

Anal. Calcd. for $C_{14}H_{18}F_6$: C, 57.92; H, 2.78. Found: C, 58.46, 58.19; H, 3.08, 3.12.

The solid residue from the steam distillation was boiled with methanol, and, from the hot alcoholic filtrate, there was obtained 0.65 g. (13.2%) of III. Leaching of the insoluble, red-brown tar, remaining from the methanol treatment, with hot dioxane gave 0.18 g. of yellow solid; m.p. 170–180° d. Several crystallizations from ethanol–benzene gave yellow-orange crystals of m.p. 185–187° d. which could not be purified further. This material appears to be III contaminated with the tarry by-product.

Anal. Found: C, 52.37, 52.50; H, 3.04, 2.77.

Ultraviolet Absorption Spectra.—A Beckman model DU quartz spectrophotometer was employed for the determinations. The dioxane employed as solvent was purified according to the procedure of Fieser.¹⁴

Acknowledgment.—We are indebted to Mr. William A. Leach of these laboratories for the determination of some of the ultraviolet absorption spectra reported herein.

(14) L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., Boston, Mass., 1941, p. 368.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Reactions of Peracids. VI. The Reaction of Acetylcyclanes with Perbenzoic Acid¹

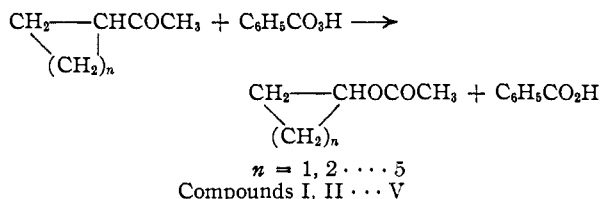
BY S. L. FRIESS² AND REX PINSON, JR.

Acetate esters are obtained in yields of 58 to 72% from the reaction of acetylcyclanes, varying in ring size from four to seven members, with perbenzoic acid in chloroform solution. Kinetic studies indicate that the reaction is a second order, acid-catalyzed process which is accelerated by an increase in the polarity of the medium. Energies, enthalpies and entropies of activation have been determined. The relative reactivities of the ketones are discussed in terms of the electronic character and steric environment of the carbonyl group.

It has previously been observed³ that cyclohexyl acetate is formed in 67% yield from the reaction of cyclohexyl methyl ketone with perbenzoic acid in chloroform, and that no analogous product can be isolated from similar treatment of cyclopropyl methyl ketone. It was therefore of interest to extend the study of the peracid reaction to a series of acetylcyclanes $\text{CH}_2\text{---CHCOCH}_3$ in which the ring size



was systematically varied, and note the effect of ring size on both the yield of acetate esters produced and the relative rates of reaction. Extension of the reaction represented by the general equation



to other members of the homologous series has now shown that, with the exception of cyclopropyl methyl ketone (I), the reaction proceeds readily and provides the corresponding acetates in yields of 58 to 72%.

In accord with the previous work,³ it was found that the peracid activity of a chloroform solution of perbenzoic acid containing I disappears very slowly, and that no ester product indicative of a normal reaction can be isolated.

Isopropyl methyl ketone (VI), taken as a typical open-chain ketone having certain features of structural similarity to the members of the cyclic series was also allowed to react with perbenzoic acid, for

comparison purposes. It provided the single product isopropyl acetate in normal yield.

The results of these experiments, summarized in Table I, point to the synthetic utility of the peracid reaction in the transformation $\text{---COCH}_3 \rightarrow \text{---OCOCH}_3$ for the acetyl group attached to an alicyclic system. In no case was there evidence for the formation of the isomeric methyl ester, corresponding to migration of the methyl group from carbon to oxygen.

Over a limited range of initial ketone and peracid concentrations in chloroform solution, the reaction for each ketone in the series II–V was observed to be a second order process. The data of each run gave excellent linearity in second order plots, and relative constancy of the specific reaction rates (k_2) with varying initial concentrations was observed for each ketone. Data representative of a typical ketone of the series are given in Table II.

Also included in Table II are data illustrating the catalytic effect of acetic or benzoic acid initially added to a reaction mixture. These and similar data for the other ketones indicate that for all reactive members of the series there is a marked increase in the observed rate constants of reactions run in the presence of either acetic or benzoic acid. This second order, acid-catalyzed behavior parallels that observed in the perbenzoic acid oxidation of acetophenones⁴ and cyclanones.⁵

Since different preparations of perbenzoic acid contain varying amounts of benzoic acid, a uniform catalytic effect could be obtained only by using identical aliquots of the same peracid solution. Evaluation of any single factor therefore necessitated the use of the same stock solution of perbenzoic acid throughout all runs in which that factor was under consideration. This procedure ensures the reliability of relative rate values, and the dependence of rate on catalyst content explains cer-

(1) Presented in part before the Division of Organic Chemistry at the 118th Meeting of The American Chemical Society, Chicago, Ill., September 3–8, 1950.

