Steric Effects in the Baeyer–Villiger Reaction of Simple Ketones

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The reactions of simple alkyl ketones with peroxytrifluoroacetic acid (PTFA) and peroxymaleic acid (PMA) have been examined. Magnitudes of steric effects in the Baeyer–Villiger reaction have been determined, the largest being a factor of 13 in neopentyl to ethyl migration in 5,5-dimethyl-3-hexanone. PMA is consistently more selective toward electronic differences in migrating groups. PTFA shows the greater sensitivity to steric effects.

On a examiné les réactions de cétones alcoyles simples avec l'acide peroxytrifluoroacétique (PFTA) et l'acide peroxymaléique (PMA). On a déterminé les grandeurs des effets stériques dans la réaction de Baeyer–Villiger, le plus grand effet étant un facteur de 13 lors de la migration du néopentyle par rapport au groupement éthyle pour la diméthyl-5,5 hexanone-3. Le PMA est régulièrement plus sélectif vis-à-vis des différences électroniques dans les groupes migrateurs. PTFA possède une plus grande sensibilité pour ce qui est des effets stériques. [Traduit par le journal]

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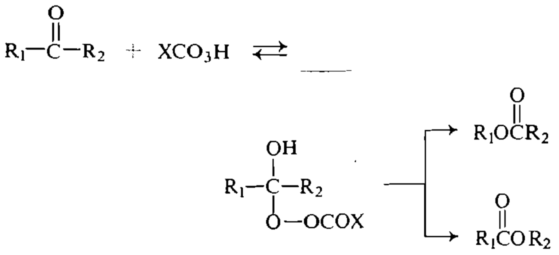
Introduction

While steric effects in the Baeyer–Villiger reaction (1) have received attention in bicyclic systems (2), ortho-substituted acetophenones (3), and benzaldehydes (4), simple aliphatic ketones have not been studied. Analytical difficulties abound and before the days of n.m.r. such study would have been impossible. While one might expect that migratory aptitudes of aliphatic groups, 3° > 2° ~ benzyl > 1° > Me, would have a steric component (the larger group always migrates in preference), Emmons and co-workers found almost no difference in the migratory aptitudes of ethyl and neopentyl when comparing the reaction of their respective phenyl ketones (5). Several years ago, one of us employed the Baeyer–Villiger reaction as a tool in the analysis of a mixture of long chain aliphatic ketones (6). It was necessary to assume indiscriminate migration of primary alkyl groups in the reaction of the ketones with peroxytrifluoroacetic acid. This seemed, in light of Emmons' results, to be a good approximation; but, as a control, 3-heptanone was subjected to these conditions. It was found that *n*-butyl migrated in preference to ethyl by 2 to 1. This paper presents the results of our study of the effect of steric bulk on the relative migratory aptitude of alkyl groups in the Baeyer–Villiger reaction.



Results

Methyl Ketones

The Baeyer–Villiger reaction was carried out at room temperature (23 ± 1°) on a series of methyl primary alkyl ketones in methylene chloride solution. The reactions were run to completion using twofold excess of peroxytrifluoroacetic acid (PTFA) in the presence of anhydrous disodium hydrogen phosphate or using fourfold excess of peroxymaleic acid (PMA) without added buffer. The reactions employing PTFA ordinarily were over in an hour, although, to ensure completion of the reaction, they were routinely stirred 90 min before working them up. Reactions employing PMA required 48 h stirring at room temperature to achieve complete reaction. No attempt was made to study the kinetics under these conditions. The former peracid requires a solid buffer in the reaction mixture, and, PMA reactions deposit solid maleic acid during the course of the reaction. Both situations make it impossible to study the kinetics of the reaction under conditions identical to this product study.

