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ENOLIZATION OF KETONES—VI[1]

THE BASE-CATALYZED DEUTERATION OF SOME CYCLIC KETONES

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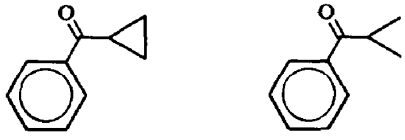
Abstract—The base-catalyzed deuteration of a number of cyclic ketones has been studied. The results deviate from previously published work. The most remarkable finding is the pronouncedly greater reactivity of the methine hydrogen of an isopropyl group compared with that of a cyclopropyl group.

IN RECENT years, the enolization of ketones has been comprehensively studied not only for its own sake, but also as a model reaction for testing and developing theoretical physical–organic concepts and definitions; e.g. hyperconjugation,[2,3] isotope effects,[4,5] acid-base catalysis,[6,7] concerted reactions,[5,8] and reactivity in cyclic compounds.[9,10] Very recently Breslow *et al.* discussed the base-catalyzed enolization of benzoylcyclopropane (1) and isobutyrophenone (2) in their important discussion



1 2

of antiaromaticity in cyclopropenyl anions.[11] Work by Dessy, Okuzumi and Chen in Shechter *et al.*[9] was referred to in which it was reported that the methine proton in benzoylcyclopropane was exchanged 14 times faster than the methine proton of isobutyrophenone in a D_2O/DMF solution using triethylamine as base.

A recent communication, however, reports results which suggest that in fact the opposite may obtain.[12] This prompts us to report the results of an investigation of base-catalyzed deuterium exchange in a number of cycloalkyl methyl ketones. Special attention is paid to a comparison in the reactivity of the methine protons in isopropyl and cyclopropyl ketones.

The rates of exchange have been measured by the NMR method described previously[13–18] in solutions of sodium deuterioxide in D_2O–dioxan (5:8 by volume). The rate constants reported (k_{CH_3} and k_{CH}) are on a *per group* basis,[15] and K_D is the rate ratio, k_{CH}/k_{CH_3}. Direct measurement of k_{CH} could not be achieved because the heavily coupled methine resonance was generally masked by ring protons. K_D was therefore determined mass spectroscopically[19] and combined with k_{CH_3} to yield a value for k_{CH}. The results are listed in Table 1.

From Table 1 it is apparent that acetophenone had the highest value for exchange at the Me group, due to the stabilizing effect of the Ph group on the enolate. The Me groups of cyclopropyl methyl ketone and cyclobutyl methyl ketone were deuterated

TABLE 1. RATES AND ORIENTATION OF BASE-CATALYZED DEUTERIUM EXCHANGE IN DIOXAN–D_2O AT 47·5°

Ketone	Volume used	$k_{CH_3} \times 10^5$	$k_{CH} \times 10^5$	K_D
Acetophenone	0·10[a]	365 ± 18	—	—
Cyclopropyl methyl	0·20	178 ± 3	0·08	$4·3 \times 10^{-4}$
Cyclobutyl methyl	0·15	179 ± 10[b]	9·1	$5·1 \times 10^{-2}$
Cyclopentyl methyl	0·10	26 ± 2	1·4	$5·3 \times 10^{-2}$
Cyclohexyl methyl	0·10	44 ± 2	5·0	$11·4 \times 10^{-2}$
Isopropyl methyl	0·20	91 ± 5	4·3	$4·7 \times 10^{-2}$

[a] This run varies from the procedure described under *Experimental* in that 1·0 ml dioxan was required for solubility reasons.

[b] This rate constant is probably overdetermined. Overlapping signals prevented direct integration over the Me resonance, so the rate of exchange was determined from the increasing DOH signal which will also contain a contribution from the slower methine exchange.

at approximately the same rate and, together, about twice as fast as the Me group in 3-methyl-2-butanone. Methyl deuteration in cyclopentyl methyl ketone and cyclohexyl methyl ketone was somewhat slower. This seems to be in agreement with results reported previously for methyl deuteration in acyclic ketones; i.e. increasing the bulk of the α′-substituent generally decreased the rate of α-Me exchange.[15]

Exchange of the methine proton was in all cases much slower than exchange of the Me protons. Since the method used to obtain the methine rates is rather imprecise, it follows that a discussion of the absolute values is not meaningful; especially as the rates of the isopropyl, cyclobutyl, cyclopentyl, and cyclohexyl methyl ketones are close together. However, it was observed that the methine proton in isopropyl methyl ketone was exchanged about 50 times as fast as the methine proton in cyclopropyl methyl ketone. This stands in contradiction to the observation of Dessy *et al.*[9] who reported the cyclopropyl proton to be favoured by a factor of 14.