(2) Naval Medical Research Institute, National Naval Medical Center, Bethesda 14, Maryland.

(3) S. L. Friess, *THIS JOURNAL*, **71**, 14 (1949).

(4) S. L. Friess and A. H. Soloway, *ibid.*, **73**, 3968 (1951).

(5) S. L. Friess, *ibid.*, **71**, 2571 (1949).

TABLE I
REACTION OF KETONES WITH PERBENZOIC ACID IN CHLOROFORM
Temperature: 23–25°; initial concentrations: 0.5–0.6 M

n	Ketone $\begin{array}{c} \text{CH}_3 \\ \\ \text{C} \\ / \quad \backslash \\ (\text{CH}_2)_n \quad \text{CHCOCH}_3 \end{array}$	Mole R ₂ COCH ₃	Mole C ₆ H ₅ CO ₂ H	Reaction time, hr.	Mole peracid consumed	Ester Product, ROCOCH ₃					M.p. of phenyl- urethan of ROH ^c
						Yield, ^a %	°C.	B.p.	Mm.	n _D ^b	
1	(I)	0.053	0.054	336	0.032	0					
		.050	.100	168 ^e	.090	0					
		.048	.100 ^f	1000	.090	0					
2	(II)	.077	.080	45	.071	58	60–62 ^d	70	1.4200	21	130–131
3	(III)	.10	.11	73	.096	61	52–53	13	1.4358	23	131–132
4	(IV)	.081	.11	77	.076	72	63–64	13	1.4430	23	80–82
5	(V)	.087	.11	49	.082	69	84–86	14	1.4430	20	83–85
	(VI)	.10	.11	48	.093	63	87–89	Atm.			118–120 ^b

^a Based on ketone initially present. ^b Melting point of the 3,5-dinitrobenzoates. ^c All derivatives were checked by mixed melting points with authentic samples; no depression was observed in any case. ^d Anal. Calcd. for C₆H₁₀O₂: C, 63.10; H, 8.84. Found: C, 62.82; H, 8.80. ^e Refluxed for 18 hours after this time. ^f 1.0 M solution.

TABLE II
REACTION OF CYCLOPENTYLMETHYL KETONE WITH PER-
BENZOIC ACID

Solvent: chloroform; temperature: 20.00°			
Ketone	Initial concn. (m./l.) Peracid	Added catalyst	k ₂ (l./mole sec. × 10 ³)
0.1606	0.2116		6.63 ± 0.08
.2007	.2116		7.09 ± .12
.2409	.2116		6.75 ± .10
.2007	.2645		6.58 ± .21
.2007	.2116	0.170 (Benzoic acid)	9.12 ± .42
.2007	.2116	0.209 (Acetic acid)	8.55 ± .16

tain deviations in absolute values obtained using different batches of peracid.

The formation of benzoic acid as a product of the reactions leads to an increase in the catalyst level of the solution as the reaction proceeds. However, the autocatalytic increase in rate as the reaction progresses is not too appreciable for the first 20 to 30% of the reaction. Accordingly, this range was used in these studies.

In order to gain further insight into the nature of the oxidation process, the effect of increasingly polar media on the rate of reaction was determined. The rate constant for the reaction of cyclohexyl methyl ketone, taken as a typical member of the series, was measured using as solvent (in order of increasing polarity): chloroform, 60% chloroform—40% *sym*-tetrachloroethane, and 40% chloroform—60% *sym*-tetrachloroethane (TCE).

Tetrachloroethane in admixture with chloroform was expected to provide a medium closely similar to chloroform but with a sufficiently greater dipole moment to provide some measure of the effect of the polarity of the medium on the reaction rate. The results of these experiments are shown in Table III.

TABLE III
THE EFFECT OF SOLVENT ON REACTION RATE OF CYCLO-
HEXYL METHYL KETONE

[Ketone]₀ = 0.165 M; [Peracid]₀ = 0.1614 M; temperature, 24.97°

Solvent CHCl ₃ , %	TCE, %	k ₂ l./mole sec. × 10 ³
100	0	4.39 ± 0.37
60	40	8.79 ± .17
40	60	12.9 ± .01

These data show a definite increase in rate constant with increasing polarity of the solvent. This sensitivity of reaction rate to the polarity of the medium points strongly to the possibility of ionic character in the rate-controlling step or steps.

