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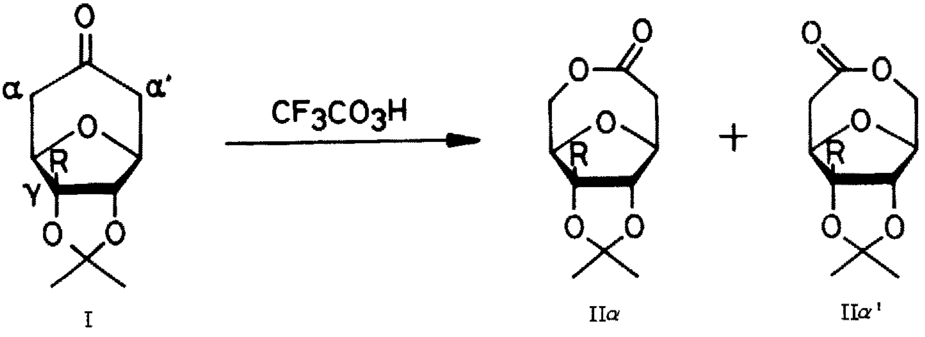
REMOTE SUBSTITUENT EFFECTS IN THE BAEYER-VILLIGER OXIDATION. II. REGIOSELECTION BASED ON THE HYDROXYL GROUP ORIENTATION IN THE TETRAHEDRAL INTERMEDIATE[1]

R. Noyori,* H. Kobayashi, and T. Sato
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Summary: A remote directing effect in the Baeyer-Villiger oxidation of 8-oxabicyclo[3.2.1]-octan-3-one derivatives has been interpreted in terms of chiral orientation of the hydroxyl nonbonding electron pairs in the tetrahedral intermediates.

In the accompanying paper,[1] we described an unusual through-bond electronic effect on the regioselectivity of the Baeyer-Villiger reaction of the 8-oxabicyclo[3.2.1]octan-3-one system. Reported herein are unique steric effects of the remote substituents on the reactivity and regioselectivity.

When the substituted oxabicyclooctanone I[2] was treated with 3 equiv of trifluoroperacetic acid in dichloromethane at 20 °C for 36 h, a mixture of the lactones IIα and IIα' was obtained. The result is summarized in Table I. The reaction of the parent oxabicyclic ketone I (R = H) proceeded smoothly, but its γ-substituted derivatives reacted only sluggishly. For instance, a competition experiment revealed that introduction of methyl group reduces the reaction rate by a factor of 4. Further, the t-butyl derivative (I, R = t-C_4H_9) was even inert to the peroxy acid oxidation. This is apparently due to steric screening effect of R group. Nucleophilic addition of trifluoroperacetic acid to the carbonyl group of I occurs selectively from the sterically less hindered side[3] to form the tetrahedral intermediate III. Here the presence of bulky R group introduces substantial steric repulsion with the hydroxyl moiety, thereby making



I

IIα

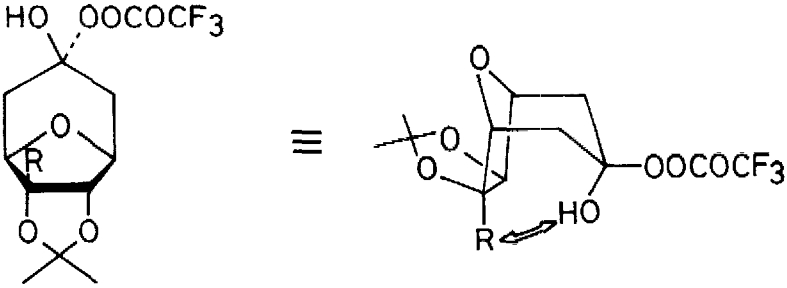
IIα'

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

R	% conversion	% yield of products[b]	IIα/IIα′ ratio[c]
CH_3	62	84	33:67[d]
$\underline{n}$-C_5H_{11}	48	85	25:75[d]
$\underline{t}$-C_4H_9	0	—	—
C_6H_5	19	82	39:61[d]
$CH_2OSi(CH_3)_2$-$\underline{t}$-C_4H_9	38	94	26:74
$CH_2OCH_2C_6H_5$	32	76	23:77
CH_2OCO-$\underline{t}$-C_4H_9	46	82	34:66
$CH_2OCOC_6H_5$	28	75	40:60

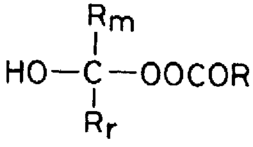
[a] All products gave consistent spectral (IR and NMR) and analytical data. [b] Based on consumed starting material. Isolated yield. [c] Determined by high-pressure liquid chromatography. [d] Obtained by NMR analysis.

the intermediate formation unfavorable. Thus the rate-determining step of the Baeyer-Villiger oxidation has been considered to be the fragmentation of the tetrahedral intermediate,[4] but equilibrium concentration of III is also important.[5]



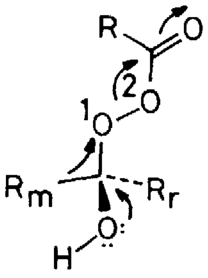
III

Even more noteworthy is the regioselectivity of the oxidation of I. The γ substituent R, regardless of the electronic properties, has proved to give bias toward the formation of IIα′ as the major regioisomer. We would propose that this regioselection is based on a yet unrecognized factor, orientation of the hydroxyl group in the transient intermediate III. In general, reaction of a peroxy acid, RCO_3H, and the carbonyl group of ketone, R_mCOR_r, produces the adduct IV. Here the intermediate causing the concerted rearrangement of R_m has the extended structure IVe[6] rather than the cyclic form IVc which requires a symmetry-forbidden fragmentation. In addition, in order for R_m to migrate to O(1) atom with concomitant

