Anomeric Effect on Kinetic Acidity: Examples for the Oxygen Atom of Ethers to Accelerate Abstraction of an α-Hydrogen Atom

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Summary: In contrast with general observation, two different types of experiments indicate that the abstraction of α-hydrogen atom of ether having proper conformation is slightly enhanced by the oxygen atom in line with our previous AM1 calculation.

An electron-donating group such as alkoxy, alkylthio, and amino groups is generally assumed to suppress the abstraction of a hydrogen atom attached to the same carbon, as exemplified by the polarity alternation rule (PAR).[1] The acidity of the hydrogen atom at the α-position is surmised to be increased by the inductive effect, whereas it is decreased by unfavorable interaction with the lone pairs on the oxygen atom, the extent of which is apt to depend on the orientation of these lone pairs. In fact, recently, we found that, in spite of the stereoelectronic effect of the nitroolefin moiety,[2] the anomeric, quasi-equatorial proton (H-1e) of the pyranosid 3-nitro-2-enitol 1 was to be slightly more readily abstracted by triethylamine to give the 1-enitol 3 than the alternative one (H-1a).[3] Semiempirical molecular orbital calculations (AM1 method[4]) could corroborate the experimental results by the use of ammonia and 4,6-O-methylene derivative 2 as model compounds and they were also applied at that time to the cyclohexanoid nitro sugar analog 5, in which H-1a was shown to have a higher acidity than H-1e due to the stereoelectronic effect.[3]

These experiments, however, gave no information whether the ring oxygen atom in 1 enhances the abstraction of H-1e or retards it as compared to the corresponding cyclohexanoid analog 4. On the other hand, if one assumes that the more reactive substrate requires the more favorable energy differences between a complex (calculated in an appropriate distance between a reagent and a reactive site) and the starting nitroalkene, the calculations suggest that H-1e of the pyranosid 3-nitro-2-enitol 1 is more readily abstracted than the more acidic H-1a of the cyclohexanoid analog 4 ; the energy differences between complexes of model compounds (2 and 5) are 8.2, 8.3, 5.8, and 2.9 kJ/mol at 1.20, 1.15, 1.10, and 1.05 Å, respectively.[3] This concept has potential utility to predict the relative reactivities, because energy maximum (transition state) is frequently not obtained, especially in ionic reactions owing to the absence of solvents in calculation.

To confirm the assumption, we have prepared cyclohexanoid analog 4 and compared its double bond migration with that of pyranosid 1.

Treatment of 4 [5] with triethylamine caused a C2 to C1 double bond migration to give 6, 50% conversion requiring ca. 1 day at room temperature. Under the same conditions half amount of the double

bond migration of **1** required only ca. 30 min. Thus, both, theoretical and experimental results show the abstraction of H-1 in **1** to be faster than that in **4**.

1 R = Ph
2 R = H

3

4 R = Ph
5 R = H

6
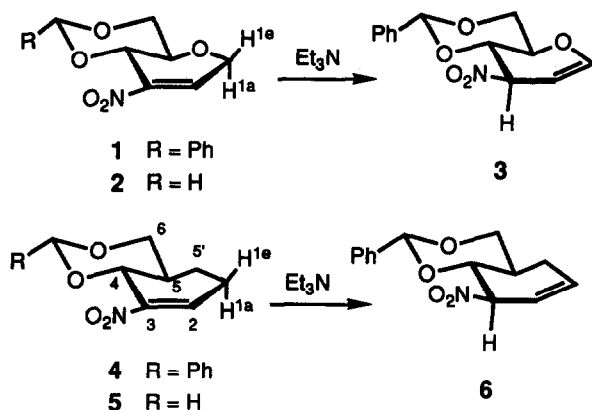
These results could be applied to the following elimination reactions. It is well known that oxidation of 1-methoxy-2-phenylselenocyclohexane **7** gave the allyl ether **8** in high yield, together with small amounts of the vinyl ether **9**.[8] However, if the hydrogen atom (H-1) could be fixed to occupy the antiperiplanar orientation to the O-Me bond, it has enough possibility, from the above results obtained in **1** and **4**, that the formation of vinyl ether predominates over allyl ether in the oxidative elimination of phenylseleninyl group.

