 0.4	19.8 ± 0.2	
7	**IIb**. X = *p*-Br	70.4 ± 0.9	31.5 ± 0.6	$>8 \times 10^6$
8	**IIc**. X = *m*-Br	63.3 ± 1.7	39.0 ± 2.8	8×10^3
9	**IId**. X = *o*-Cl	50.2 ± 3.6	46.8 ± 1.9	3×10^5
10	**IIe**. X = *m*-Cl	0.4 ± 0.1	103.6 ± 4	15
11	**IIf**. X = *p*-Cl	17.3 ± 1.7	84.7 ± 3.4	3×10^3
12	**IIg**. X = *p*-I	71.9 ± 2.2	23.2 ± 2.1	

[a] All reactions were run in AN at 61 °C for 47 h in the presence of 3–5% AIBN with [**IIa–g**] = [DMBI] = 0.05 M. In the absence of AIBN, there was no reaction (yield <2%). [b] Average of two runs. [c] The cleavage rate constant of $XC_6H_4COCH_3^{\bullet-}$ in AN, taken from ref 9.

Results and Discussion

Photostimulated catalysis by tris(2,2′-bipyridyl)ruthenium(II) diperchlorate[17] was used to initiate the reaction at 20 °C, or di-*tert*-butyl peroxyoxalate (DBPO) was used as a room temperature initiator (23 °C).[7]

α-Substituted Acetophenones. The chain reactions for the reduction of the α-haloacetophenones have been published previously.[7] The results obtained for a number of other α-substituents are reported in Table I. For the reaction of these less reactive new substituents ($PhCO_2^-$, $CH_3CO_2^-$, PhO^-, *p*-$TolSO_2^-$, and PhS^-), no appreciable reactions with DMBI (<5%) occurs in the absence of 5 mol % of AIBN. Substituted acetophenones with these α-substituents have been reported[18] to undergo ketyl fragmentation using other reducing agents, eq 8.

$$PhCOCH_2Y^{\bullet-} \rightarrow PCOCH_2^{\bullet} + Y^- \qquad (8)$$

$$Y = PhCO_2,\ CH_3CO_2,\ PhO,\ ArSO_2,\ PhS$$

Ring-Halogenated Acetophenones. A series of ring-halogenated (Cl, Br, I) acetophenones were reduced with DMBI. The reductions were initiated by (3–5%) AIBN. No appreciable dehalogenation (<2%) was observed under these conditions (AN, 61 °C, 47 h) in the absence of the initiator, see Table II.

In all cases, the chain reduction yielded acetophenone as the only detectable product, Scheme IV. In the case of *m*-chloroacetophenone, chain reduction was not observed. The observation that acetophenone is formed by electron-transfer reduction (see Scheme IV) is consistent with the products formed from the electrochemical reduction of these substrates.[19]

Scheme IV

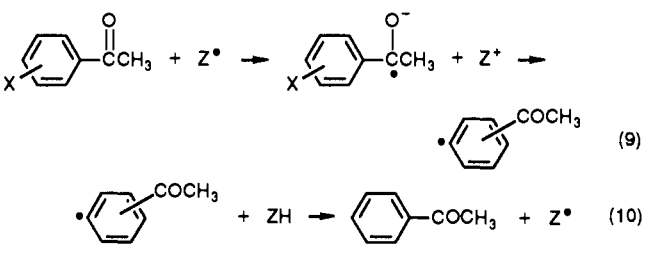

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Table III. Comparison of the Relative Ketyl Cleavage Rate in DMF and AN[a]

$XC_6H_4COCH_2Y$		k_{fY}/k_{fX}[b]	
X	Y	AN	DMF
p-Br	OCOPh	136 ± 30	61 ± 13
o-Br	OCOPh	1.3 ± 0.3	1.1 ± 0.4

[a] All the reactions were carried out at 61 °C in the dark with less than 1 equiv of DMBI in the presence of 2–6% of AIBN. $[XC_6H_4COCH_2Y] = 0.05$ M. [b] Calculated from the product ratio: $k_{fY}/k_{fX} = [XC_6H_4COCH_3]/[C_6H_5COCH_2Y]$. Average of two runs.

The absolute rate constants for fragmentation of several of the ring-halogenated acetophenone ketyls have been reported.[9] The known values are also listed in Table II. The absence of chain reduction for *m*-chloroacetophenone is no doubt due to the low rate of its ketyl fragmentation. Presumably the fragmentation is too slow to allow the aryl radical to carry the chain during the DMBI reduction.

Ring- and α-Substituted Acetophenones. Since the DMBI reductions of α-substituted acetophenones and the ring-halogenated acetophenones both proceed via an ET hydrogen abstraction chain mechanism (Schemes I and IV), the DMBI reduction of an acetophenone that is both α-substituted and ring halogenated is expected to proceed via a similar ET chain mechanism (Scheme II). The disubstituted acetophenone ketyl undergoes competitive cleavage to give either an aryl radical (eq 4a) or an enolyl radical (eq 4b). Hydrogen abstraction by these two radicals yields the α-substituted acetophenone (eq 5) and the ring-halogenated acetophenone (eq 6). The product ratio of these two ketones is determined by the ratio of the cleavage rate constants, k_{fX} and k_{fY}. If we assume that substitution at the α-position of acetophenone does not appreciably affect the cleavage rate of a ring-halogenated acetophenone ketyl (i.e., $k_{fX}(XC_6H_4COCH_2Y^{\bullet-}) \simeq k_{fX}(XC_6H_4COCH_3^{\bullet-})$ and that ring halogen does not significantly affect the cleavage rate of an α-substituted acetophenone ketyl (i.e., $k_{fY}(PhCOCH_2Y^{\bullet-}) \simeq k_{fY}(XC_6H_4COCH_2Y^{\bullet-})$, the reported cleavage rate of the ring-halogenated acetophenone ketyl (k_{fX}, eq 4a) can be used as an internal clock to calibrate the cleavage rates, k_{fY}, of a series of α-substituted acetophenone ketyls (vide infra). The cleavage reaction of *p*-bromoacetophenone ketyl, the fastest cleavage reaction among the ring-halogenated acetophenone ketyls with a known k_{fX}, was used as a standard for the calibration of the cleavage rate constants, k_{fY}, for the α-substituted acetophenone ketyls. The fragmentation rate constant for *p*-bromoacetophenone ketyl has been measured electrochemically in both acetonitrile (AN) and DMF (k_f: AN[9], $>8 \times 10^6$ s^{-1}; DMF,[8a] 3.2×10^7 s^{-1}). Since a very small solvent effect (AN vs DMF) on the cleavage reaction of several halobenzophenone ketyls has previously been reported,[10b] it is safe to assume that k_{fX} is approximately the same in the two solvents. 4,4′-Dibromobenzophenone ketyl cleaves at the same rate in AN and DMF (k_f(DMF)/k_f(AN) = 1.04).[10b] The fragmentation rate of *p*-bromoacetophenone ketyl in DMF, k_{fX}, was used as a standard in the calculation of the cleavage rate constants, k_{fY}. Consistent with the above argument, it was found that the competitive intramolecular relative ketyl cleavage rates, k_{fY}/k_{fX}, are the same in AN and the DMF for $XC_6H_4COCH_2Y$ (X = *p*-Br, *o*-Br; Y = OCOPh) (see Table III).