Extent of methyl migration was assayed by n.m.r. The methyl resonance, in all cases, was well resolved and upfield of the methylene resonance of the corresponding isomeric ester. The small amounts of methyl esters produced required calibration of the attenuator. Calibration data, including correlation coefficients, are presented in detail in the experimental section. The methyl resonances were scanned at increased amplitude and the weight of the methyl peak was divided by its amplification factor. The very small values of methyl migration in methyl isobutyl ketone and methyl neopentyl ketone were calibrated by interpolating from known mixtures of the appropriate pure esters. We estimate the error in these measurements to be approximately ±5%. The limit of our ability to detect methyl ester under these conditions is about 0.05%.

The extent of methyl migration for the ketones studied is collected in Table 1. The amount of methyl migration in methyl *n*-propyl ketone is half that observed in methyl ethyl ketone. Further homologation of the alkyl chain results in much smaller changes in extent of methyl migration. These differences are probably real, since they are outside of experimental error and are reflected in the amount of methyl migration found with both peracids. They may reflect conformational differences of the chains in methylene chloride solution. 2-Undecanone poses a peculiar problem here in that the product nonyl acetate is unusually sensitive to hydrolysis. Nonyl alcohol interferes with the assay procedure. The methylene protons adjacent to the OH fall on top of the ester O-methyl singlet. The product of the PMA oxidation underwent enough hydrolysis in 24 h reaction (3–10%) to obscure measurement of the extent of methyl migration in this case. Even with PTFA, when worked up in the usual way and allowed to stand at room temperature in CCl_4 in an n.m.r. tube, nonyl acetate underwent extensive hydrolysis.

TABLE 1. Methyl migration for $RCOCH_3$

R	CF_3CO_3H	R/CH_3	PMA	R/CH_3
Ethyl	1.38%[a]	72[b]	0.37%[a]	270[b]
Propyl	0.69	150	0.22	450
Butyl	0.78	130	0.25	400
Pentyl	0.51	200	0.15	670
Nonyl	0.65	150	—[c]	—[c]
Isobutyl	0.32	310	0.13	770
Neopentyl	0.12	830	0.10	1000
Benzyl	<0.05	>2000	<0.05	>2000

[a] Percent methyl migration.
[b] Ratio of migratory aptitude alkyl/methyl.
[c] Could not be measured due to partial ester exchange.

PMA is consistently more selective in the oxidation of methyl ketones. This difference of three- to fourfold increase in the selectivity probably reflects an increase in its sensitivity to electronic effects, when compared to PTFA. As the steric bulk of the alkyl group increases, this selectivity diminishes, suggesting that electronic and steric requirements lead to opposing effects.

Ethyl Ketones

The Baeyer–Villiger reaction of ethyl *n*-alkyl ketones was carried out under conditions identical to those described above. Both n.m.r. and mass spectral assays were employed. In the cases of 1-phenyl-2-butanone and neopentyl ethyl ketone, the CH_2—O protons of the respective esters were clearly resolved at 60 MHz. The esters from the reaction of isobutyl ethyl ketone could be resolved clearly only at 100 MHz. Partial resolution could be obtained at 60 MHz. The normal 3-alkanones did not lend themselves to an n.m.r. assay. Partial resolution was observed at 220 MHz for these reaction products. These partially resolved spectra were very useful since they allowed estimation of migratory aptitudes, which served as a convenient check on the more rigorous analyses.

Attempts to separate the product esters by g.l.c. failed, except in the case of 3-hexanone. Ethyl butanoate and propyl propanoate could be separated on a carefully packed 30 ft Carbowax 4000 column or on a 150 ft Carbowax 4000 coated capillary column. Our assay for 3-alkanones depended upon the propensity of ethyl alkanoates to give an intense ion in the mass spectrum at *m*/*e* 88, whereas propanate esters give peaks at *m*/*e* 57 and 75. The mass spectrometer was calibrated, in each instance, with known mixtures of the product esters and the composition of the Baeyer–Villiger product mixture was determined from the *m*/*e* 88/75 ratio by interpolation.