7

8
ratio 95

9
: 5

10

11
ratio 1

12
: 2

13

11

12

ratio 10 : 1 (80°C)
ratio 33 : 1 (50°C)
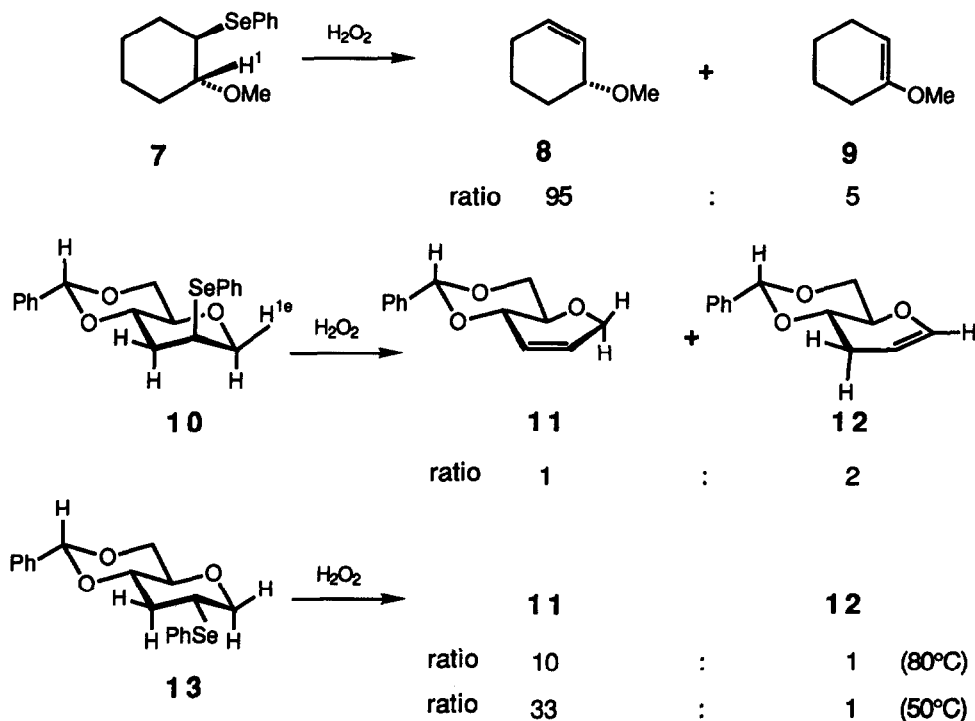
To confirm this hypothesis, we have prepared 2-phenylseleno-D-*arabino*-hexitol **10**, in which the anomeric, equatorial hydrogen atom (H-1e) satisfies this conformational requirement.

After oxidation of **10** [9] with aqueous hydrogen peroxide in THF,[11] the product extracted with ethyl acetate was concentrated, dissolved in 1,4-dioxane, and heated for 20 min at 80°C to give quantitatively a ca. 2 : 1 mixture of the 1-enitol (vinyl ether) **12** and 2-enitol (allyl ether) **11**. Of the two enitols, **12** should be more stable than **11**, because the former is less destabilized by the 4,6-*O*-benzylidene group than the latter and stabilized by conjugation of the double bond with the ring oxygen. In fact MM2 prime[12] and AM1 calculations revealed that methylene derivative of 1-enitol corresponding to **12** was more stable than that of 2-enitol by 15.7 and 10.2 kJ/mol, respectively. Therefore, it is possible that the predominant formation of **12** is caused by product stabilization rather than by the acidity of the hydrogen atoms. To exclude the possibility the 2-epimer **13** was subjected to a similar elimination reaction. As expected from the preceding examples[8] and previous work, [3] oxidative elimination of the *ribo*-isomer **13** afforded the 2-enitol **11** in high yield, together with small amount of the 1-enitol **12** as judged from ^{1}H-NMR spectroscopy (the ratios of **11** : **12** = 10 : 1 for 30 min at 80°C and 33 : 1 for 3 h at 50°C). When 3-axial deuterio derivative of **13** was similarly treated with hydrogen peroxide, the required reaction time increased from 30 min for nondeuterio derivative **13** to 1 h at 80°C (still remained small amounts of the starting material as judged from ^{1}H-NMR spectrum) and the product ratio of **11** to 3-deuterio derivative of **12** was changed to 2.7 : 1, suggesting that abstraction of hydrogen atom is a crucial step in these elimination reactions.

