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REMOTE SUBSTITUENT EFFECTS IN THE BAEYER-VILLIGER OXIDATION. I. THROUGH-BOND γ SUBSTITUENT EFFECT ON THE REGIOSELECTIVITY[1]

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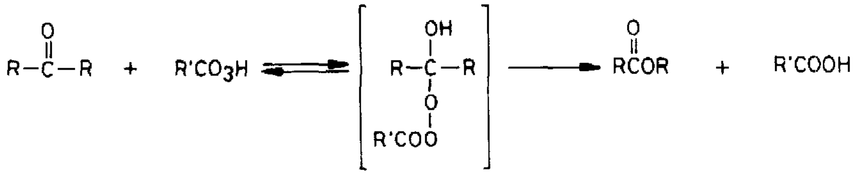
Summary: Regioselectivity of the Baeyer-Villiger oxidation of 8-oxabicyclo[3.2.1]octan-3-one derivatives is markedly affected by the electronic nature of substituents at position γ to the carbonyl function.

The Baeyer-Villiger oxidation[2] of ketones by peroxy acids proceeds via transient tetrahedral intermediates,[3] which undergo alkyl migration with retention of configuration. When the ketone is unsymmetrically substituted, the group possessing greater positive-charge supporting ability tends to migrate more readily.[4] Conformational factors are also important.[5] 8-Oxabicyclo[3.2.1]octan-3-one derivatives serve as excellent models that elucidate factors controlling the reactivities and selectivities in the oxidation, because the rigid basic skeleton with a plane of symmetry is not distorted to any great extent upon introduction of substituents. In connection with our project on C-nucleoside synthesis,[6] we have examined the oxidation of the derivatives bearing an alkyl group(s) at position α to the carbonyl group and found a complete regioselectivity.[7] Here we disclose an unusually remote substituent effect on the regioselectivity.



$$R-\overset{O}{\overset{\|}{C}}-R \;+\; R'CO_3H \rightleftharpoons \left[\begin{array}{c} OH \\ | \\ R-C-R \\ | \\ O \\ | \\ R'COO \end{array}\right] \longrightarrow R\overset{O}{\overset{\|}{C}}OR \;+\; R'COOH$$

When the ketonic substrates of type I[8] were exposed to 3 equiv of trifluoroperacetic acid in dichloromethane at 20—25 °C for 12 h, the regioisomeric lactones IIIα[9] and IIIα'[9] were obtained in high yields (80—100%). As summarized in Table I, the product ratio appeared to be highly dependent on the nature of the γ substituent X. Inspection of models as well as the general trend shown in the table indicates that the regioselectivity is governed by electronic effects of X group rather than the steric or conformational factors. When X is hydrogen or alkyl, no or slight preference for the production of IIIα was noted. By contrast, an electron-withdrawing group attached to the γ position favors the α' methylene migration over the α

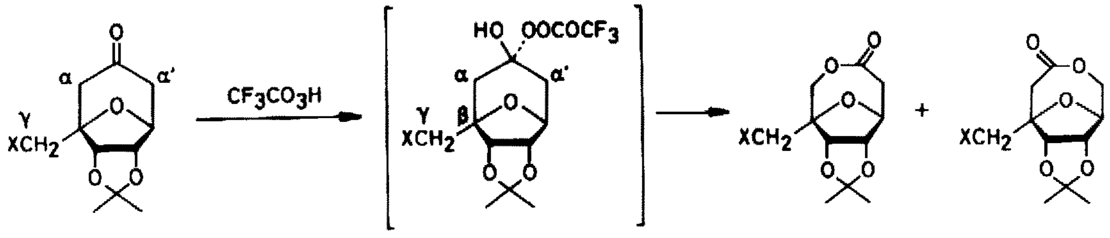
Table I. Remote Substituent Effect on the Regioselectivity in the Baeyer-Villiger Oxidation of I and IV[a]

X	IIIα/IIIα' ratio[b]	VIα/VIα' ratio[c]
H	53:47	—
$\underline{n}$-C_4H_9	50:50	—
$OCH_2C_6H_5$	48:52	30:70
$OCOCH_3$	35:65	46:54
OCO-$\underline{t}$-C_4H_9	31:69	35:65
$OCOC_6H_5$	28:72	35:65
$OCOCF_3$	23:77	—
OSO_2CH_3	19:81	—
OSO_2CF_3	14:86	—

[a] All compounds gave consistent spectral data (IR and NMR) and elemental analysis. [b] Determined by NMR analysis. [c] Determined by high-pressure liquid chromatography.

