drolysis products determined as previously described in the incompleted reaction and the initial substrate concentration.

Rate coefficients are symbolyzed and were computed as follows: k_{obsd} is the pseudo-first-order coefficient for the disappearance of the substrate as determined from the slope of the plot of ln $(A_\infty - A_t)$ vs. time, k_A is the second-order rate coefficient for the aminolysis reaction and equals k_{obsd}(fractional yield of aminolysis product)/$(RR'NH)_{eff}$, k'_H is the pseudo-first-order coefficient for the hydrolysis reaction and equals k_{obsd}(fractional yield of hydrolysis product), and k_H is the second-order rate coefficient for the hydrolysis reaction and equals $k'_H/[HO^-]$.

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Registry No. 1, 14545-01-8; piperidine, 110-89-4; *n*-butylamine, 109-73-9; 2,4-dinitrochlorobenzene, 97-00-7; imidazole, 288-32-4.

Rates of Acid- and Base-Catalyzed Enolization of *trans*-Hexahydrofluorenone. Concerning Stereoelectronic Control of Enolization

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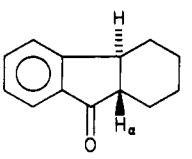
Rates of both acid-catalyzed and base-catalyzed enolization of *trans*-hexahydrofluorenone (*trans*-HHF) have been measured and compared with those for a variety of other ketones. It was found that *trans*-HHF enolizes substantially faster than cyclohexyl phenyl ketone (CPK) in both acid (1800-fold) and base (2650-fold). This rate variation is thought to be due to two factors. (1) In *trans*-HHF the cleaving C–H bond is held rigidly parallel to the π orbital of the ketone. About a factor of 25- to 60-fold is attributed to this stereoelectronic effect. (2) There are steric interactions in the enol of CPK which decrease its rate of enolization by about 40- to 50-fold.

The nature of the transition state for the enolization of aldehydes and ketones has been the object of much attenation in the last 3 decades. In 1956, Corey and Sneen[1] proposed the theory of stereoelectronic control to account for the preferential removal of the 6β proton over the 6α proton in the acid-catalyzed enolization of 3β-acetoxycholestan-7-one to the Δ^6-en-7-ol. This theory requires that the proton be lost in a direction parallel to the π orbital of the carbonyl group. This orientation allows continuous overlap between the C–H bond which is being broken and the π orbital of the carbonyl. Although this idea has been widely accepted[2] and has received theoretical support,[3] the original experimental evidence upon which it is based is inconclusive. In fact the observed selectivity between the axial (6β) and equatorial (6α) hydrogens is only 1.2-fold with HBr as the catalyst in chloroform.[1] For the reverse reaction (ketonization of the enol), the axial hydrogen is gained 1.5 times as often as the equatorial hydrogen; with acetic acid, the relative rates are 9:1. These relatively small rate differences were explained by the authors[1] as being due to an opposing steric effect of the C-10 methyl group.

Subsequent kinetic investigations of enolizations have confirmed a preference for axial reaction but the observed discriminations are generally quite small. For example, Metzger and Casadevall[4] found that the axial hydrogens of *trans*-2-decalone exchange 2- to 3-fold faster than the equatorial hydrogens at both the 1 and 3 positions in acetic acid–sulfuric acid solution. Similarly, Trimitsis and Van Dam[5] showed that the axial protons of 4-*tert*-butylcyclohexanone exchange more rapidly than the equatorial protons in alkaline Me_2SO–water solution (k_{ax}/k_{eq} = 5.5). Lamaty[6] has found similar results for both acid- and base-catalyzed enolizations of *tert*-butylcyclohexanone and 9-methyl-1-decalone (k_{ax}/k_{eq} = 1.6–3.8).

More recently, Fraser and Champagne[7–9] demonstrated that a large stereoselectivity can be observed in suitably designed systems. They found a rate ratio of 73:1 for base-catalyzed exchange of the α protons of a dibenzocycloheptadienone and 290:1 for the protons α to the carbonyl in twistan-4-one. Similarly, Spencer[10] has found that the α protons of *trans*-decalone derivatives are abstracted greater than 100-fold more readily than the equatorial protons.