The DMBI reductions of a series of α-substituted *p*-bromoacetophenones, IIIa–i (*p*-$BrC_6H_4COCH_2Y$, Y = Br, Cl, F, OCOPh, $OCOCH_3$, OPh, *p*-$TolSO_2$, SPh) were carried out in AN. The cleavage rate constants, k_{fY}, were calculated from the product ratios (*p*-$BrC_6H_4COCH_3$/$PhCOCH_2Y$) and the reported cleavage rate for *p*-bromoacetophenone ketyl ($k_{fX} = 3 \times 10^7$ s^{-1}). The results of these reductions are shown in Table IV. From the measured cleavage rate constants of the α-substituted acetophenone ketyls (k_{fY}), a similar competitive reduction can be carried out to calibrate the cleavage rates of new ring-halogenated acetophenone ketyls (k_{fX}). The results of these indirect determinations are listed in Table V. The DMBI reductions of α,*p*-dibromoacetophenone (IIIa) and α-chloro-*p*-bromoacetophenone (IIIb) were carried out at room temperature. The reductions were inhibited by *p*-dinitrobenzene (DNB). The DMBI reduction of other α-substituted *p*-bromoacetophenones (*p*-$BrC_6H_4COCH_2Y$, Y = F, OCOPh, $OCOCH_3$, OPh, *p*-$TolSO_2$, SPh) required initiation by AIBN (61 °C); in the absence of AIBN, very little or no reaction occurred (<5%). Several reductions were also carried out at room temperature using DBPO as an initiator.

The tris(2,2′-bipyridyl)ruthenium(III) ($Ru(bpy)_3^{2+}$)[17] sensitized reductions of a number of organic substrates by *tert*-amines and by NADH model compounds have recently been reported.[20-25] The key step in these reductions is the electron transfer from $Ru(bpy)_3^+$ to the substrate. $Ru(bpy)_3^+$ is generated by ET from the NADH model compounds or NEt_3 to the excited [$Ru(bpy)_3$]$^{2+}$.[21-25]

The DMBI reductions of IIIf or IIIk were carried out at 20 °C in the presence of 3.3% of $Ru(bpy)_3^{2+}$. Under irradiation from two 200-W incandescent light bulbs through a band-pass filter solution of $K_2Cr_2O_7$–$NaNO_3$–NaOH (>470 nm),[21] two products were formed from both reactions (reaction 23, Table IV, or reaction 34, Table V). Control reactions carried out in the absence of $Ru(bpy)_3^{2+}$ gave only small amounts of the reduction products (reaction 24, Table IV, or reaction 35, Table V). Since the $Ru(bpy)_3^{2+}$-sensitized reductions of IIIf and IIIk gave essentially the same product ratios (i.e., competitive cleavage rates) as the corresponding product ratios obtained by using DBPO (reactions 22 and 23, Table IV, reactions 33 and 34, Table V), the $Ru(bpy)_3^{2+}$-sensitized reduction most probably also proceeds through a similar ET mechanism. As predicted, the product ratios are not dependent upon the nature of the electron donor.

The temperature dependence of the relative cleavage rates was found to be small (see reactions 21–23, Table IV, and reactions 31–34, Table V). It is justified, therefore, to use the electrochemical rates determined at room temperature and the relative cleavage rates (or product ratios) determined chemically at 61 °C to calculate the new cleavage rate constants at room temperature.

In order to substantiate the validity of the assumption that the fragmentation rate of Y was not appreciably affected by X or that the fragmentation rate of X was not effected by Y, another determination of the same value (k_{fY}) was carried out by using a different substituent, X.

The cleavage rate of *o*-chloroacetophenone was reported to be 3×10^5 s^{-1} in AN,[9] and that of *p*-bromoacetophenone was 3.2×10^7 s^{-1} (DMF).[8] The intramolecular competitive reductions of *o*-chloro-α-phenoxyacetophenone (IIIg) and *p*-bromo-α-phenoxyacetophenone (IIIh) gave an average cleavage rate constant of $(9.5 \pm 6.0) \times 10^6$ s^{-1} for α-phenoxyacetophenone ketyl; see reactions 21–23 and 25, Table IV.

The reduction of α,*p*-dibromoacetophenone (IIIa) and α-chloro-*p*-bromoacetophenone (IIIb) gave only *p*-bromoacetophenone (reactions 13–16, Table IV). The limit for detection of the α-haloacetophenones was experimentally estimated (GC and GC/IR) to be $<10^{-3}$–10^{-4} M, and a lower limit, $k_{fY} > 10^9$ s^{-1}, could be placed on the cleavage rates of the α-bromo- and α-chloroacetophenone ketyls. An estimated value, $<1 \times 10^6$ s^{-1}, has been reported for the bromide fragmentation from the ketyl of α-bromoacetophenone.[26] This result, obtained from a study of the products following the quenching of the photoexcited state

