linear function of their E_I's. The equation for the E_I–σ_I correlation was found to be[13]

$$E_I = 9.62 + 13.8\sum\sigma_I\,(R)\ (eV) \qquad (2)$$

Using, however, IP data very recently obtained[5] by the PES method (which yields vertical rather than the adiabatic E_I's by the PI method[14]), one obtains an excellent correlation with the new gas-phase σ_I values (with $r = 0.991$) for the complete series of primary amines discussed here. The new E_I–σ_I correlation equation is given by

$$E_I(RNH_2) = E_I(NH_3) + a_I\sigma_I = 10.19 + 11.49\sigma_I\,(R)\ (eV) \qquad (2a)$$

Eliminating σ_I (R) from eq 1b and 2a leads to

$$PA(RNH_2) = 18.44 - 0.966E_I\ (eV) \qquad (3)$$

from which good estimates of proton affinities can be made directly from the experimental ionization potentials, or vice versa. (The correct chronology of the relationships given above is, of course, ref 13, 1b, and 5 and eq 1a and 1b of the present paper.)

Good linear plots of PA vs. E_I for primary amines have previously been published.[1b,5] In accord with eq 3, as has already been demonstrated for the alcohols[15] and ethers,[16] the greater the basicity at the atom with a lone pair of electrons, the lower is the ionization potential at that atom.

In view of the fact that Figure 1 represents a nearly perfect correlation, it is tempting to actually *define* the σ_I (R) values in terms of the gas-phase proton affinities of primary amines. If this is done from the relation

$$-\sigma_I\,(R) = \Delta PA/258 + 0.046 \qquad (4)$$

the results for the alkyl groups in the order they appear in Table I are 0.046, 0.056, 0.061, 0.063, 0.066, 0.065, 0.070, 0.069, 0.074, and 0.079, almost precisely the same as the σ_I values obtained by detailed statistical analysis of ionization potential data.[10]

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A General Procedure for the Base-Promoted Hydrolysis of Hindered Esters at Ambient Temperatures

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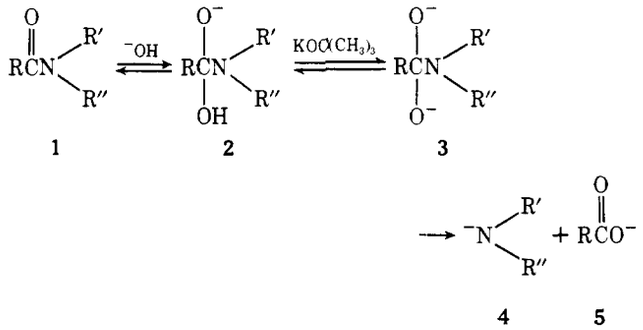
Recently, we reported that essentially "anhydrous hydroxide" was an excellent reagent for the hydrolysis of tertiary amides at ambient temperatures.[1] This reagent was generated via the reaction of 2 equiv of potassium *tert*-butoxide with 1 equiv of water.[2] Mechanistically, it appeared that the relatively unsolvated hydroxide added to the tertiary amide, **1**, to produce **2**. Removal of a hydroxylic proton from **2** would then produce the dianion, **3**. Fragmentation of **3** then produced the most stable pair of anions, which in this case was **4** and **5**. Utilizing this concept, a series of tertiary amides was



1 **2** **3** **4** **5**

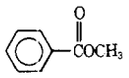
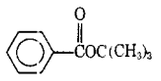
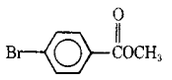
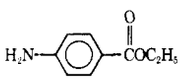
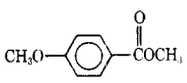
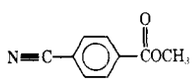
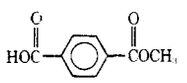
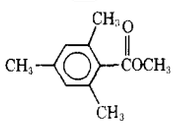
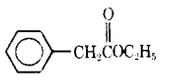
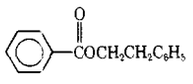
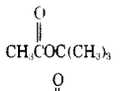
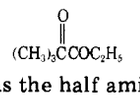
hydrolyzed in yields ranging from 65 to 100% in relatively short reaction times at room temperature. The facility of this process suggested to us that similar reaction conditions might permit the base-catalyzed hydrolysis of hindered esters at room temperature. This report provides the details of our study of the base-promoted hydrolysis of esters at ambient temperatures.