Table 2 lists the ratio of ethyl migration to

TABLE 2. Product ratios for ethyl ketones

R/Ethyl	CF_3CO_3H	Calcd.[a]	PMA	Calcd.[a]
Propyl	1.75[b]	2.0	1.89[b]	1.7
Butyl	1.56	1.8	2.13	1.5
	1.6[c]		1.7[c]	
Pentyl	1.85	2.8	2.08	2.5
	1.7[c]		2.0[c]	
Nonyl	2.04	2.1	2.38	—
Isobutyl	4.76[d]	4.3	4.54[d]	2.9
Neopentyl	13.3[e]	11.6	11.9[e]	3.7
Benzyl	17.5[e]		25.0[e]	

[a] Calculated from the ratio of alkyl/methyl migration in the pertinent 2-alkanone to ethyl/methyl migration in 2-butanone.
[b] Mass spectrometric assay.
[c] 220 MHz n.m.r. assay.
[d] 100 MHz n.m.r. assay.
[e] 60 MHz n.m.r. assay.

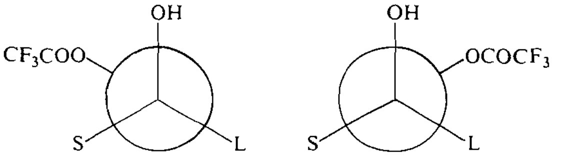
alkyl migration for both peracids. Also included in the table is the ratio of alkyl to ethyl migratory aptitudes, calculated from the methyl ketone data by comparing the ratio of alkyl/methyl migration to ethyl/methyl migration. It is interesting to note that, unlike the methyl ketones, the ethyl ketones show little change in selectivity in changing from PTFA to PMA as the peracid. Increasing the steric bulk of the alkyl group increases its tendency to migrate. *n*-Propyl acts as though it is larger than ethyl. Isobutyl contributes a factor of three over *n*-butyl to the relative migratory aptitude of the alkyl moiety, and neopentyl approximately another factor of three. The large migratory aptitude for benzyl indicates that electronic considerations are also important in the migration of this group.

Discussion

Steric Effects

Substitution of methyl groups on the β-carbon of 2- and 3-alkanones causes fairly small changes in the migratory aptitudes of the alkyl portion relative to methyl and ethyl. Extent of alkyl migration increases fairly regularly with the bulk of the alkyl group. Parallel effects are seen in the methyl and ethyl ketones and with both peracids. The largest difference is a factor of 13.3 seen in the reaction of ethyl neopentyl ketone with PTFA. This represents a difference in the free energy of activation ($\Delta\Delta G^{\ddagger}$) of neopentyl over ethyl migration of 1.5 kcal/mol.

We favor a steric origin for this change in migratory aptitude. One easily can visualize the origin of this steric effect in Newman projections of the Criegee intermediate by assuming that migration takes place *anti*-periplanar to the departing carboxylate and that the product-determining transition state has similar steric demands. This argument has been advanced before (5). It is well to remember Curtin's admonition (8) that, if migration is slow with respect to rotation, the product ratio is determined solely by the ratio of the energies of the two transition states and not by the rotamer populations of the intermediate.



Comparison of the Peracids

Two papers by Emmons present examples of the change in relative migratory aptitude as a function of peracid. Emmons noted initially (5) that phenyl cyclohexyl ketone suffered 22% phenyl migration with PTFA and 11% phenyl migration with peroxyacetic acid in the presence of 1 *M* CF_3CO_2H. In later work (7), he observed that, in the reactions of desoxybenzoin, PMA gave a 7:1 ratio of benzyl to phenyl migration, whereas with PTFA, equal amounts were found. In both examples he concluded that migration was concerted with O—O bond cleavage and that the reaction involving the poorer leaving group was more selective.