The discrepancy between the k₂ value obtained above in 100% chloroform and that determined elsewhere in this study is understandable on the basis of a low level of catalytic activity in this particular solution of perbenzoic acid. A simultaneous check on relative rates with another ketone of the series gave a rate ratio comparable to that determined in the relative rate experiments of Table V.

Energies, Enthalpies and Entropies of Activation.—The thermodynamic quantities of activation were obtained from rate runs of the series in chloroform, made at three temperatures. Arrhenius activation energies were determined graphically and applied, with the rate constant at 24.97° to calculate the values of ΔS[‡], ΔH[‡] and ΔF[‡]. The values obtained are shown in Table IV.

TABLE IV
ENERGIES, ENTHALPIES AND ENTROPIES OF ACTIVATION
Temperatures: 20.20 ± 0.02°; 24.87 ± 0.02°; 30.20 ± 0.02°.

Ketone	E ^a kcal./mole	At 24.87°		
		ΔH [‡] , kcal./mole	ΔF [‡] , kcal./mole	ΔS [‡] , e.u.
II	10.1	9.5	22.3	-43
III	11.5	10.9	22.7	-40
IV	11.0	10.4	22.7	-41
V	10.5	9.9	22.8	-43

It is interesting to note that approximately the same mean value of ΔS[‡] is found for the reaction of substituted acetophenones with perbenzoic acid in chloroform,⁴ and is constant for a variety of substituents on the benzene ring.

Relative Rates.—A comparison of the relative rates of reaction among members of the series subjected to identical reaction conditions is provided in Table V.

The rate constant for the reaction of cyclopropyl methyl ketone (I) represents less than 5% of stoichiometric completion of the reaction, and serves only to indicate the relatively slow rate at which perbenzoic acid is consumed in its presence, since no products were ever isolated from this reaction.

TABLE V

RELATIVE RATES OF REACTION OF KETONES

Temperature: 24.90°; solvent: chloroform; [Ketone]₀ = 0.190–0.210 M; [Peracid]₀ = 0.258 M

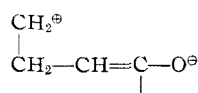
Ketone	k_2 , 1./mole sec. $\times 10^4$	Relative rate	Carbonyl absorption in infrared, λ , μ
I	0.22 \pm 0.01	0.16	5.90
II	3.19 \pm .04	2.26	5.86
III	1.13 \pm .01	0.80	5.87
IV	1.41 \pm .03	1.00	5.87
V	1.14 \pm .01	0.81	5.87
VI	1.17 \pm .04	0.83	5.87

Isopropyl methyl ketone (VI) was taken as a typical open-chain ketone for comparison, as it was in the preparative experiments.

Since the carbonyl addition of perbenzoic acid or some ionic entity derived from it is apparently the rate-controlling step in the reaction, the observed magnitudes of relative rates should be susceptible to correlation with the ease of that process. Since it is probable too that the addition of any reagent to a carbonyl group depends both on the electronic character and steric environment of that group,⁶ both factors should be considered.

It is first to be noted that the differences in relative reactivity of the ketones are small, and are obtained from rate constants which are probably the most sensitive measure of the combined effect of all those factors which govern reactivity. Further, the thermodynamic quantities of activation indicate, within the limits of their precision, that any electronic effects arising from the alkyl groups are constant, or nearly so, throughout the series cyclobutyl to cycloheptyl methyl ketone and isopropyl methyl ketone. This view is further supported by the constancy of the wave length of absorption of the carbonyl group in the infrared, as shown in Table V, on changing the size of the cycloalkyl groups. It appears that the electronic effects which would predominate in determining the force constant for carbonyl stretching are the same in these four compounds. The only significant variation appears in the case of cyclopropyl methyl ketone which absorbs radiation of longer wave lengths, indicating some degree of conjugation with the cyclopropane ring and consequently enhanced single bond character of the C–O linkage. Although such bond character might be expected to increase reactivity of the carbonyl group toward addition, through the

contribution of forms such as $\overset{\oplus}{\text{C}}\text{---}\overset{\ominus}{\text{O}}$, to the hybrid, the effects of forms such as



should also be considered in view of the unsaturated character of the cyclopropane ring.^{7,8} Although both forms are significant in determining the C–O

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. 7.

(7) I. M. Klotz, *This Journal*, **66**, 88 (1944).