In view of the apparent requirement for orbital overlap in the enolization of ketones, it might be expected that a ketone with an enolizable proton which is conformationally locked into the correct orientation would enolize exceptionally rapidly compared to a model compound with free rotation. Should this be the case, the implications for the mechanism of a variety of enzymatic reactions is obvious. Of particular interest in this regard is the compound *trans*-hexahydrofluorenone (*trans*-HHF). Molecular



trans-HHF

models show that the cyclopentane ring in *trans*-HHF is

(1) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.
(2) For a good discussion of "stereoelectronic control" of enolizations, halogenations, and alkylations of carbonyl compounds, see: House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 469–473, 587–594 and references therein.
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Table I. Rates of Acid-Catalyzed Bromination in 90% Acetic Acid–10% Water at 25 °C[a]

substrate	$10^5 k_A$, s^{-1} 0.45 N HBr	0.072 N HBr	k_A^{rel} [b]
trans-HHF	1280	44.2	1805
	1320[c]	46.8[c]	
cis-HHF	966	34.7[c]	1342
1-indanone	13.6	1.0	18.5
	13.0[c]		
acetophenone	2.16	0.187	3.0
cyclohexyl phenyl ketone	0.72		1.0
cyclohexanecarboxaldehyde	73.2[c]	2.68	102
propionaldehyde	28.8	1.34	40.0
acetaldehyde[d]	4.53	0.305	6.3
cyclopentanone	7.44	0.620	10.3
acetone	2.17	0.223	3.0

[a] From zero-order rates unless otherwise indicated; k_A is per enolizable hydrogen. Duplicate runs showed deviations of less than 10%. [b] Relative rates at 0.45 N HBr. [c] Under first-order conditions. [d] Corrected for amount of acetaldehyde present as the hydrate (15% in 90% acetic acid–10% water).

rigid and that the C–H_α bond is aligned parallel to the orbital of the carbonyl. If stereoelectronic considerations are important in determining reaction velocity, then *trans*-HHF should enolize more rapidly than analogous compounds without this conformational restriction.

Results

Rate constants for acid-catalyzed enolization for a variety of ketones and aldehydes were measured by following the rate of bromination spectrophotometrically in 90% acetic acid–water. Hydrobromic acid was chosen as the acid catalyst and bromination was followed in 0.45 N and 0.072 N HBr at 25 °C under both zero-order and pseudo-first-order conditions.[11] The calculated first-order rate constants *per enolizable hydrogen* are shown in Table I. Under zero-order conditions the rate of bromine disappearance was linear until 90% of the bromine had reacted. Under first-order conditions only the theoretical amount of bromine was taken up (i.e., 1 equiv of Br_2 for each α-H) and the absorbance decrease showed excellent first-order behavior except in the case of 1-indanone. The bromination of 1-indanone appeared to consist of two reactions, the introduction of the second bromine atom being somewhat slower than the first bromine. Therefore, the kinetic data for 1-indanone were analyzed in terms of a two-exponential equation as described in the Experimental Section. The rate constant for monobromination of 1-indanone determined in this manner agrees with that measured under zero-order conditions (Table I) while the rate constant for introduction of the second bromine is 8.2-fold slower.

Rate constants for base-catalyzed enolization (k_B) were measured by following the rate of deuterium incorporation at the α carbon in CD_3OD–benzene (85–15 v/v). The increase in the "-OH" signal in the NMR spectrum was followed, rather than the disappearance of the α-carbon hydrogen, because the α-CH signal for *trans*-HHF overlapped with other peaks in the spectrum.

Increases in the integrated area of the "-OH" peak showed excellent pseudo-first-order kinetics, and second-order rate constants (Table II) were obtained by dividing the observed rate constants by the stoichiometric concentration of base used (OD^-). Exchange was only ca. 85% complete at equilibrium which means that the observed rate constant is actually the sum of the constants for the forward and reverse processes. However, since the contribution from the reverse reaction to the measured rate should be small in all cases examined, it will be ignored in the following discussion.