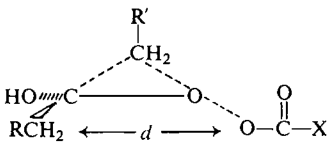
Our results indicate that the situation is not so simple. PMA here is consistently more selective than PTFA when one is comparing two groups, which differ in the ability to stabilize positive charge by delocalization in the transition state. In the comparison of methyl with primary alkyl, PMA is about four times more selective. Comparing primary alkyl with benzyl, PMA is 1.4 times as selective. Where the comparison is between two primary alkyl groups (and one might expect a similar electronic demand) very small differences are observed between the two peracids.

Robertson and Swelin (9) visualize a homolytic pathway for O—O bond cleavage in the Criegee intermediate, derived from the reaction of peroxyacetic acid and benzophenones containing electron withdrawing groups. The normal Baeyer–Villiger products are produced by a 1,2 radical migration of one of the phenyl groups. A change in reaction mechanism, they assert, is responsible for the change in migratory aptitudes of phenyl and *p*-nitrophenyl when peroxyacetic acid is used instead of PTFA. To our knowledge, alkyl migrations to radical centers are not known (10), and the absence of methyl migration in the *t*-butoxy radical argues against a radical pathway in our experiments. In addition, maleic acid is a much stronger acid than acetic acid ($pK_a = 1.83$ *vs.* 4.75, respectively, in water) (11) and a better leaving group from the Criegee intermediate.

We are well aware of the dangers of trying to present mechanistic conclusions based upon small differences in relative rate constants. With this in mind, we would like to comment on some of our more surprising data: in the reaction with methyl ketones, there is a pronounced decrease in the selectivity of PMA as the bulk of the alkyl groups increases. PMA is about fourfold more selective than PTFA in reaction with 2-butanone, three times as selective in the homologous 2-alkanones, and, in neopentyl methyl ketone, the selectivity drops to 20%. This suggests that PTFA, which carries out this Baeyer–Villiger reaction 50 times faster than PMA (as estimated from half-times for reaction), is more sensitive to steric effects.

This trend abates in the ethyl ketones where the two peroxyacids show very similar selectivity toward ethyl/alkyl migration. In one case, however, PTFA, is the more selective peroxyacid. It shows 11% increased selectivity over PMA in the oxidation of neopentyl ethyl ketone.

Likely sources of diminished steric sensitivity of PMA may be visualized in the drawing below. The assumption of *anti*-periplanar migration implies that the leaving group is in the staggered conformation with respect to the non-migrating group and the hydroxyl, which eventually becomes the ester carbonyl. Migration takes place with relief of steric interaction between the non-migrating and leaving groups.



A source of the smaller steric requirement for migration, when maleic acid is the leaving group, might be a later transition state in that reaction and hence a greater distance *d* between these groups. Another source, which is tempting to invoke, particularly in methylene chloride solution, involves specific hydrogen bonding requirements, for the second carboxyl function in PMA, which render the leaving group rigid and sterically remote from the non-migrating group. We have no specific evidence on either point. We have carried out a few experiments with trichloroperoxyacetic acid, which has a bulkier X group, but these reactions are not as clean as those with PMA and PTFA.

PMA asserts its more selective nature in the oxidation of 1-phenyl-2-butanone, suggesting that there is an electronic component to benzyl migration in the Baeyer–Villiger reaction. The electronic contribution to benzyl migration here, however, can be estimated to be less than 1 kcal per mol. If we assume the benzyl function to be approximately isosteric with the isobutyl group,[1] less than a factor of four need be explained by the ability of benzyl to stabilize a positive charge in the transition state for migration.

Experimental

Materials

All ketones, with the exception of 5,5-dimethyl-3-hexanone, were obtained commercially. All esters, excluding ethyl decanoate (K and K laboratories) and ethyl acetate (Fisher Scientific Co.), were prepared by standard methods. In each case, the compound was checked on a Varian T-60 n.m.r. spectrometer and a Perkin-Elmer 337 grating i.r. spectrophotometer. Purification was effected by careful distillation through a 10 in. Vigreux column or through a Nester–Faust spinning band column, depending on the nature of the impurities. Before use, each compound was assayed by gas chromatography using a Varian Aerograph Model 1440-2 gas chromatograph equipped with a flame ionization detector. No compound was used unless shown to be greater than 99% pure on two of the following columns: (1) 11 ft. × 1/8 in. 10% Carbowax 4000 on Chromasorb P 80/100 mesh; (2) 10 ft. × 1/8 in. 10% diethylene glycol succinate on Chromasorb W 100/120 mesh; (3) 150 ft × 0.02 in. capillary with SE-30 coating.