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Table IV. Intramolecular Competitive DMBI Reduction of the Disubstituted Acetophenones **IIIa–i** for the Determination of the Cleavage Rate Constants for α-Substituted Acetophenone Ketyls

reaction	$XC_6H_4COCH_2Y$ **IIIa–i**, X, Y	reaction conditions[a,b]	material balance (%)	product (%)[c] $XC_6H_4COCH_3$	product (%)[c] $PhCOCH_2Y$	k_{fY} (s^{-1})[d]
13	**IIIa**, X = *p*-Br, Y = Br	23 °C, 20 h	97	47.8	<2[e]	
14		23 °C, 20 h, 2% DNB		3.1	<2	
15	**IIIb**, X = *p*-Br, Y = Cl	23 °C, 17 h	96	95.4	<0.4[f]	
16		23 °C, 17 h, 4% DNB		3.4	<0.4[f]	
17	**IIIc**, X = *p*-Br, Y = F	61 °C, 2% AIBN, 53 h	97	56.7	0.42	5.2×10^9
18	**IIId**, X = *p*-Br, Y = OCOPh	61 °C, 3% AIBN, 48 h	>99	100.3	0.82	4.4×10^9
19		20 °C, 4.7% DBPO, 48 h	>99	42.5	0.14	8.2×10^9
20	**IIIe**, X = *p*-Br, Y = $OCOCH_3$	20 °C, 4.7% DBPO, 48 h	>99	32.5	0.88	9.6×10^8
21	**IIIf**, X = *p*-Br, Y = OPh	61 °C, 4% AIBN, 47 h	99	10.3	73.8	4.3×10^6
22		23 °C, 5% DBPO, 48 h	>99	1.0	7.7	4.3×10^6
23		20 °C, 3.3% sens,[g] $h\nu$,[h] 12 h	>99	6.3	38.8	5.1×10^6
24		20 °C, $h\nu$,[h] 12 h	>99	0.65	1.4	14.8×10^6
25	**IIIg**, X = *o*-Cl, Y = OPh	20 °C, 1.7% sens,[g] $h\nu$,[h] 35 h	97	34.6	0.6	19.2×10^6[i]
26		20 °C, $h\nu$,[h] 35 h	>98	1.3		
27	**IIIh**, X = *p*-Br, Y = *p*-$TolSO_2$	61 °C, 5% AIBN, 59 h	100	44.5	2.7	5.3×10^8
28	**IIIi**, X = *p*-Br, Y = SPh	61 °C, 2% AIBN, 48 h	99	8.0	31.8	9.3×10^6

[a] All reactions were carried out in AN in the dark, except where specified in the table, with less than 1 equiv of DMBI. [**IIIa–i**] = 0.05 M. [b] In the absence of AIBN, **IIIc–i** showed little reaction (<5%). [c] The product yield of a representative run. The product yields plus recovered substrate were all between 96–100%. [d] Calculated by using k_{fX}(*p*-Br) = 3.2×10^7 s^{-1}. Average of at least two individual experiments (except reactions 23 and 24). The reproducibility of duplicate experiments was in all cases better than ±11%. [e] The detection limit by GC/IR was >1×10^{-3} M. [f] The detection limit by GC/IR was >2×10^{-4} M. [g] Sens = $Ru(bpy)_3(ClO_4)_2$. [h] A filter solution of $K_2Cr_2O_7$–$NaNO_3$–NaOH[21] was used. The light source was two 200-W incandescent light bulbs. [i] Calculated by using k_{fX}(*o*-Cl) = 3×10^5 s^{-1}.

Table V. Intramolecular Competitive DMBI Reduction of the Disubstituted Acetophenones **IIIj–m** for the Determination of the Cleavage Rate Constants of the Ring-Halogenated Acetophenone Ketyls

reaction	$XC_6H_4COCH_2Y$ **IIIj–m**, X, Y	reaction conditions[a,b]	material balance (%)	product (%)[c] $XC_6H_4COCH_3$	product (%)[c] $PhCOCH_2Y$	k_{fX} (s^{-1})[d]
29	**IIIj**, X = *o*-Br, Y = F	61 °C, 4% AIBN, 36 h	96	14.7	4.6	2.0×10^9
30		90 °C, 6% AIBN, 1.5 h	89	21.7	8.5	2.1×10^9
31	**IIIk**, X = *o*-Br, Y = OCOPh	61 °C, 6% AIBN, 72 h	90	12.9	9.1	5.0×10^9
32		90 °C, 14% AIBN, 2.3 h	>99	8.9	13.8	8.3×10^9
33		23 °C, 5% DBPO, 48 h	91	17.2	13.9	5.5×10^9
34		20 °C, 3.4% sens,[e] $h\nu$,[f] 13 h	94	12.5	15.7	7.9×10^9
35		20 °C, $h\nu$,[f] 13 h		3.0 ± 0.1	trace	
36	**IIIl**, X = *p*-I, Y = OCOPh	61 °C, 3% AIBN, 19 h	100	10.8	29.2	2.3×10^9
37		61 °C, 3% AIBN, 19 h	100	3.1	4.4	4.4×10^9
38		61 °C, 3% AIBN, 19 h	100	19.6	35.0	3.9×10^9
39	**IIIm**, X = *m*-I, Y = OCOPh	61 °C, 4% AIBN, 29 h	84	39.1	0.70	1.1×10^8
40		61 °C, 3.5% AIBN, 29 h	85	26.9	1.14	2.7×10^8

[a] All reactions were carried out in AN in the dark, except where specified in the table, with less than 1 equiv of DMBI. [**IIIj–m**] = 0.05 M. [b] In the absence of AIBN, **IIIj–m** showed little reaction (<5%). [c] The product yields of a representative run. The product yields plus recovered substrate were all between 89–100% except reactions 39 and 40, which were in 84% yield. The lack of material balance in this reaction appears to be due to the uncertainty in the analysis of the recovered unreacted starting material. [d] Calculated by using the measured k_{fY}: $k_{fF} = 5.2 \times 10^9$ s^{-1}; $k_{fOCOPh} = 6.3 \times 10^9$ s^{-1}. Average of at least two individual experiments (except reactions 34 and 35). The reproducibility of duplicate experiments was always better than ±11%. [e] Sens = $Ru(bpy)_3(ClO_4)_2$. [f] A filter solution of $K_2Cr_2O_2$–$NaNO_3$–NaOH[21] was used. The light source was two 200-W incandescent light bulbs.

of the carbonyl, does not appear to be in agreement with our electrochemically based determination.

In aprotic solvents, simple alkyl halides (I, Br, Cl) and benzyl halides (I, Br, Cl) are now believed to undergo dissociative ET reactions.[27-31] Since neither ring-halogenated α-chloro- nor α-bromoacetophenones gave any competitive cleavage (only α-halogen fragmentation), ET's to both α-haloacetophenones are also likely to be dissociative. A dissociative electron transfer, since it is not truly a competitive ketyl cleavage, proceeds by a transition state that involves the donor molecule, and only if it is not dissociative can an estimate of its competitive cleavage rate (k > 10^9 s^{-1}) be obtained. In a recent study of the photoreduction of α-bromoacetophenone by 10-methyl-9-acridan ($AcrH_2$) in acetonitrile, α-bromoacetophenone ketyl was proposed to be a discrete intermediate; however, no direct evidence for its presence was obtained.[32] This result does not appear to be in agreement with our electrochemically based estimate of the fragmentation rate.