In any study of the saponification of hindered esters, the classes of esters which must be considered include esters of pivalic acid, mesitoic acid, and *tert*-butyl alcohol. Table I lists the yields obtained in the room temperature hydrolysis of these and other esters. In a typical procedure, approximately 1 equiv of ester, 2 equiv of water, and 8 equiv of potassium *tert*-butoxide were stirred as a slurry for 2–48 h at room temperature. As shown in Table I, close to quantitative yields could be obtained from most of the simple esters in relatively short times at room temperature. For highly hindered esters, longer reaction times were required, but hydrolysis could still be accomplished at room temperature.

While the heterogeneous nature of the reaction mixture made accurate kinetic data virtually unattainable, qualitative studies could be made. As shown in Table I, time vs. yield determinations were made for the hindered esters *tert*-butyl benzoate and methyl mesitoate. It would appear from this data that given sufficient time (5–6 days) even a very hindered ester such as methyl mesitoate could be saponified in close to quantitative yield at room temperature.

The mechanistic aspects of this ester hydrolysis are of interest. The mechanism of hydrolysis of hindered esters has been studied in detail[3–7] both in acid and in base. Although the vast majority of esters are saponified via a $B_{AC}2$ mechanism,[4,5,7] evidence has been presented that in special cases a $B_{AL}2$ mechanism can predominate.[5,6] In the normal hydrolysis of methyl mesitoate, acyl–oxygen cleavage has been shown to occur in aqueous media.[4,5] However, methoxide has been shown to react with methyl mesitoate to yield the mesitoate anion via alkyl–oxygen cleavage. Since little is known about

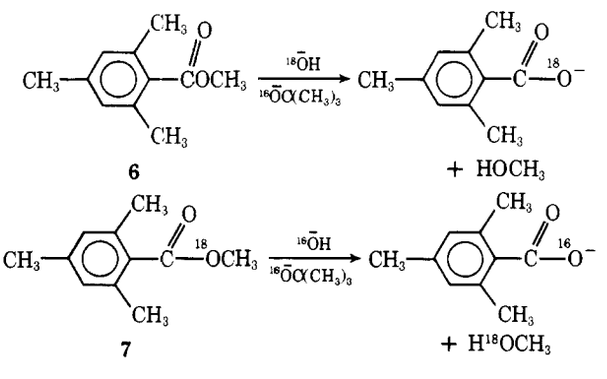
Table I. Hydrolysis of Esters with Potassium *tert*-Butoxide–Water at Ambient Temperatures

Registry no.	Ester	Hydrolysis time, h	% yield of acid isolated
93-58-3		0.5, 2	44, 100
774-65-2		0.5, 1, 2, 5	41, 70, 92, 100
586-76-5		1	100
94-09-7		16	100
121-98-2		24	80
1129-35-7		48	90[a]
1679-64-7		43	83
2282-84-0		24, 48, 72	50, 63, 72
101-97-3		16	80
94-47-3		24	97[b]
540-88-5		3	97[c]
3938-95-2		3	94[c]

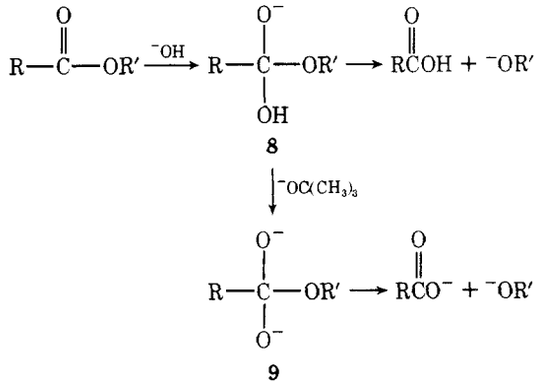
[a] Isolated as the half amide–half acid. [b] In addition, the alcoholic portion was isolated in 92% yield. [c] Aliphatic acids were analyzed according to our previously described method.[1]

the characteristics of the relatively anhydrous hydroxide prepared by our methods, we felt that it would be instructive to use the technique of Bender and co-workers to determine whether methyl mesitoate was hydrolyzing under our reactions conditions through acyl–oxygen or alkyl–oxygen cleavage.