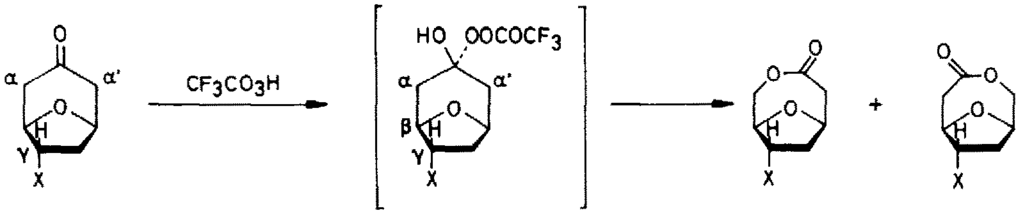
methylene rearrangement. The relative α'-directing abilities are: $OSO_2R > OCOR > OR$; $OSO_2CF_3 > OSO_2CH_3$; $OCOCF_3 > OCOC_6H_5 > OCOCH_3$. Since migratory aptitude is related to the capability of stabilizing the electron-deficient center of the transition state of the II → III conversion, the observed trend can be rationalized by considering the generally accepted mode of transmission of through-bond electronic effects. The C—X bond polarization caused by an electronegative X group decreases electron densities of the γ and α positions in the tetrahedral intermediate II, whereas the α' position is unaffected by the nature of X group. As a consequence, a marked α'-regioselection is obtained. The feeble but definite α-selection achieved with the parent ketone (I, X = H) is also compatible with this view. Greater α/α' ratio, 88:12, has been obtained by the replacement of the CH_2X group by phenyl.[10]

A similar directing effect has been found in the oxidation of another type of γ-substituted substrates. Thus reaction of the ketone IV[11] possessing an electronegative X group with tri-



I II IIIα IIIα'

fluoroperacetic acid in dichloromethane (3 equiv, 15 °C, 12 h) gave a mixture of the lactones VIα[12] and VIα'.[12] The result obtained with some substrates is given in Table I (>80% yield). The substituent effect in the intermediate V would be less straightforward compared with the case of II, because X group accomodated in the seven-membered ring exerts electronic influence not only on the α carbon but also on the α' position (though less effectively). Nevertheless the observed α'-regioselection agrees qualitatively with the above described explanation.



IV V VIα VIα'

These unprecedented remote interactions between the directing substituent and the migrating group should be a reflection of the rigidity of the σ framework that facilitates the through-bond electronic influence. Some indication for the efficiency of electronic transmission in these systems may be provided by ^{13}C NMR measurement of a series of the ketonic substrates; the carbonyl carbon signal of I or IV shifted *upfield* considerably with an increase in electron-accepting ability of X substituents.[13]

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7. T. Sato, M. Watanabe, and R. Noyori, *Tetrahedron Lett.*, 4403 (1978).
8. I ($X = OCOCH_3$) was prepared from $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and furfuryl acetate. T. Sato and R. Noyori, unpublished work.
9. The ^1H NMR spectrum of IIIα gave an AB quartet due to $C\underline{H}_2OC{=}O$ protons, whereas the IIIα' spectrum exhibited the same pattern of signal arising from $C\underline{H}_2COO$ protons.
10. T. Sato, M. Watanabe, and R. Noyori, *Heterocycles*, submitted for publication.
11. IV ($X = OCOC_6H_5$) was prepared in six steps from 8-oxabicyclo[3.2.1]oct-6-en-3-one [1. $(\textit{i}\text{-}C_4H_9)_2AlH$/toluene. 2. 2,3-dihydropyran-pyridinium *p*-toluenesulfonate/CH_2Cl_2. 3. B_2H_6/THF, then 30% H_2O_2-NaOH. 4. C_6H_5COCl/C_5H_5N. 5. pyridinium *p*-toluenesulfonate/CH_3OH. 6. pyridinium chlorochromate/CH_2Cl_2].
12. In ^1H NMR, the $C\underline{H}X$ signal of VIα occurred at a lower field as compared with that of VIα'
13. Typical substituents and chemical shifts ($CDCl_3$, ppm downfield from tetramethylsilane internal standard) follow. Ketone I: H, 205.59; $OCH_2C_6H_5$, 205.41; $OCOCH_3$, 204.19; $OCOC_6H_5$, 204.49; $OCOCF_3$, 203.34; OSO_2CH_3, 203.62; OSO_2CF_3, 202.74. IV: H, 206.67; $OSi(CH_3)_2\text{-}\textit{t}\text{-}C_4H_9$, 205.76; $OCH_2C_6H_5$, 205.66; $OCOCH_3$, 204.78; $OCOC_6H_5$, 204.86.

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