Table II. Rates of Base-Catalyzed Deuterium Exchange in CD_3OD–Benzene (85–15) at 34 °C[a]

substrate	$10^3[OD^-]$,[b] M	k_B,[c] M^{-1} s^{-1}	k_B^{rel}
trans-HHF	0.808	7.67 ± 0.59	
	1.26	7.48 ± 0.39	2600
		avg 7.58 ± 0.43	
cis-HHF	0.867	8.35 ± 0.37	
	1.76	8.29 ± 0.80	2900
		avg 8.32 ± 0.56	
1-indanone	0.412	2.16 ± 0.03	
	0.910	2.53 ± 0.08	840
		avg 2.34 ± 0.05	
acetophenone	0.910	1.27 ± 0.03	
	1.76	1.32 ± 0.03	470
		avg 1.30 ± 0.03	
cyclohexyl	23.2	2.89 ± 0.19 × 10^{-3}	
phenyl ketone	45.4	2.67 ± 0.37 × 10^{-3}	1.0
		avg 2.78 ± 0.21 × 10^{-3}	

[a] Rates per enolizable hydrogen. [b] Initial stoichiometric deuteroxide concentration. [c] Errors are standard deviations.

An alternative procedure[13] is to treat the exchange as irreversible during the first half-life and use the theoretical infinity point (obtained assuming 100% exchange). Application of this procedure led to pseudo-first-order rate constants which are 25–30% lower than those calculated by allowing the reaction to reach equilibrium. However, the *relative* values of k_B for *trans*-HHF, *cis*-HHF, 2-indanone, and acetophenone (6.2, 6.5, 1.7, 1.0) are essentially unchanged from those in Table II. Because the precision of the observed rate constants was much better when the reaction was followed to completion (i.e., >90% reaction), the values of k_B obtained by using this procedure were judged more accurate in reflecting the relative rates of exchange.

As previously noted by others,[13,14] the observed first-order rate constants for exchange obtained by NMR methods are rate constants *per enolizable hydrogen* and require no statistical correction.

In order to abstract the true rate constant for enolization of acetaldehyde in acetic acid–water, it is necessary to correct the observed rate constant for the amount of acetaldehyde present as the hydrate. The NMR spectrum of acetaldehyde in 90% acetic acid–water revealed that the relative areas of the quartet (corresponding to the methine hydrogen of $CH_3CH(OH)_2$) and the singlet due to the aldehydic proton were 3:17, showing that ca. 15% of the aldehyde is hydrated. No hydration was detected for the other aldehydes under these conditions.

Discussion

Acid Catalysis. A comparison of enolization rates in 0.072 N and 0.45 N HBr shows that k_A increases more rapidly than the stoichiometric concentration of hydrobromic acid. Similar results have been reported[12,15] for HCl-catalyzed enolization in 90% acetic acid. Although

(11) Use of HCl as the catalyst led to long induction periods for most of the substrates. Addition of NaBr to HCl solutions completely suppressed this problem as did use of HBr as the catalyst. This problem with HCl has been observed previously[12] and was attributed to traces of peroxides in the ketone samples which can oxidize Br^- back to Br_2.

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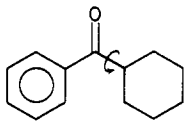
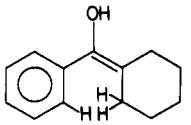
hydronium ion and water are presumed to be the acid–base pair involved in enolization in 90% acetic acid,[12] extensive ion pairing certainly occurs in this nonpolar solvent system.[16] Therefore, the stoichiometric concentration of HBr is not a valid guide to hydronium ion activity.

Somewhat more surprising are the different rate increases exhibited by the various substrates upon increasing acid concentrations. Cyclohexanecarboxaldehyde, *trans*-HHF, and *cis*-HHF all show 28-fold increases in k_A as [HBr] increases 6-fold, whereas most of the other substrates show rate increases of only 10- and 12-fold. Although the reason for this difference is obscure, it is interesting to note that the largest rate increases are shown by substrates with two α-alkyl substituents and that the smallest increases are observed for substrates having only hydrogen on the active-site carbon. This trend implies that steric effects may become more important as the acid concentration is lowered. A more detailed investigation involving more substrates and different solvent systems would be necessary to fully explain the variation of k_A with [HBr]. In any case, the following arguments are not significantly affected by this solvent effect.