The competitive reductions of the disubstituted acetophenones **IIIc–f** each give two products, $XC_6H_4COCH_3$ and $PhCOCH_2Y$. The value of the ketyl cleavage rate constants for these α-substituted acetophenones, k_{fY}, can be calculated from the product ratios and k_{fX} (see Table IV). All of the α-substituted acetophenones studied undergo fast ketyl cleavage (k_{fY} > 10^6 s^{-1}). Qualitatively k_{fY} decreases in the order F ≈ OCOPh > $OCOCH_3$ > *p*-$TolSO_2$ > SPh ≈ OPh.

In an attempt to correlate the cleavage rate constants, k_{fY}, with the leaving group ability of Y^-, a Brønsted plot of the pK_a values of the conjugate acids of Y^- in an aprotic solvent (DMSO)[33] vs the relative rate of ketyl–Y bond cleavage was plotted. As expected, the first-row nucleophuges give a linear correlation, while the sulfur-centered nucleophuge deviated from the line.

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Table VI. Reported Cleavage Rate Constants (k_f) for Several Halobenzophenone Ketyls

halobenzophenone	k_f (s^{-1})	solvent	technique	ref
4-ClC_6H_4COPh	10.5 ± 0.8	DMF	potential step chronocoulometry	10a
	33.5	AN	derivative cyclic voltammetry (DCV)	10b
	51.2	DMF	DCV	10b
	40	DMF	double potential step chronoamperometry	8a
	10	DMF	linear sweep voltammetry (LSV)	10c
	av 29 ± 15	AN, DMF		
4-$ClC_6H_4COC_6H_4$-4-Cl	5.9	AN	DCV	10b
	7.5	DMF	DCV	10b
3-BrC_6H_4COPh	794	DMF	LSV	10c
	9	AN	LSV	10c
4-BrC_6H_4COPh	2.2×10^4	AN	DCV	10b
	4×10^4	AN	fast cyclic voltammetry	9
	8×10^4	DMF	LSV	10c
	10×10^4	DMF	homogeneous redox catalysis	8a
	av $(6 \pm 3) \times 10^4$	AN, DMF		
4-$BrC_6H_4COC_6H_4$-4-Br	1.09×10^4	AN	DCV	10b
	1.13×10^4	DMF	DCV	10b

Table VII. Photoinitiated Intramolecular Competitive DMBI Reduction of Dihalobenzophenones IVa–d at 20 °C

reaction	$XC_6H_4COC_6H_4Y$ IVa–d	reaction conditions[a]	product (%)[b] XC_6H_4COPh (V)	product (%)[b] YC_6H_4COPh (VI)	material balance (%)	product ratio[c] V/VI
38	IVa, X = 3-Br, Y = 4-Br	52 h[e]	1.2			
39		8% AIBN, 52 h[e]	10.4	0.04	100	216 ± 21
40	IVb, X = 4-Cl, Y = 3-Br	96 h[d]	19.0	0.18	100	106
41		4% $Ru(bpy)_3^{2+}$, 96 h[d]	57.0	0.21	>99	215 ± 57
42		98 h (no DMBI)[f]	3.2			
43		98 h (with DMBI)[f]	66.7[g]	0.34	100	196 ± 1 av 172 ± 44
44	IVc, X = 2-Cl, Y = 3-Br	68 h[d]	6.2	0.5	100	12
45		2% $Ru(bpy)_3^{2+}$, 68 h[d]	56.6[g]	4.2	88[j]	14 ± 1 av 13 ± 1
46	IVd, X = 4-Br, Y = 3-I	DMF, 120 h[d]	28.1	0.96	>99	29
47		DMF, 2.6% $Ru(bpy)_3^{2+}$, 120 h[d]	52.1[h]	1.1	97	68 ± 21
48		4% AIBN, dark, 61 °C[i]	15.4	0.54		28 av 42 ± 18

[a] All the reactions were carried out in AN with less than 1 equiv of DMBI, except where specified in the Table; [IV] = 0.03–0.05 M. [b] The product yield of one representative run. [c] An average of two independent runs, and the error represents the standard deviation from the mean. [d] Irradiation with two 200-W incandescent lamp bulbs through a filter solution of $NaNO_3$–NaOH–$Na_2Cr_2O_7$. Ishitani, O.; Yanagida, S.; Takamura, S.; Pac, C. *J. Org. Chem.* **1987**, *52*, 2790. [e] The reactions were carried out in an AN/THF (3/1, v/v) mixture. [f] Irradiation with two 200-W incandescent lamp bulbs through Pyrex filter. [g] About 0.2–0.4% yield of benzophenone was also detected by GC/IR. [h] 4.0% yield of benzophenone was also detected by GC/IR. [i] The reactioins were carried out in the dark at 61 °C in an AN/C_6H_6 (1/2, v/v) mixture. [j] In the event that all of the missing material was either V or VI, the calculated rates will only differ by a factor of <1.7.

Although the leaving group ability (nucleofrugality) for a reaction series does not necessarily correlate with the pK_a of the conjugate acid, the reactions do correlate reasonably well with the limited kinetic data available.[33b]

The intramolecular competitive reduction of the disubstituted acetophenones can also be used to determine the cleavage rate constants (k_{fX}) for a series of new ring-halogenated acetophenone ketyls that have not been determined directly (Scheme II). The competitive DMBI reductions of IIIj, IIIk, IIIl, and IIIm were carried out to determine indirectly the k_{fX} values of the *o*-bromo-, *p*-iodo-, and *m*-iodoacetophenone ketyls; see Table V. The same k_{fX} value, $(3.5 \pm 1.5) \times 10^9$ s^{-1} (61 °C), was obtained for *o*-$BrC_6H_4COCH_2Y^{\bullet-}$ from the reduction of both IIIj and IIIk. These results further support the original assumption that the presence of an α-substituent (Y) does not significantly affect the cleavage rate of a ring-halogenated acetophenone ketyl.

Cleavage Rates of Halogenated Benzophenone Ketyls. The cleavage rates of a number of halogenated benzophenone ketyls have been determined electrochemically. A listing of the available rate data for the cleavage reactions of monohalo- and dihalobenzophenones is given in Table VI. Originally, the cleavage rates in AN were reported to be smaller than those in DMF.[10c] However, the electrochemical reductions of several halobenzophenones were reexamined, and the cleavage rates in both solvents were found to be almost the same.[10b]

Since the cleavage rates of the symmetrical 4,4′-dihalobenzophenone ketyls are only 2–6 times slower than those of the corresponding monohalobenzophenone ketyls, competitive fragmentation rates could be determined for the cleavage reaction of the ketyl of unsymmetrically substituted dihalobenzophenones; see Scheme III. From a comparison of the product ratios of the two monohalobenzophenones produced in these reductions, and from the known fragmentation rates of the monosubstituted benzophenone ketyls, a series of fragmentation rate constants can be determined for benzophenone substituents that have not been previously determined electrochemically. Table VII lists the results of these competitive fragmentation reactions.