(8) For further discussion of this point see: M. T. Rogers, *ibid.*, **69**, 2544 (1947); C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949); A. D. Walsh, *Nature*, **159**, 165 (1947).

force constant and hence vibration frequency, any important contribution by the latter form would impede addition to the carbonyl group and result in a low order of reactivity.

It would be expected that any difference in reactivity of ketones due to steric factors should be reflected in differences in the values of ΔS^\ddagger . However, the variation in ΔS^\ddagger which would appear in connection with slight differences in reactivity might well not be detected within the limits of error of the determination of this quantity. Although it is by no means certain from the experimental data which factors, steric or electronic, are the major contributors to differences in reactivity, possible steric influence on the addition step should be pointed out.

Cyclopropyl methyl ketone clearly has the most favorable geometry for addition at the carbonyl site, with the adjacent methylene groups held back by the ring structure well away from the zone of possible interference with reaction at the carbonyl function. Consequently, the marked effect of the cyclopropane ring toward reduction of carbonyl activity, as observed for this ketone, must be attributed solely to the electronic interaction^{7,8} between the ring and the carbonyl function.

An examination of the molecular model of cyclobutyl methyl ketone indicates that its carbonyl group is sterically unencumbered. If in addition the cyclobutyl group exhibits little more electronic effect on the carbonyl addition than any other simple alkyl group, the net result would be a relatively rapid rate of reaction.

Further examination of the molecular models involved provides a possible explanation of the small differences in rate observed in the case of cyclopentyl, cycloheptyl and isopropyl methyl ketones (relative rate 0.8), as compared to a cyclohexyl methyl ketone (1.0). An acetyl group attached to a cyclohexane ring in either configuration is free to rotate around its bonding axis with essentially no strain to the bond angles of the molecule. Further, any rotational position of the acetyl function provides almost equal opportunity for attack on the carbonyl group.

On the other hand, it appears from the models that an acetyl group attached to a cyclopentane or cycloheptane ring, or to an isopropyl group, is not free to rotate completely about its bond to the ring without some degree of bond deformation or interference. Rotation of the acetyl group in such a system through 360° brings it successively through positions where attack on the carbonyl group might be favored and through those where it is not, with the net effect of greater steric hindrance than is to be found in the cyclohexyl analog.

Without attempting to extend the information to be gained from an examination of the models beyond normal limitations, the conclusion might be drawn that steric conditions for addition to the carbonyl function of cyclohexyl methyl ketone appear more favorable than those found in the homologous five- and seven-membered ring compounds.

Experimental⁹

Materials.—Cyclobutyl methyl ketone was prepared by the reaction of dimethylcadmium with cyclobutanecarboxylic

(9) Melting points are corrected; boiling points are uncorrected.

acid chloride.¹⁰ Cyclopentyl, cyclohexyl and cycloheptyl methyl ketone were prepared by an adaptation of the procedure of Newman and Booth,¹¹ involving the addition of the appropriate alkylmagnesium halide to acetic anhydride at -70° . Cycloheptyl methyl ketone (b.p. $86-87^{\circ}$ at 16 mm.; n_{D}^{20} 1.4622; *Anal.* Calcd. for $C_8H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.27; H, 11.36) formed a 2,4-dinitrophenylhydrazone, orange-yellow needles from ethanol, m.p. $117-118^{\circ}$, and a semicarbazone, colorless plates from 50% ethanol, m.p. $175-176^{\circ}$.

Commercial samples of cyclopropyl methyl ketone and isopropyl methyl ketone were purified by distillation. Perbenzoic acid was prepared according to Braun.¹²

Preparative Scale Reactions.—In a typical reaction of the series given in Table I, approximately 0.1 mole of the ketone was mixed with that volume of a standardized chloroform solution of perbenzoic acid containing roughly a 10–15% stoichiometric excess of the peracid, and the reaction progress was followed by removal of 1-ml. aliquots of the reacting solution at intervals and determination of residual peracid iodimetrically.³

On completion of the reaction, the benzoic and perbenzoic acids were removed by extraction with a 1 *M* sodium bicarbonate solution, followed by a water wash. The combined aqueous phases were extracted with ether, and the ether and chloroform solutions combined and dried. Distillation of the solvent, followed by fractionation of the residual oil, gave the ester products whose properties are indicated in Table I.

(10) R. Pinson, Jr., and S. L. Friess, *THIS JOURNAL*, **72**, 5333 (1950).

(11) M. S. Newman and W. T. Booth, *ibid.*, **67**, 154 (1945).

(12) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 431.

Further identification of each ester was provided by its saponification equivalent and the preparation of a derivative of the alcohol and/or acid fraction after alkaline hydrolysis.