The rate constant for acid-catalyzed enolization of *trans*-HHF is the largest of all the substrates studied (Table I). In order to assess the importance of stereoelectronic factors an appropriate substrate for comparison must be found. Superficially, cyclohexyl phenyl ketone (CPK) might appear to be a good compound for comparison due to its structural similarity to *trans*-HHF. However, a closer examination of the results suggests that a substantial fraction of the (1.8×10^3)-fold larger value of k_A for *trans*-HHF compared to CPK is due to unfavorable steric effects which retard the acid-catalyzed enolization of CPK. The formation of the enol of CPK requires the juxtaposition of the ortho hydrogen of the phenyl ringwith two of the ring hydrogens of the cyclohexyl ring 1. This



CPK



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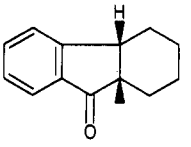
interaction, which can only be removed by rotation of the phenyl group at a cost of loss of resonance, should substantially retard the rate of enolization of CPK. In CPK itself, of course, this steric hindrance can be alleviated simply by rotation about the bond between the carbonyl carbon and the cyclohexyl ring.

In light of this steric factor, CPK is clearly a poor compound to compare with *trans*-HHF if the importance of stereoelectronic control alone is sought. It would be more appropriate to compare the rate of enolization of *trans*-HHF to the corresponding rate for acetophenone, in which this effect should be minimal.[17] In order to do this it is necessary to correct the observed rate difference (600-fold in 0.45 N HBr, 250-fold in 0.072 N HBr) for the rate difference expected due to the increased alkyl substitution at the enolizing site of *trans*-HHF. Using the relative rates of cyclohexanecarboxaldehyde and acetaldehyde (16:1 and 8.8:1 in 0.45 N and 0.072 N HBr, respectively) as a model for this effect, we can estimate that there is a rate increase of about 25- to 40-fold (depending on acid concentration) attributable to stereoelectronic control in the acid-catalyzed enolization of *trans*-HHF. The difference of 1800-fold between *trans*-HHF and CPK then would represent a stereoelectronic factor of about 40-fold and a steric effect of 45-fold. These results suggest that, even in the absence of steric effects in the enol, there is a substantial rate acceleration due to locking the molecule in the preferred orientation for enolization.

Although the carbonyl function in *trans*-HHF is contained in a five-membered ring, while the keto group in acetophenone is not, no significant correction for this difference is deemed necessary. The rate constant for indanone, which is also a cyclopentanone derivative, is 5- to 6-fold faster than that for acetophenone in 0.45 and 0.072 N HBr. This increase in reactivity is essentially the same as that predicted for the introduction of an alkyl group at the reactive α carbon; i.e., the relative rates of CH_3CH_2CHO and CH_3CHO (Table I) are 6.4 in 0.45 N HBr and 4.4 in 0.072 N HBr. Furthermore, the relatively small increase in k_A for cyclopentanone compared to acetone shown in Table I (3.4- and 2.8-fold in 0.45 and 0.072 N HBr) also suggests that the five-membered ring exhibits no significant increase in reactivity beyond that expected for introduction of an alkyl group at the α carbon.

Differences in conjugation between the carboxyl group and the phenyl ring among acetophenone, CPK, *trans*-HHF and indanone may also be eliminated as a cause of rate variations. Hedden and Brown[19] have shown that steric hindrance to conjugation is minimal in acetophenone, indanone, and isobutyrophenone (and presumably CPK) on the basis of similar extinction coefficients of the primary bands in the UV (240–245 nm). *trans*-HHF also has a comparable extinction coefficient for this absorption band, so it is reasonable to assume that differences in conjugation among these compounds is negligible. Thus, *trans*-HHF remains ca. 30- to 40-fold more reactive toward acid-catalyzed enolization than expected in comparison with acetophenone.

The rate of acid-catalyzed enolization for *cis*-HHF is also relatively large and only slightly less than k_A for the trans isomer. The cis ring juncture increases the flexibility of



cis-HHF

the cyclohexane ring and allows a limited amount of rotation around the C_α-C=O bond. Although the preferred conformation of *cis*-HHF is unclear,[20] the large value of k_A suggests that the structure is one in which the C–H_α bond and the carbonyl π orbital are parallel. It should also be noted that attack of bromine on the enol of HHF is reported[21] to give mostly the α-bromo cis isomer, presumably due to steric hinderance to attack leading to the trans isomer. In addition, if the equilibrium ratio of *cis*- to *trans*-HHF is the same in 90% acetic acid as the ratio estimated by House et al. for ethanol as solvent (~5.5),[21] then the relative rates of ketonization (calculated using the

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(17) Although the enol of acetophenone has steric hindrance between a vinyl hydrogen and an ortho hydrogen of the phenyl ring, this interaction is also present in the keto form so it is expected to have a modest effect (if any) on the rate. Evidence for this assertion can be found in the report of Rappe and Sachs[18] who found that the acid-catalyzed rate of proton exchange of the methyl groups of a series of compounds, CH_3COR, varies only slightly with the bulkiness of the R group.