The DMBI reductions of the dihalobenzophenones IVa–d were carried out in AN. For the reductions of 3,4′-dibromobenzophenone (IVa) and 4-bromo-3′-iodobenzophenone (IVd), a mixture of AN/THF, AN/C_6H_6, or DMF was used as the solvent due to the poor solubility of the two ketones in pure AN.

Reactions initiated by photostimulation of $Ru(bpy)_3^{2+}$ [21–25] or by direct photostimulation[34] gave the same results with the exception that higher conversions were obtained in the $Ru(bpy)_3^{2+}$ catalyst reductions. Initiated reactions (AIBN) that also proceed by an electron-transfer mechanism[7] gave, within experimental error, the same product ratios as those catalyzed by light.

The competitive reduction of 3,4′-dibromobenzophenone, IIIa, gave two fragmentation products in the ratio of 3-bromo/4-bromobenzophenone of 216/1. From the rate of fragmentation of the electrochemically generated ketyl of 4-bromobenzophenone, 6×10^4 s^{-1}, the rate of fragmentation for 3-bromobenzophenone

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Table VIII. Summary of the Cleavage Rate Constants of Substituted Acetophenone and Benzophenone Ketyls in Acetonitrile at Room Temperature

$XC_6H_4COCH_3$ X	k_{fX} (s^{-1})	$PhCOCH_2Y$ Y	k_{fY} (s^{-1})	$XC_6H_4COC_6H_5$ X	k_{fX} (s^{-1})
m-Cl	15	Br	$>10^9$	*p*-Cl	29
p-Cl	3×10^3	Cl	$>10^9$	*o*-Cl	61
o-Cl	3×10^5	F	5.2×10^9	*m*-Br	7.9×10^2
m-Br	8×10^3	OCOPh	6.3×10^9	*p*-Br	6×10^4
p-Br	3.2×10^7	$OCOCH_3$	9.6×10^8	*m*-I	2.5×10^6
o-Br	5.1×10^9	OPh	9.5×10^6		
m-I	1.9×10^8	*p*-$TolSO_2$	5.3×10^8		
p-I	3.5×10^9	SPh	9.3×10^6		

ketyl is calculated to be 2.8×10^2 s^{-1}. A comparison of this value with that of the known fragmentation rate constant of 3-bromobenzophenone ketyl, 7.9×10^2 s^{-1}, gives some confidence in this indirect method.[35]

Another confirmation of the indirect method is the calculation of the fragmentation rate for 4-chlorobenzophenone ketyl, 29 s^{-1}. The competitive production of fragmentation products of 3-bromo-4'-chlorobenzophenone ketyl is 172/1, [4-chloro]/[3-bromobenzophenone]. Since the reported[10c] rate constant, k_{fX}, for 3-bromobenzophenone is 7.9×10^2 s^{-1}, then the indirectly calculated value of 4.6 s^{-1} is close to the average value of 29 s^{-1} reported for the electrochemically determined fragmentation rate.

The cleavage rate constants for 2-chlorobenzophenone ketyl and 3-iodobenzophenone ketyl were calculated to be 61 and 2.5 $\times 10^6$ s^{-1} from the competitive reductions of 3-bromo-2'-chlorobenzophenone (IVc) and 4-bromo-3'-iodobenzophenone (IVd) using the reported k_{fX} values for 3-bromo- and 4-bromobenzophenone ketyls; see Table VII.

Conclusion

A summary of all of the rate constants for the three systems, ring-substituted acetophenones, α-substituted acetophenones, and ring-substituted benzophenones, is listed in Table VIII. The rate constants reported span a range of 10^1 to $>10^{10}$ s^{-1}. Ketyl fragmentation rates can be used as diagnostic probes for reactions of ketones suspected of proceeding by ketyl intermediates and can be further used as indicators of the lifetimes of such intermediates (i.e., as electron-transfer clocks).

The free radical cyclization clocks have been useful in calibrating the rate constants of a variety of competing reactions.[36] Similarly the electron-transfer clock reactions can be used for the calibration of fragmentation–rearrangement, fragmentation–cyclization, fragmentation–dimerization, or fragmentation–hydrogen atom abstraction reactions of ketyl intermediates.

Experimental Section

Instrumentation. Melting points were measured on a Fisher-Johns hot stage instrument or on a Mel-Temp melting point apparatus, and are uncorrected. ^1H NMR spectra were recorded on a Bruker WP-200 spectrometer (20 MHz) with deuteriochloroform as solvent and residual chloroform (δ 7.24 ppm) as the standard. Gas chromatograph–mass spectra (GC/MS) were recorded on a VG-70 E mass spectrometer with a 1125 data system. The products were separated on a Varian Vista 6000 gas chromatograph fitted with a gas capillary column (DB-5, 30 m × 0.25 mm × 0.25 μ, J & W Scientific). Gas chromatograph–infrared spectra (GC/IR) were obtained with a HP 5965A IRD spectrometer interfaced to a HP 5890 gas chromatograph (Hewlett-Packard) that was fitted with a glass capillary column (ultra 2, 25 m × 0.32 mm × 0.52 μ, Hewlett-Packard).

Materials. The preparation and purification of acetophenone, α-bromoacetophenone, α-chloroacetophenone, α-fluoroacetophenone, *p*-di-*tert*-butylbenzene, α,α-azoisobutyronitrile (AIBN), *p*-dinitrobenzene (DNB), di-*tert*-butyl peroxyoxalate (DBPO), and 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) have previously been described.[3,7,37] The purification of the solvents (benzene tetrahydrofuran, acetonitrile, and dimethylformamide) was described previously.[37]

Bromo- and chloroacetophenone (ortho, meta, para) (IIa–f) (Aldrich), 4-bromobenzophenone (Fluka), 2-chlorobenzophenone (Aldrich), and 4-chlorobenzophenone (Aldrich) were used as supplied. Their purity, checked by GC, was >97%.