Hydrogen peroxide (98%) (FMC corporation) was standardized by permanganate titration. Trifluoroacetic anhydride (Eastman or Baker) and maleic anhydride (Fisher Scientific Co.) were used without further purification.

5,5-Dimethyl-3-hexanone

Dry, finely powdered cadmium chloride (16.5 g, 0.09 mol) was added to an ice-cold solution of ethyl magnesium bromide (0.18 mol) in 65 ml of dry ether.

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[1] Benzyl is more closely isosteric with isoamyl. If benzyl is larger than isobutyl in the region of interest, the electronic enhancement of benzyl migration is even smaller than this value (Keith Yates, private communication).

TABLE 3. N.m.r. assay of methyl ketones[a]

Mixture	% methyl ester	Slope[b] (*M*)	Intercept[b] (*C*)	Correlation coefficient
Methyl propanoate - ethyl acetate	0.256–0.840	0.973	0.024	0.997
Methyl hexanoate - pentyl acetate	0.106–0.675	1.02	0.027	0.989
Methyl 3-methyl butanoate - isobutyl acetate	0.072–0.337	1.21	0.030	0.999
Methyl 3,3-dimethyl butanoate - neopentyl acetate	0.095–0.250	1.11	0.026	0.991
Ethyl 3,3-dimethyl butanoate - neopentyl propanoate	8.30–11.78[c]	1.04	−0.025	0.990

[a] Measured by peak weights.
[b] Known composition = M (measured composition) + C.
[c] Percent ethyl ester.

The suspension was stirred at room temperature for 40 min before being cooled again to 5°. To this cold reaction mixture, 10 ml (0.106 mol) of *t*-butyl acetyl chloride in 30 ml of dry ether was added slowly, after which the mixture was refluxed with stirring for 90 min. Cooled to room temperature, the final product mixture was poured onto ice, leading to the formation of a white precipitate. Concentrated sulfuric acid was added dropwise until this precipitate just dissolved. The ethereal layer was separated, washed with successive portions of water, 10% sodium carbonate, and water, and then dried over magnesium sulfate. Distillation through a 10 in. Vigreux column gave the ketone (10.1 g or 79%), b.p. 136°.

Trifluoroperoxyacetic Acid

The peracid solution (*ca.* 1 *M*) was prepared fresh for each oxidation reaction. Trifluoroacetic anhydride (6.1 g, 0.029 mol) in methylene chloride was carefully added to 98% hydrogen peroxide (0.87 g, 0.025 mol) in 15 ml of methylene chloride at 0°. Once the addition was completed, the reactants were periodically agitated until a homogenous solution was observed. The solution was then diluted to 25 ml at room temperature and a 1 ml aliquot titrated iodometrically.

Peroxymaleic Acid

Maleic anhydride (2.45 g, 0.025 mol) was added to a suspension of 98% hydrogen peroxide (0.73 g, 0.021 mol) in 10 ml of methylene chloride at room temperature. Once the anhydride had dissolved, the methylene chloride was brought to reflux and maintained there for 30 min. The peroxymaleic acid solution thus formed was cooled and used directly in the oxidation reaction. This procedure was found to be superior to all other methods for producing this peracid.