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k_A values for *trans*- and *cis*-HHF shown in Table I) favor cis formation by a factor of about 4. Therefore, steric hinderance may be greater for the enolization of *trans*-HHF than *cis*-HHF.

Base Catalysis. The relative rates (per enolizable hydrogen) for base-catalyzed deuterium exchange given in Table II show *trans*-HHF to be more reactive than acetophenone by about a factor of 6-fold. Unfortunately, the enolization rates of the aldehydes could not be measured under basic conditions due to rapid aldol condensation and, therefore, a correlation for the effect of increased substitution at the α carbon could not be determined. However, some light can be shed on the importance of stereoelectronic control in base-catalyzed enolizations by comparing the rates for *trans*-HHF and CPK. The rate ratio (ca. 2650-fold) is quite large and has to be corrected for the steric effect in CPK. If this effect is similar for both acid- and base-catalyzed enolizations (45-fold), then the stereoelectronic effect in the base-catalyzed enolization may be estimated to be about 60-fold.

It should be emphasized, however, that steric effects in base-catalyzed enolizations appear to be larger than they are for acid-catalysis.[7,13,18] Consequently, conclusions concerning the magnitude of the stereoelectronic effect in the base-catalyzed enolization must remain somewhat speculative.

Conclusions. Although the exact magnitude of the stereoelectronic effect is in doubt, it is clear that there is only a modest rate acceleration due to locking the cleaving C–H bond into the correction orientation for reaction. A reasonable estimate of the magnitude of this effect is between 10- and 100-fold. A more precise value cannot be obtained from the present results due to the complicating steric factors. This effect can most simply be accounted for by a consideration of differences in rotational entropy between reactants and products. A rate acceleration of this order of magnitude due to freezing of the rotation about one bond is in line with what has previously been observed in other reactions. Bruice and Pandit[22,23] found that the rate of anhydride formation from succinate and maleate half-esters is accelerated by about 200-fold for each bond rotation which is frozen (by ring formation, etc.) in the reactants. Relative rates of acid-catalyzed lactonizations[24] of several hydroxy acids also show similar effects for restriction of bond rotation in the reactants. A somewhat higher effect for freezing of one bond rotation (3×10^4)-fold) has been estimated[25] for the lactonizations of *o*-hydroxyhydrocinnamic acids.[26] Several theoretical discussions[27-30] of the magnitude of rate accelerations to be expected from the loss of entropy upon freezing out of one bond rotation support a factor of about 10–100-fold.

Experimental Section

Materials. Glacial acetic acid, hydrobromic acid, and benzene were obtained from commerical sources and distilled before use. Heavy water (99.7% D, Aldrich), CD_3OD (99.5% D, Aldrich), 40% NaOD (99% D, Stohler), and bromine (Baker) were used as received. Commercially available liquid ketones and aldehydes were purified by distillation (except for acetaldehyde which was used as received from Aldrich, 99+%) or by recrystallization.

cis-1,1a,2,3,4,4a-Hexahydrofluoren-9-one (*cis*-HHF) was prepared from α-bromocyclohexyl phenyl ketone as previously reported[21] (mp 40–41 °C; lit.[21] 40–41 °C).

trans-1,1a,2,3,4,4a-Hexahydrofluoren-9-one (*trans*-HHF) was synthesized from *trans*-2-phenylcyclohexanecarboxylic acid according to the procedure of House et. al.[21] Fractional recrystallization from hexane gave the pure trans isomer (mp 90–91 °C; lit.[21] mp 91–92 °C). NMR spectra agreed with those previously reported[20] for both the cis and the trans isomer. The synthesis of *trans*-2-phenylcyclohexanecarboxylic acid was carried out by using a modification of the procedure of Alder et. al.[31] given below.