In order to establish that our reaction conditions led to acyl–oxygen ($B_{AC}2$) cleavage, two labeling experiments were run. Methyl mesitoate (**6**) was hydrolyzed with hydroxide generated from 22.7% enriched oxygen-18 water. The methanol generated in this hydrolysis was analyzed by chemical ionization mass spectrometry[8] and was found to contain no excess oxygen-18. Aqueous workup gave mesitoic acid which was found to have 16% excess oxygen-18. The relatively large amount of oxygen-18 remaining in the acid, after neutralization with aqueous acid, agreed with the relatively slow rate of oxygen exchange previously observed for mesitoic acid.[4] In a second labeling experiment, methyl mesitoate prepared from 22% oxygen-18 methanol was hydrolyzed under our reaction conditions. We found that **7** hydrolyzed to yield mesitoic acid with no excess oxygen-18 and methanol containing 22% oxygen-18. Thus, it was firmly established that, under our hydrolysis conditions, acyl–oxygen cleavage predominated. In an additional mechanistic endeavor, the benzoate of 2-phenylethanol was hydrolyzed. The isolation of 2-phenylethanol established the absence of any type of elimination process when β hydrogens were present on the alcohol moiety.



In summary, we have illustrated that even very hindered esters can be hydrolyzed by essentially anhydrous hydroxide at room temperature. While acyl–oxygen cleavage has been established, we do not know whether cleavage occurs from the monoanion **8** or whether a dianion of general structure **9**[9] is



involved. Our present experiments do not allow us to distinguish between these two possibilities. However, the observation that methyl benzoate hydrolyzes only ca. 50 times faster than methyl mesitoate under our conditions indicates that our reaction may be more mechanistically complicated than normal hydrolyses in aqueous base.[10]

Experimental Section

General Procedure for the Hydrolysis of Benzoate Esters. To a stirred suspension of 2.66 g (0.026 mol) of potassium *tert*-butoxide in 50 ml of dry ether, cooled to 0 °C, was added 0.12 ml (0.0067 mol) of water via syringe. This slurry was stirred for 5 min. To this was added the benzoate ester (0.003 mol). The ice bath was removed and the reaction mixture was stirred at room temperature until the reaction was complete. The hydrolysis was monitored by TLC for the disappearance of the ester and was considered to be complete when the ester was no longer observed. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The acidified solution was extracted three times with 50-ml portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated to give the acid which was characterized by melting point and infrared spectra. The following acids were recovered by this method: benzoic acid, mp 121–122 °C; *p*-bromobenzoic acid, mp 252–253 °C; *p*-aminobenzoic acid, mp 184–186 °C; *p*-methoxybenzoic acid, mp 184.5–185 °C; 1,4-benzenedicarboxylic acid, sublimes ca. 300 °C; 1,4-benzenedicarboxylic acid monoamide, mp 345–348 °C; mesitoic acid, mp 153–154 °C.

General Procedure for the Hydrolysis of Aliphatic Esters. To a stirred suspension of 2.66 g (0.026 mol) of potassium *tert*-butoxide in 50 ml of dry ether, cooled to 0 °C, was added 0.12 ml (0.0067 mol)

of water via syringe. This slurry was stirred for 5 min. To this reaction mixture was added the aliphatic ester (0.003 mol). The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and stirred over acid-washed ion exchange resin (Amberlite IR-120) until a flame test for potassium ion was negative. The resin was removed by filtration and the filtrate was titrated with a standardized sodium hydroxide solution using phenolphthalein as indicator. The percent hydrolysis as determined by titration of the acid was as follows: acetic acid (97%), pivalic acid (94%). Routine titration of the acetic acid gave 92%. However, standardization of the procedure with sodium acetate showed that 5% of the acetic acid was taken up by the resin. The 97% yield reflects an adjustment for the method of analysis.

Synthesis of $CH_3{}^{18}OH$. Trimethyl phosphate (4.0 g, 0.0285 mol) and labeled water (3.67 g, 0.204 mol) containing 22.7 mol % oxygen-18 were sealed in a thick-walled glass tube.[11] This was heated in an oil bath at 105 °C for 26 h. After cooling to room temperature, the reactants were distilled at reduced pressure to yield 2.64 g of a water and methanol mixture. This mixture was distilled at atmospheric pressure to give 0.63 g of a mixture of methanol and water. The water was used as a chaser solvent in order to obtain the maximum yield of methanol. The distillation was stopped when the temperature of the distillate reached 90 °C.

Synthesis of Oxygen-18 Labeled Methyl Mesitoate. Freshly distilled mesitoyl chloride (9.44 g, 0.051 mol) was added dropwise to 0.63 g of the oxygen-18 labeled water–methanol mixture in 50 ml of dry ether which was cooled to 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 24 h. Water was added to hydrolyze the excess acid chloride. The mesitoic acid was extracted from the ether layer with two 25-ml portions of saturated sodium bicarbonate solution and one 25-ml portion of a 10% sodium hydroxide solution. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated to yield 2.47 g of labeled methyl mesitoate (49% based on trimethyl phosphate): IR (neat) 1730, 1270, 1090 cm^{-1}; mass spectrum *m/e* 180, 178, 148, 147, 146.