α,*p*-Dibromoacetophenone (IIIa) (Aldrich, Fluka) was recrystallized from ethanol; mp 108–109.5 °C (lit.[38] mp 108–109 °C). *p*-Iodoacetophenone (IIg),[39] *m*-iodoacetophenone (IIh),[40] and tris(2,2'-bipyridyl)ruthenium diperchlorate[41] were prepared according to the literature procedures.

p-Bromo-α-chloroacetophenone (IIIb) was prepared by the chlorination of *p*-bromoacetophenone with sulfuryl chloride.[42] Recrystallization from ethanol gave white crystals: mp 118–119.5 °C (lit.[43] mp 119–120 °C); ^1H NMR δ 4.68 (s, 2 H), 7.65 (m, 2 H), 7.85 (d, 2 H).

α-(*p*-Methylbenzenesulfonyl)acetophenone (Id) and α-(*p*-methylbenzenesulfonyl)-*p*-bromoacetophenone (IIIh) were prepared according to the literature procedure given for the synthesis of β-ketosulfones.[44] Id and IIIh were recrystallized from ethanol. Id: mp 108–109 °C (lit.[45] mp 109–109.5 °C); ^1H NMR δ 2.4 (s, 3 H), 4.7 (s, 2 H), 7.3–8.0 (m, 9 H). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.68; H, 5.14; S, 11.69. Found: C, 65.93; H, 5.20; S, 11.55. IIIh: mp 147–148 °C (lit.[46] mp 145–147 °C); ^1H NMR δ 2.68 (s, 3 H), 4.85 (s, 2 H), 7.5–8.0 (m, 10 H).

α-(Phenylthio)acetophenone (Ie) and α-(phenylthio)-*p*-bromoacetophenone (IIIi) were synthesized according to Ono's general procedure for the preparation of sulfides,[47] and were recrystallized from ethanol. Ie: mp 51–52 °C (lit.[48] mp 49 °C); ^1H NMR δ 4.2 (s, 2 H), 7.2 (m, 8 H). 7.8 (m, 2 H). IIIi: mp 60–61 °C (lit.[48] mp 60 °C); ^1H NMR δ 4.2 (s, 2 H), 7.0–8.0 (m, 9 H).

All the bromomethyl aryl ketones ($ArCOCH_2Br$) used in this study were either commercially available or prepared from the corresponding methyl aryl ketones ($ArCOCH_3$) and copper bromide according to the literature procedure given for the bromination of ketones.[49] They were purified either by distillation or by recrystallization. All the esters $ArCOCH_2OCOPh$ were prepared from $ArCOCH_2Br$, $PhCO_2H$ (or CH_3CO_2H), and diazabicyclo[5.4.0]undec-7-ene (DBU) according to Ono's general procedure for the preparation of esters.[50] The phenyl ethers $ArCOCH_2OPh$ were prepared via the same procedure as the esters.[50] The esters and ethers were purified by recrystallization from ethanol or by distillation. Following is a list of compounds prepared by this procedure.

α-(Benzoyloxy)acetophenone (Ia): mp 119–119.8 °C (lit.[51] mp 119–121 °C); ^1H NMR δ 5.62 (s, 2 H), 7.42–7.7 (m, 6 H), 8.0–8.2 (m, 4 H).

(35) The agreement in the fragmentation rate constant also substantiates the argument put forward by Parker[10b] that the difference in the cleavage rate constants for halobenzophenone ketyls in AN and DMF is small. The rate constant reported in AN (9 s^{-1}) is inconsistent with the ketyl cleavage rate constants in the two solvents; see Table VI.

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α-Acetoxyacetophenone (1b): mp 48–49 °C (lit.[52] mp 49 °C); ^{1}H NMR δ 2.25 (s, 3 H), 5.39 (s, 2 H), 7.45–8.0 (m, 5 H).

α-(Benzoyloxy)-*p*-Bromoacetophenone (111d): mp 119–120 °C (lit.[53] mp 120–121 °C); ^{1}H NMR δ 5.5 (s, 2 H), 7.5 (m, 2 H), 7.65 (m, 3 H), 7.85 (d, 2 H), 8.15 (d, 2 H). Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.21; H, 3.48.

α-Acetoxy-*p*-bromoacetophenone (111e): mp 84.5–85.5 °C (lit.[50] mp 85–86 °C): ^{1}H NMR δ 2.25 (s, 3 H), 5.3 (s, 2 H), 7.4–7.8 (m, 4 H).

α-(Benzoyloxy)-*o*-bromoacetophenone (111k): mp 65–6 °C; ^{1}H NMR δ 5.5 (s, 2 H), 7.25–7.65 (m, 7 H), 8.05–8.15 (dd, 2 H). Anal. Calcd for $C_{15}H_{11}BrO_3$: C. 56.45; H, 3.47. Found: C, 56.32: H, 3.33.

α-(Benzoyloxy)-*p*-iodoacetophenone (111l): mp 127.5–128.5 °C (lit.[54] mp 128 °C): ^{1}H NMR δ 5.55 (s, 2 H), 7.4–7.7 (m, 5 H), 7.8–8.0 (d, 2 H). 8.1–8.2 (d, 2 H).

α-(Benzoyloxy)-*m*-iodoacetophenone (111m): mp 102–103 °C; ^{1}H NMR δ 5.5 (s, 2 H), 7.2–7.6 (m, 4 H), 7.8–8.3 (m, 5 H). Anal. Calcd for $C_{15}H_{11}IO_3$: C, 49.21: H, 3.03. Found: C, 49.23; H. 2.95.

α-Phenoxyacetophenone (1c): mp 72–72.5 °C (lit.[55] mp 71–72 °C); ^{1}H NMR δ 5.3 (s. 2 H), 7.0–8.1 (m, 10 H).

p-Bromo-α-phenoxyacetophenone (111f): mp 91.5–92.5 °C (lit.[56] mp 92–93 °C): ^{1}H NMR δ 5.37 (s, 2 H), 7.1 (m, 3 H), 7.45 (m, 2 H), 7.9 (d, 2 H), 8.05 (d, 2 H). Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found: C, 57.38: H, 3.82.

o-Chloro-α-phenoxyacetophenone (111g): bp 185–188 °C (3 mmHg); ^{1}H NMR δ 5.2 (s. 2 H), 6.9–7.1 (m, 3 H), 7.25–7.7 (m, 6 H); MS *m/e* 248.04 and 246.04. GC/IR, ^{1}H NMR, and GC showed that it contained 4.3% of *o*-chloroacetophenone. This amount was corrected for the *o*-chloroacetophenone formed in the reduction of 111g with DMBI.

p-Bromo-α-fluoroacetophenone (111c) was prepared by the fluorination of α,*p*-dibromoacetophenone with potassium fluoride.[57] Recrystallization from water–ethanol gave pale yellow crystals: mp 70–72 °C: ^{1}H NMR δ 5.5 (d, 2 H, *J* = 11.5 Hz), 7.75 (m, 4 H). Anal. Calcd for C_8H_8BrFO: C, 44.27: H, 2.79. Found: C, 44.18; H, 2.68. *o*-Bromo-α-fluoroacetophenone (111j) was synthesized by the same procedure as *p*-bromo-α-fluoroacetophenone: bp 100–120 °C (4 mmHg); ^{1}H NMR δ 5.4 (d, 2 H, *J* = 12 Hz), 7.3–7.7 (m, 4 H). GC, GC/IR. GC/MS, and ^{1}H NMR showed that it contained 11% of *o*-bromoacetophenone. The calculation of the amount of *o*-bromoacetophenone formed in the reduction of 111j with DMBI was corrected for this impurity.