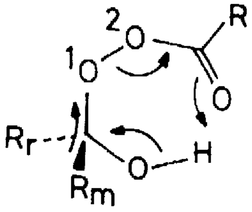


$\mathrm{HO{-}\overset{R_m}{\underset{R_r}{C}}{-}OOCOR}$

IV

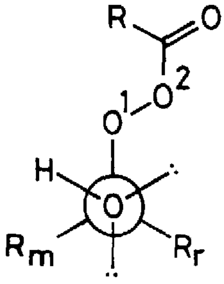


IVe

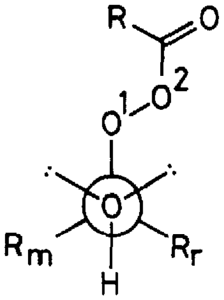


IVc

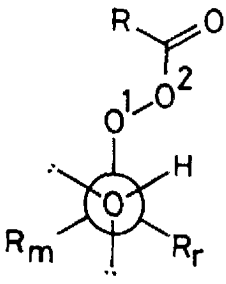
R_m = migrating group; R_r = remaining group



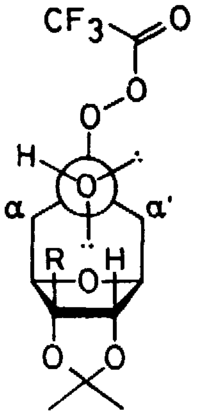
IVA



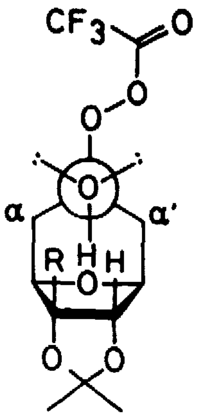
IVB



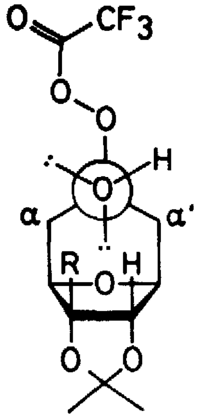
IVC



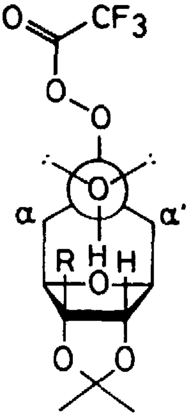
IIIA



IIIB



IIIA'



IIIB'

carboxylic acid ejection, two prerequisites must be satisfied. Firstly, R_m—C—O(1)—O(2) should lie in a trans-antiparallel manner. Secondly, since the electron release from the hydroxyl oxygen to the migration origin attached to it is crucial to promote the shift of R_m,[7] one of the hydroxyl nonbonding electron pairs has to be anti to R_m. Based on such stereoelectronic requirements, only IVA and IVB are the reactive conformers; IVC is unreactive. When this concept is applied to the present substrate system, IIIA and IIIB, which lead to the lactone IIα, and IIIA' and IIIB', giving IIα', are the reactive conformers. In view of the nonbonded repulsion between R and the hydroxyl hydrogen, the relative stabilities are $\mathrm{IIIA'} > \mathrm{IIIA} \gg \mathrm{IIIB} \sim \mathrm{IIIB'}$, in agreement with the observed regiochemical outcome.[8]

We would like to emphasize that chiral arrangement of the hydroxyl hydrogen and nonbonding electron pairs in the transient tetrahedral intermediate is quite significant in determining the regiochemistry of the Baeyer-Villiger reaction. In this system, unlike that reported in the previous paper,[1] electronic effects of the γ substituents are much less important, because the stereochemical arrangement is unfavorable for the transmission.[9]

REFERENCES AND NOTES

1. C-Nucleoside Synthesis. 15. Part 14: Preceding paper.
2. Prepared from α,α,α',α'-tetrabromoacetone and 3-substituted furans. See R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978).
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4. M. F. Hawthorne and W. D. Emmons, J. Am. Chem. Soc., 80, 6398 (1958); B. W. Palmer and A. Fry, ibid., 92, 2580 (1970); T. Mitsuhashi, H. Miyadera, and O. Simamura, Chem. Commun., 1301 (1970); Y. Ogata and Y. Sawaki, J. Am. Chem. Soc., 94, 4189 (1972); Y. Ogata and Y. Sawaki, J. Org. Chem., 37, 2953 (1972).
5. For the related phenomenon, see T. Momose, S. Atarashi, and O. Muraoka, Tetrahedron Lett., 3697 (1974).
6. Probably in a protonated form.
7. V. A. Stoute, M. A. Winnik, and I. G. Csizmadia, J. Am. Chem. Soc., 96, 6388 (1974).
8. Possible hydrogen bonding between the hydroxyl group and oxygen atom of R group in III would not affect the regioselectivity, because (1) alkyl groups and ether- or ester-containing substituents exhibit the same directing effect and (2) the hydrogen-bonded conformer does not satisfy the stereoelectronic prerequisite described in the text (model inspection).
9. ^{13}C NMR shift of carbonyl carbon of I is little affected by the nature of R. Typical substituents and the chemical shifts ($CDCl_3$, ppm downfield from tetramethylsilane internal standard) follow: H, 204.32; n-C_5H_{11}, 205.07; C_6H_5, 204.54; $CH_2OSi(CH_3)_2$-t-C_4H_9, 204.60; $CH_2OCH_2C_6H_5$, 204.56; CH_2OCO-t-C_4H_9, 204.23; $CH_2OCOC_6H_5$, 204.20.

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