Rate Runs.—A known amount of the ketone was weighed, or pipetted from a standard solution of the ketone in dry chloroform, into a glass-stoppered volumetric flask used for the reaction. An aliquot of a standard solution of perbenzoic acid was added and the solution made nearly to volume with dry chloroform. The flask was placed in a constant temperature bath controlled to 0.02° , allowed to come to temperature and made to volume, and the course of the reaction followed by the withdrawal of 2-ml. aliquots for iodimetric determination of residual peracid.

In runs designed to investigate acid catalysis, weighed amounts of acetic or benzoic acid were added to the ketone solution before the addition of the perbenzoic acid.

When 40 or 60% *sym*-tetrachloroethane in chloroform was employed as the solvent, a 10-ml. aliquot of a standard solution of the ketone in a tetrachloroethane was placed in a 25-ml. volumetric flask and a 10-ml. aliquot of standard chloroform solution of perbenzoic acid added. After thermostating, the solution was made to volume with chloroform or tetrachloroethane, providing a 40 or 60% solution, respectively.

Runs for the evaluation of any one factor were carried out at the same time, using identical aliquots of the same solution of perbenzoic acid.

Infrared Spectra.—Sample and blank tracings in the carbonyl region were obtained using a Perkin-Elmer Recording Infrared Spectrometer, Model 12 A-B. Purified liquid samples were used without solvent in a cell of 0.025 mm. thickness.

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Reactions of Peracids. VII. Nuclear Oxidation of Aromatic Ethers with Perbenzoic Acid

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The methyl ethers of certain phenols have been found to undergo extensive and rapid nuclear oxidation on treatment with perbenzoic acid in chloroform solution. In general, sensitivity to peracid attack in terms of moles of peracid consumed per mole of compound was observed to be a function of both the degree of methoxylation present in the molecule and the relative positions of these groups. The fully methylated ethers of hydroquinone, phloroglucinol, pyrogallol and resorcinol furnished *p*-quinones as isolable products following spontaneous reaction with limited amounts of peracid; veratrole yielded dimethyl muconate as a primary fragment. No stable product could be isolated from the peracid reaction with anisole, although the ether consumed well over two moles of peracid in a reaction characterized by the usual production of color. Some kinetic studies were made at -12.4° on the initial portion of the highly exothermic reaction of phloroglucinol trimethyl ether with perbenzoic acid. The results obtained seem to be best fitted by a reaction scheme involving the consumption of two moles of peracid in the initial oxidation phase.

Introduction

Previous work in the field has indicated that aromatic nuclei which are quite reactive toward electrophilic agents are also readily attacked by peracids. For example it was found³ that active aromatic carcinogens such as methylcholanthrene and benzpyrene react rapidly with perbenzoic acid. It has also been noted⁴ that mesitylene, acetomesitylene and trimethylgallic acid spontaneously consume more than two moles of perbenzoic acid per mole of each respective compound. From the reactions of the latter two compounds, products were isolated which indicated that extensive ring cleavage had accompanied the general peroxidation process.

Also, several naphthols and phenols were found⁵ to react with peracetic acid, with the formation of *o*- and *p*-quinones in appreciable yield accompanying the normal ring cleavage⁶ process. Similarly, Fernholz⁷ has observed that certain phenyl and naphthyl ethers are oxidized by perbenzoic and peracetic acids to yield quinones and esters as isolable products. Finally, in quite recent work, Christensen and co-workers⁸ and also Bader⁹ have observed the formation of a complex naphthoquinone in the molybdate-catalyzed hydrogen peroxide oxidation of β -naphthol.

(5) J. Böeseken and M. L. von Königfeldt, *Rec. trav. chim.*, **54**, 313 (1935); J. Böeseken and C. F. Metz, *ibid.*, **54**, 345 (1935).

(6) A. von Wacek and R. Fiedler, *Monatsh.*, **80**, 170 (1949).

(7) H. Fernholz, *Angew. Chem.*, **60A**, 82 (1948); *Ber.*, **84**, 110 (1951).

(8) I. D. Raacke-Fels, C. H. Wang, R. K. Robbins and B. E. Christensen, *J. Org. Chem.*, **15**, 627 (1950).

(9) A. R. Bader, *THIS JOURNAL*, **73**, 3731 (1951).

(1) Naval Medical Research Institute, Bethesda, Md.

(2) Beannit Mills Fellow in Chemistry, 1950–1951.

(3) H. J. Eckhardt, *Ber.*, **73**, 13 (1940).

(4) S. L. Friess and A. Miller, *THIS JOURNAL*, **72**, 2611 (1950).