Acknowledgment. We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant which supported this investigation and to Mr. P. C. Price for the chemical ionization mass spectral measurements.

Registry No.—Benzoic acid, 65-85-0; 4-bromobenzoic acid, 586-76-5; 4-aminobenzoic acid, 150-13-0; *p*-anisic acid, 100-09-4; 4-(aminocarbonyl)benzoic acid, 6051-43-0; 1,4-benzenedicarboxylic acid, 100-21-0; mesoic acid, 480-63-7; benzeneacetic acid, 103-82-2; acetic acid, 64-19-7; pivalic acid, 75-98-9; $CH_3{}^{18}OH$, 5770-05-8; mesitoyl chloride, 938-18-1; ^{18}O labeled methyl mesitoate, 61076-10-6.

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(8) Chemical ionization mass spectrometry was carried out on a Du Pont 21-490 B mass spectrometer modified as described by I. C. Wang, H. S. Swofford, Jr., P. C. Price, D. P. Martinsen, and S. E. Buttrill, Jr., *Anal. Chem.*, **48**, 491 (1976).
(9) A referee has suggested that O^{2-} might be formed and add directly to the ester to form **9**. We think that this is unlikely, although we cannot unequivocally rule out this possibility.
(10) In many respects, our results parallel those of Roberts and Whiting,[7] who explored the use of hydroxide in dimethyl sulfoxide as a solvent. In relation to our earlier work,[2] it is possible that the conditions used by both Roberts and Whiting and us involve the same intermediates.
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Conformational Control. An Important Factor in the Stereoselective Reduction of Ketones by Bulky Hydride Reagents

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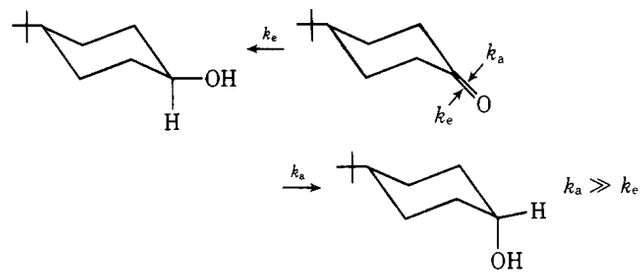
The recent interest accorded the development of highly hindered hydride reagents capable of stereoselective reduction of ketones to afford one diastereomer preferentially[1-5] prompts this discussion of an important factor which is frequently neglected but which subtly affects the product profile of such reductions.[6] This effect involves the conformational equilibria present in mobile ketones which is often at least partly responsible for decreasing the apparent stereoselectivity of hydride attacks.

The conformational effect is adequately illustrated by the reduction results from a series of alkyl substituted cyclohexanones by various di- and trialkyl borohydrides recently introduced[1-4] and recommended for their stereoselectivity of attack. Thus, the reagents approach predominantly from the equatorial side to afford largely the axial alcohol. As a case in point, 4-*tert*-butylcyclohexanone yields almost entirely *cis*-4-*tert*-butylcyclohexanol with various bulky hydrides as shown in Table II and illustrated in Scheme I. From the table,

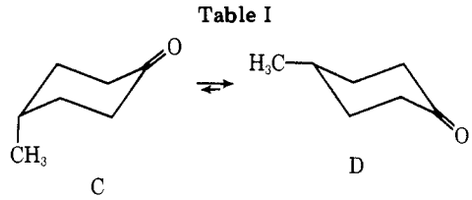
Scheme I



k_a must be substantially greater than k_e. In addition, the selectivity increases as the temperature is lowered as expected since a given difference in E_a between axial and equatorial attack is translated into a greater rate ratio as temperature decreases. The bulky trialkylborohydrides then, especially LTMBH and LTSBH, appear to offer an extremely high degree of discrimination toward equatorial attack which, for the *conformationally homogeneous* 4-*tert*-butylcyclohexanone, produces almost entirely one diastereomer (cis).

The expected situation is different for conformationally heterogeneous cyclohexanones. As presented in Scheme II, irrespective of the relative rate of ring inversion compared to

Table I



C D

Temp, T°C	$K_{eq}{}^{10}$	% more stable equatorial isomer
100	9.87	90.8
25	17.57	94.7
0	22.86	95.8
−40	39.11	97.5
−78	79.91	98.8