***trans*-2-Phenylcyclohexanecarboxylic Acid.** Reaction of *trans*-cinnamic acid with 1,3-butadiene, followed by catalytic hydrogenation of the intermediate cyclohexene derivative, is the reported procedure for the synthesis of the title compound.[31,32] Use of this procedure, however, led to a low yield of the required compound which was contaminated with reduced starting material (3-phenylpropionic acid). Therefore, the methyl ester of *trans*-cinnamic acid was used in order to facilitate separation of unreacted starting material by vacuum distillation.

Methyl cinnamate (20 g, 0.12 mol) and hydroquinone (0.4g) were placed in a small (ca. 50 mL) high-pressure bomb and cooled in a dry ice–acetone bath. Cold 1,3-butadiene (25 mL, 0.30 mol) was added, and the bomb was sealed and then heated to 130–135 °C for 48 h. After cooling to room temperature, the crude residue was taken up in 300 mL of 95% ethanol. The solution was decanted from an insoluble polymeric gel (ca. 9 g), placed in a Parr hydrogenation vessel containing 200 mg of 10% palladium on carbon, and hydrogenated at 40–50 psi until uptake of hydrogen ceased (~1 h). Filtration through Hyflo-super cell and removal of the solvent gave 19.5 g of a clear oil. (NMR analysis indicated the presence of ca. 30% reduced starting material). Distillation under vacuum though a 25-cm Vigreux column yielded 12.2 g (47% overall yield) of methyl *trans*-2-phenylcyclohexane-1-carboxylate (bp 110 °C, 1.0 mm): NMR ($CDCl_3$, Me_4Si) δ 7.15 (5 H, Ph), 3.25 (3 H, OCH_3), 2.4–2.9 (2 H, -CH-), 1.0–2.1 (8 H, $-CH_2-$).

The above ester (12.2 g, 0.056 mol) was hydrolyzed by dissolving it in 725 mL of 65% dioxane–35% water, adding 75 mL of concentrated hydrochloric acid, and refluxing for 20 h. After distilling off ~250 mL of the solvent (dioxane–water azeotrope, bp 88 °C), the remaining solution was saturated with NaCl and extracted with ether (2×200 mL). The combined ether extracts were washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated under vacuum to give 11.1 g of a white solid (mp 100–104 °C). Recrystallization from hexane afforded 10 g (87% yield) of *trans*-2-phenylcyclohexanecarboxylic acid (mp 107–108 °C, lit.[31] mp 108–109 °C): NMR (CCl_4, Me_4Si) δ 11.8 (1 H, COOH), 7.1 (5 H, Ph), ca. 2.6 (br, 2 H, -CH-), 1.0–2.1 (8 H, $-CH_2$).

Kinetics

Acid-Catalyzed Bromination. Kinetic measurements were carried out by using either a Gilford 2000 or 2400

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spectrophotometer at 25.0 ± 0.02 °C. Two different acid concentrations in 90% acetic acid were used: the 0.45 N HBr solution was prepared by mixing 5.0 mL of concentrated (48%) HBr with 5.0 mL of distilled water and then diluting to 100 mL with acetic acid, and the 0.072 N HBr solution was obtained by mixing 2.0 mL of concentrated HBr with 23.0 mL of water and then diluting to 250 mL. A stock solution of bromine was prepared by diluting 9.32 g of bromine to 100 mL with acetic acid, and ca. 10 μL of this solution was usually pipetted directly into the cuvette containing the solvent immediately prior to addition of the ketone or aldehyde.

The disappearance of bromine was monitored at 390 nm; at this wavelength the extinction coefficients (ϵ_{Br_2}) in 0.45 N HBr and 0.072 N HBr are 683 and 644, respectively. The rates of acid-catalyzed bromination were determined for most substrates under pseudo-zero-order conditions; i.e., the initial concentration of substrate ($[S]_0$) was ≥40-fold greater than that of bromine ($[Br_2] \sim 2 \times 10^{-3}$ M). The observed zero-order decrease in absorbance ($-dA/dt$) was related to the first-order rate constant (k) by eq 1. All

$$\frac{-dA}{dt} = k[S]_0\epsilon_{Br_2} \quad (1)$$

runs were done in duplicate and reproducibility was 5–10%. No induction periods were observed and the decrease in absorbance was linear until >90% of the bromine had reacted. Varying the initial concentration of bromine from 8×10^{-4} M to 3×10^{-3} M did not significantly affect the zero-order rate constants.