3-Bromobenzophenone was prepared by the Friedel–Crafts reaction of 3-bromobenzoyl chloride and benzene according to the procedure given for the preparation of 2-chlorobenzophenone;[58] mp 75–76 °C (lit.[59] mp 77 °C). 3-Iodobenzophenone was prepared according to the same procedure: mp 40–41 °C (lit.[60] mp 42.5 °C).

3,4′-Dibromobenzophenone (1Va). 3-bromo-2′-chlorobenzophenone (1Vb), and 4-bromo-3′-iodobenzophenone (IVd) were prepared from the corresponding halobenzoyl chloride. halobenzene, and ferric sulfate by Morely's general procedure[61] for the Friedel–Crafts acylation reactions. The pure ketone was obtained by several successive recrystallizations. 1Va was prepared from 3-bromobenzoyl chloride and bromobenzene, and purified by successive recrystallization from benzene: mp 135–136 °C (lit.[62] mp 132 °C). 1Vb was prepared from 3-bromobenzoyl chloride and chlorobenzene, and purified by successive recrystallization from ethanol; mp 119.0–120 °C. Anal. Calcd for $C_{13}H_8BrClO$: C, 52.83: H, 2.73. Found: C, 52.90; H, 2.68. 1Vd was prepared from 3-iodobenzoyl chloride and bromobenzene, and purified by successive recrystallization from ethanol: mp 156–158 °C (lit.[63] mp 155 °C).

3-Bromo-2′-chlorobenzophenone (1Vc) was prepared through the oxidation of 3-bromo-2′-chlorobenzhydrol with the Jone's reagent;[64] bp 209–212 °C (15 mmHg). Anal. Calcd for $C_{13}H_8BrClO$: C. 52.83: H, 2.73: Found: C. 52.66: H, 2.77. 3-Bromo-2′-chlorobenzhydrol was prepared from (3-bromophenyl)magnesium bromide (made from 1,3-dibromobenzene and Mg) and α-chlorobenzaldehyde according to the procedure given for the preparation of 2-chlorobenzhydrol:[65] bp 235–237 °C (15 mmHg): ^{1}H NMR δ 2.7 (d, 1 H), 6.25 (d, 1 H), 7.2–7.8 (m, 8 H). Anal. Calcd for $C_{13}H_{10}BrClO$: C, 52.47; H, 3.39, Found: C, 52.73; H, 3.46.

Quantitative Gas Chromatograph (GC) Analyses. GC analyses were carried out on a Hewlett-Packard 5840A gas chromatograph fitted with a flame ionization detector and a HP 5840A integrator terminal. The yields of reaction products were determined by using standard calibration curves constructed with known mixtures of the authentic materials. The products were identified by a comparison of their retention times. Their GC/IR spectra and GC/MS spectra were identical to those of authentic samples.

The following columns were employed for GC analysis: (A) a stainless steel column (10 ft × 1/8 in.) packed with 5% OV-101 on Chromosorb WAW DMCS 100/200 mesh; (B) a stainless steel column (10 ft × 1/8 in.) packed with 5% SE-30 on Chromosorb WAW DMCS 80/100 mesh; (C) a stainless steel column (10 ft × 1/8 in.) packed with 5% FFAP on Chromosorb WAW DMCS 60/80 mesh; and (D) a DB-5 megabore column (30 m, J & W Scientific Inc.). The internal standard was either *p*-di-*tert*-butylbenzene or bibenzyl.

Column D was used with a Varian 3700 gas chromatograph equipped with a TCD detector. The chromatograms were recorded and the areas were integrated by using a Varian CDS 401 data station. Other columns were used with an HP 5840A gas chromatograph interfaced to an HP 5840A integrator. The GC analyses of the reaction mixture of α-fluoroacetophenone derivatives 111c and 111h were carried out on columns D or C. The reaction mixture for 1Vd was analyzed by using column D. The reaction mixture of all other ketones were analyzed by GC using column A or B. The separation of products was achieved by using either one of the two columns A or B for all these reactions.

The product ratio 3-BrC_6H_4COPh/4-BrC_6H_4COPh in the reduction of IVa was determined from GC analysis on a Rt_x-1 column (105 m × 0.25 mm × 0.25 μ, Restek Corp.).

The yields of reaction products in the competitive reduction of disubstituted acetophenones and benzophenones were determined from GC/IR spectra for yields lower than 2%. For yields higher than 2%, the same results were obtained from GC/IR and GC measurements. The quantitative calculation of yields from GC/IR experiments used the relative intensities of the IR spectra and the relative areas obtained from the FID detector connected to the GC/IR. A standard solution was run to obtain the response factor. A known concentration of a standard solution was analyzed by GC/IR to obtain its detection limit for the compound (see Tables I–VII).

General Procedure for the Reduction. A mixture of the substrate (0.03–0.05 M), the reducing reagent (DMBI, 0.025–0.06 M), the internal standard (0.02 M), and the additive (AIBN, DNB, DBPO, or Ru(bpy)$_3^{2+}$. 1.7–14%) in a desired solvent (C_6H_6, THF, AN. DMF) was placed in a Pyrex ampule. The ampule was degassed three times, sealed, and thermostated at the desired temperature for the time specified in Tables I–V and VII. The ampule was opened, and the contents were analyzed by GC. For each new reaction the products were further identified by the comparison of their GC/IR and GC/MS spectra with those of authentic samples.

The reductions of 111a–b and the reductions initiated by DBPO were modified to avoid possible reactions during degassing. A solution (1 mL) of the substrate, internal standard, and the additives and a solution (1 mL) of DMBI were each put in the separate arms of an H-form ampule. After being degassed, sealed, and thermostated at room temperature, the solutions in the two arms were mixed and kept at room temperature in the dark for the specified time.