The pronouncedly higher reactivity of the methine group in the iso-C_3 ketone than in the cyclo-C_3 ketone could be observed preliminarily by direct observation of the multiplicity of the Me and methylene signals in the NMR spectra, thus excluding mistakes in the more complicated calculation of the rate constants.[20] The Me doublet in the iso-C_3 ketone collapsed within a few hours, while under the same conditions, the methylene signal from the cyclo-C_3 ketone remained unchanged after several days.

Since the kinetics of exchange studied by Dessy *et al.*[9] are carried out in a different solvent system (the active base, deuterioxide, was the same) and since the differences involved are in general small, we could of course not expect a complete parallelism between the two series. Nevertheless, the complete reversal in behaviour of the cyclopropyl and isopropyl methine proton is highly remarkable.

Repeat of the study of benzoylcyclopropane (1) and isobutyrophenone (2), the ketones studied by Dessy *et al.*[9] was therefore warranted. The stock ketones were found to neutralize the catalyst. Purification was attempted by preparative GLPC, but complete separation from minor impurities was not possible. Thus no meaningful rate constants can be given for the deuteration of these ketones. Nevertheless, we could observe from the increasing DOH-peak a measurable exchange in 2 ($k = 10^{-4}$–10^{-5} sec^{-1}), while 1 was completely unchanged (rate constant less than 10^{-6}

sec^{-1}) under our conditions (D_2O–dioxan). A study of the multiplicity of the peaks, as above, gave the same result.

In addition, valuable information was obtained by following the deuteration of the two phenyl ketones, 1 and 2, competitively. As above, the multiplicity of the iso-C_3 Me doublet and of the cyclo-C_3 multiplet was the object of observation. These two multiplets overlap, so if exchange of the two α-protons had occurred at comparable rates, analysis would have been impossible. However, complete collapse of the isopropyl doublet to a singlet occurred within 12 hr, revealing an unchanged cyclopropyl multiplet which remained unchanged after an additional 96 hr. While this does not permit quantitative evaluation of the rates of exchange, it definitely allows the conclusion that exchange at a cyclopropyl group is pronouncedly slower than at an isopropyl group.

Our results show that acid- *and* base-catalyzed methine exchange in cyclopropyl ketones is very slow compared with ketones bearing an sp^3 hybridized α-carbon. This is in harmony with predictions based upon the inability of the highly strained cyclopropyl ring to form part of the double bond of an enol or enolate anion.

EXPERIMENTAL

Mass spectra were recorded on an LKB 9000 combination mass spectrometer–gas chromatograph. NMR spectra were recorded on a Varian A-60 instrument equipped with a variable temperature programmer. A Perkin Elmer F-21 preparative gas chromatograph equipped with a differential trigger-level programmer and a 1·8 m column (20% silicon rubber on Chromosorb A) was used to purify the indicated ketones.

Materials. The catalyst was prepared by diluting 0·161 g of NaOD to 25 ml with D_2O (>99·7%). 1 ml of this soln was diluted to 10 ml to yield the catalyst used in the kinetic determinations. Dioxan was purified according to Wiberg[21] and distilled from Na under N_2 prior to use. Isopropyl, cyclobutyl,[22] cyclopentyl,[23] and cyclohexyl[23] methyl ketone were purified by preparative GLPC Complete separation of cyclobutyl methyl ketone from minor impurities (<1%) could not be achieved, and cyclohexyl methyl ketone (homogeneous to GLPC) neutralized the catalyst by the end of 1 hr. (Ketone is in excess of catalyst by at least 100:1 on a molar basis). Commercial cyclopropyl methyl ketone (Aldrich) and acetophenone were homogeneous to GLPC and used as supplied.

Kinetics. The kinetics were carried out directly in capped NMR tubes in duplicate at ambient probe temp (maintained at 47·5 ± 0·5° by the temp programmer). D_2O-dioxan solns of 0·8 ml dioxan and 0·5 ml catalyst under N_2 were first brought to probe temp, after which the ketone was pipetted in and the mixture shaken vigorously. A stop-watch was started and the tube placed in the probe. Integrations were performed over the Me singlets and a reference peak until a predominant trace was apparent (usually 4–8 repetitions). One half-life was of the order of 30 min. A duplicate run was made immediately. Data were treated by the method of linear least-squares and the uncertainties reported in the rate constants are the standard variances[24] in the slopes. The rate constants have not been corrected for apparent changes in catalyst concentration resulting from changes in total volume due to changes in the volume of ketone used to meet solubility requirements.

At the finish of a run, the contents of the NMR tube was extracted with ether, the ether phase dried over $MgSO_4$, and a mass spectrum recorded on the ketonic component. The spectra were analyzed for deuterium content at the α- and α'-positions.[19] K_D was determined from this data and multiplication by k_{CH_3} gave k_{CH}.

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Note added in proof:

Professor H. Schechter of Ohio State University has kindly informed us that in a parallel study soon to be published involving the rates of neutralization of nitro alkanes, and a repeat of the work on cyclopropyl and isopropyl phenyl ketone, the error in the Dessy investigation has been recognized.