The rates of bromination of substrates containing only one α hydrogen were also followed under pseudo-first-order conditions at 390 nm. Thus, when $[S]_0 \approx [Br_2]_0$ ($\sim 2 \times 10^{-3}$ M), k was calculated from a nonlinear least-squares analysis of the absorbance decrease. The first-order decrease in $[Br_2]$ was followed for at least 3 half-lives and observed infinity readings showed that the theoretical amount of bromine was consumed. First-order rate constants (k) determined in this manner had standard deviations of less than 1% and reproducibility was within 5%. For some ketones, values of k_A were determined under both zero-order and first-order conditions and agreement was usually within 10%.

The bromination of indanone was also followed to completion (i.e., until 2 equiv of Br_2 were consumed) under conditions where $[S]_0 \approx {}^1/_2[Br_2]_0$. The decrease in absorbance at 390 nm was fit to a two-exponential equation (eq 2) by a procedure previously described[33] for an analogous system.

$$\frac{A - A_\infty}{A_0 - A_\infty} = ae^{-k_1t} + be^{-k_2t} \quad (2)$$

In this equation, k_1 and k_2 are the rate constants for formation of the mono and dibromo α derivatives, respectively, and the preexponential terms are defined[34] as $a = (k_1 - 2k_2)/[2(k_1 - k_2)]$ and $b = k_1/[2(k_1 - k_2)]$. Equation 2 gave an excellent fit to the experimental data, and standard deviations for k_1 and k_2 were <1%. The value of k_1 determined in this way for 1-indanone was in excellent agreement with the first-order rate constant derived under zero-order conditions. Statistically corrected rate constants (k_A) were obtained by dividing k by the number of α hydrogens (n), i.e., $k_A = k/n$, and are summarized in Table I.

Base-Catalyzed Exchange. Incorporation of deuterium was monitored by following the increase in the "–OH" signal in the NMR spectra (δ 4.75). Measurements were carried out in the probe of a Hitachi Perkin-Elmer R-20A NMR spectrometer maintained at 34 °C. The solvent used was CD_3OD containing benzene (15% by volume) in order to increase the solubility of the ketone. In order to remove acidic impurities all ketones were shaken with aqueous sodium carbonate. Erratic results were obtained for the reaction of *cis*-HHF even after washing with Na_2CO_3. Therefore, *cis*-HHF (1.6 g) was dissolved in dimethoxyethane (12 mL), 1.0 mL of 0.1 N aqueous NaOH was added, and the solution was allowed to remain at room temperature. After 1 h, water (150 mL) was added, the aqueous layer was extracted with ether (2 × 75 mL), and the ether extracts washed with saturated aqueous NaCl solution. The ether extracts were dried over K_2CO_3, filtered, and evaporated under vacuum to give a white solid. Several recrystallizations from hexane yielded 865 mg of *cis*-HHF (mp 40–41 °C) which no longer gave anomalous kinetic results.

A solution of the ketone (50 mg) in the CD_3OD–benzene solvent (0.43–0.48 mL) was placed in an NMR tube and brought to 34 °C in the probe. After integrating the initial spectrum, 5.0 μL of a solution of NaOD in D_2O was added in order to achieve the desired base strength (0.40–45 × 10^{-3} M). The NMR tube was shaken, the timer was started, and integrals of the "OH" peak were recorded at appropriate time intervals. Because half-lives for most reactions were short ($t_{1/2} \leq 15$ min), internal standards were not used. Integrations of spectra recorded after completion of the reactions revealed no significant drift in sensitivity.

Increases in the integrated area (I) of the "OH" peak with time were followed to completion. Fitting the data of eq 3 (using a nonlinear least-squares analysis) gave

$$(I_\infty - I) = (I_\infty - I_0)e^{-k_{obsd}t} \quad (3)$$

pseudo-first-order rate constants (k_{obsd}) with standard deviations usually <5% and infinity points (I_∞) in good agreement with observed values. Division of the observed pseudo-first-order constants by the stoichiometric concentration of base yielded the second-order constants shown in Table II. ($k_B = k_{obsd}/[OD^-]_0$). All ketones were examined at two different base concentrations.

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