Ru(bpy)$_3^{2+}$ Photosensitized Reduction of Disubstituted Acetophenone and Benzophenones. The reaction mixture was placed in a double-wall degassed Pyrex reaction vessel. The outer compartment contained a filter solution of aqueous $K_2Cr_2O_7$–NaOH–$NaNO_3$ with a UV band-pass of >470 nm (1 cm).[22] The reaction vessel was thermostated in a Pyrex water bath (20 °C) and irradiated with a 200-W incandescent lamp placed outside the bath.

Direct Photoinitiated DMBI Reduction of IVb. A mixture of 1Vb, DMBI, and internal standard in AN was placed in a Pyrex ampule. The ampule was degassed, sealed, and thermostated in a Pyrex water bath at 20 ± 1 °C. The reaction mixture was irradiated with a 200-W incandescent lamp from the outside of the bath.

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Registry No. Ia, 33868-50-7; Ib, 2243-35-8; Ic, 721-04-0; Id, 31378-03-7; Ie, 16222-10-9; IIa, 2142-69-0; IIb, 99-90-1; IIc, 2142-63-4; IId, 2142-68-9; IIe, 99-02-5; IIf, 99-91-2; IIg, 13329-40-3; IIIa, 99-73-0; IIIb, 4209-02-3; IIIc, 403-30-5; IIId, 7506-12-9; IIIe, 7500-37-0; IIIf, 36372-16-4; IIIg, 135774-33-3; IIIh, 31377-97-6; IIIi. 27047-19-4; IIIj, 135774-34-4; IIIk, 135774-35-5; IIIl, 135774-36-6; IIIm, 135774-37-7; IVa, 83699-51-8; IVb, 75762-56-0; IVc, 135774-38-8; IVd, 96464-18-5; DMBI, 3652-92-4.

Neutron Diffraction Study of the Hydrogen Bonding in Partially Deuterated γ-Cyclodextrin·15.7D_2O at T = 110 K†

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Abstract: A single-crystal neutron diffraction study of partially deuterated γ-cyclodextrin (γ-CD) hydrate, $(C_6D_3H_7O_5)_8$·15.7D_2O, was carried out at T = 110 K. The crystal is monoclinic, space group $P2_1$, with cell dimensions a = 16.899 (7) Å, b = 10.891 (5) Å, c = 20.226 (6) Å, β = 105.06 (2)°, Z = 2, and V = 3595 (2) Å^3. A total of 10688 reflections were collected with λ = 1.3196 Å on an area detector to the nominal resolution of 0.92 Å, yielding 4906 unique reflections with an R_{merge} = 0.064 on F^2. All H and D atoms for the cyclodextrin molecule and most of the D atoms for the water molecules were located, and the structure was refined to an R factor of 0.093 for 4538 observed reflections ($F^2 \geq \sigma(F^2)$). In the crystal structure, the γ-CD molecules are arranged in a herringbone pattern forming a cage-type packing. A narrow intermolecular interstitial channel, which is filled with water molecules, runs along the crystallographic b axis at $a \sim 1/2$ and $c \sim 0$. Compared with the β-CD hydrate, which crystallizes in a similar packing arrangement, the cavities of the γ-CD molecules are not as completely closed at the narrow O(6) hydroxyl group end by adjacent molecules and are connected with the interstitial channel. All glucose residues are in the usual $^4C_1$ chair conformation with a relatively strong distortion of glucose residue **1** (θ_2 = 14.5°). Glucose residue **8**, which closes the cavity of a symmetry-related γ-CD molecule at the wider O(2),O(3) end, and even slightly intrudes into it, is somewhat disordered as a whole. The 15.7 water molecules in the asymmetric unit are distributed over 25 positions. A total of 8.8 water molecules are located in the hydrophobic γ-CD cavity; they are all positionally disordered and distributed over 17 positions with occupation factors in the range 0.31–0.95. The hydrogen-bond network in the cavity is very complicated due to the severe disorder of the water molecules and could not be reliably assigned in any detail. One water molecule acts as a bridge connection and has hydrogen bonds both to water molecules enclosed in the γ-CD cavity and to water molecules in the intermolecular interstice, and one water molecule donates a hydrogen bond to glycosidic O(4) of the cavity wall. There are 6.9 water molecules located over 8 sites in the intermolecular interstitial channel, 5 of them are fully occupied, the others are partially occupied, with occupation factors in the range 0.13–0.88. The water molecules in the interstice are better ordered than those in the γ-CD cavity and have a clearer hydrogen-bonding scheme. One water molecule, which is 2-fold disordered, is isolated from all other water molecule sites and forms hydrogen bonds only to hydroxyl groups of γ-CD molecules; the others have hydrogen bonds to adjacent water molecules and/or to γ-CD hydroxyl groups or donate hydrogen bonds to ring oxygen atoms O(5). Of 71 symmetry-independent hydrogen bonds in this crystal structure, 25 (=35%) are of the three-center type, if a 2.8-Å cutoff criterion is used. All O(2) and O(3) hydroxyl groups of neighboring glucose units form interresidue, intramolecular hydrogen bonds, which are major components of unsymmetrical three-center hydrogen bonds donating relatively strong intramolecular components to the corresponding glycosidic O(4) atoms. One primary hydroxyl group donates a minor intraglucose hydrogen-bonding component to O(5) of the same residue; O(5) and O(6) of two glucose accept chelated three-center hydrogen bonds, and in two glucose residues, O(2) and O(3) of the same glucose accept three-center hydrogen bonds. All O–D···O hydrogen bonds are interconnected to form an infinite spatial network, with infinite chains, cycles, and finite chains as motifs, reminiscent of α-CD and β-CD hydrates. Homodromic arrangements of hydrogen bonds dominate in the network and indicate the strong influence of the cooperative effect.

Introduction

The cyclodextrins (CD) are a family of macrocyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD), or nine (δ-CD) D-glucose units in the $^4C_1$ chair conformation linked by α-1,4-interglycosidic bonds.[1-3] They have a "round", slightly conical form with all the secondary hydroxyl groups O(2)–H and O(3)–H located on the wider end and all the primary hydroxyl groups O(6)–H on the narrower end and an intramolecular, relatively hydrophobic cavity, the surface of which is dominated by C–H hydrogen atoms and glycosidic O(4) oxygen atoms. In aqueous solution, they accommodate guest molecules of suitable size in their central cavities and thereby form inclusion complexes that readily crystallize and can be used for X-ray and neutron diffraction studies. If cyclodextrins are crystallized from a pure water solution, the uncomplexed hydrates are formed with water molecules included in their cavities and located in interstices between the cyclodextrin macrocycles. In these crystals, the

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