Oxidations with Trifluoroperoxyacetic Acid

One procedure was found to give smooth, facile oxidation of all the ketones studied. The peracid solution (10 ml, *ca.* 0.010 mol) was added slowly from a pressure-equalizing dropping funnel to a mechanically stirred suspension of disodium hydrogen phosphate (4.25 g, 0.030 mol, previously dried over phosphorus pentoxide) in a solution of the ketone (*ca.* 0.005 mol) in 10 ml of methylene chloride, maintained at 23° ± 1°. Vigorous stirring was continued for 90 min to insure complete reaction. The reaction was quenched with water and the organic phase washed twice with water. The aqueous layers were combined and back-washed with 30 ml of methylene chloride. The combined organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The reaction products were dissolved in carbon disulfide or carbon tetrachloride to be assayed by n.m.r., as described below.

Oxidations with Peroxymaleic Acid

To the entire solution of peroxymaleic acid (*ca.* 0.025 mol), prepared as above and maintained at 23° ± 1°, was added a solution of the ketone (*ca.* 0.005 mol) in 10 ml of methylene chloride. The contents of the reaction flask were stirred vigorously for 48 h after which they were mixed with 30 ml of water. This was enough to dissolve the white precipitate of maleic acid formed during the oxidation. The organic layer was separated, washed three times with 25 ml portions of phosphate buffer (0.5 *M*, p*H* 6.5) and once with a further 30 ml portion of water, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. The reaction products were taken up in carbon disulfide or carbon tetrachloride before being assayed by n.m.r.

N.m.r. Analysis of Ester Mixtures

This assay was used for the product mixtures from oxidation of all the methyl ketones and of 5-methyl-3-hexanone, 5,5-dimethyl-3-hexanone, and phenyl-2-butanone. In every case, the two well-resolved signals, corresponding to the groups *alpha* to the ester oxygen in each of the two products, were scanned on a Varian T-60 n.m.r. spectrometer using a sweep width of 100 Hz and a sweep time of 50 s. The smaller of the two signals was then scanned 5 to 10 times at each of two increased amplitudes. Each scan was retraced several times to insure the reproducibility of the instrument and the phase was always carefully adjusted to make the base line of the peaks as straight as possible. The filter dial was always set at 2 so that, at the sweep width used, the peaks were smooth as well as broad. The areas under the peaks (in Xerox copies of these spectra) were then carefully cut out, weighed, corrected to the same amplitude, and the weight contribution, made by one hydrogen to each ester signal, calculated.

In the case of the products from 5-methyl-3-hexanone and 5,5-dimethyl-3-hexanone, similar spectra were run on a Varian HA 100 as well. Here the relative concentrations of the two esters were such that the signals could be compared at one amplitude.

The procedure was calibrated by subjecting series of known mixtures of esters to the same assay. For each series examined, plots were made of the known com-

TABLE 4. Mass spectrometric assay of ethyl esters[a]

Mixture	Alkyl/ethyl ester	Slope[b] (M)	Intercept[b] (C)	Correlation coefficient
Ethyl butanoate – propyl propanoate	1.39–1.85	0.631	0.222	0.999
Ethyl pentanoate – butyl propanoate	1.40–2.20	1.84	−0.560	0.989
Ethyl hexanoate – pentyl propanoate	2.49–3.64	1.84	−0.774	0.999
Ethyl decanoate – nonyl propanoate	1.50–3.66	2.34	−0.681	0.999

[a] Measured by peak height.
[b] Alkyl/ethyl ester ratio = M [(intensity at m/e 75)/(intensity at m/e 88)] + C.

positions versus the measured values. Slopes, intercepts, and correlation coefficients are collected in Table 3.

Mass Spectrometric Analysis of Ester Mixtures

This method was used for the product mixtures from the reaction of all ketones of the type $RCH_2CH_2\overset{O}{\overset{\|}{C}}CH_2$-$CH_3$. All spectra were run on neat samples, using a Bell and Howell mass spectrometer model 21-490, at 70 eV and source temperature of 100° ± 10°. Four traces were collected for each sample. The m/e 75/88 values obtained for known mixtures were plotted against the alkyl/ethyl ester ratio as indicated in Table 4. Baeyer–Villiger product ratios were determined from their m/e 75/88 values by interpolation on these plots.

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