The present investigation shows that the acidity of α-hydrogen atom of ether is expectedly affected by the orientation of lone pairs on the oxygen atom and it is enough possible that the oxygen atom does not always suppress the acidity of the α-hydrogen atom but slightly enhances it in a suitable conformation.

References and Notes

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5 Compound **4** was prepared as follows. Ozonolysis of 3-hydroxymethylcyclopentene,[6] followed by nitromethane cyclization, and benzylidenation, gave the nitro compound, which was then converted into the nitroolefin **4** by conventional method.[7]
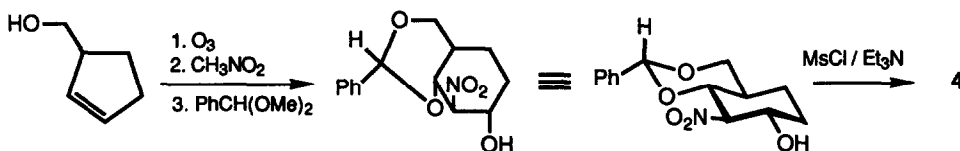
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9. Compounds **10** and **13** were synthesized according to the following Scheme started from 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enitol, which was prepared from tri-*O*-acetyl-D-glucal by a three-step procedure involving treatment with triethylsilane,[10] deacetylation, and benzylidenation.

10 **13**
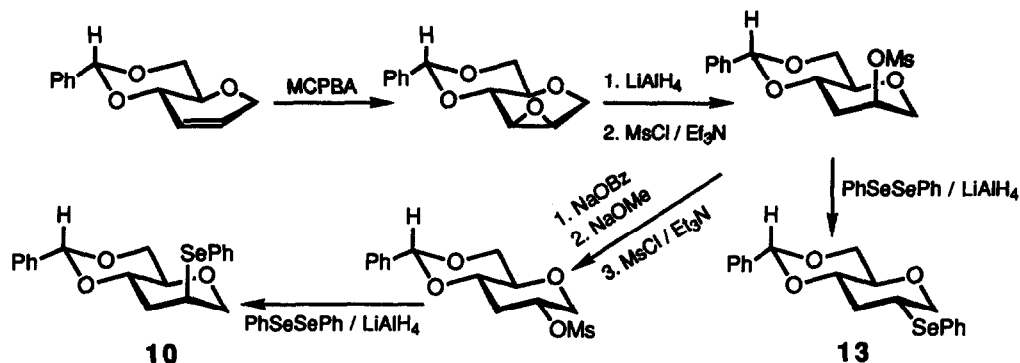
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13. All new compounds gave satisfactory elemental analyses. Compound **4**, mp 87.0 - 88.5 °C; I.R. 1510 cm^{-1} (NO_2); ^{1}H-NMR (CDCl$_3$) δ=2.47 (m, 2H, H-1qa, and H-1qe), 7.04 (bs, 1H, H-2), and 4.74 (ddt, 1H, $J_{2,4}$=1.5, $J_{1qa,4}$=$J_{1qe,4}$=2.0 Hz, $J_{4,5}$=8.3 Hz, H-4). Compound **6**, mp 80.5 - 82.0 °C; I.R. 1550 cm^{-1} (NO_2); ^{1}H-NMR (CDCl$_3$) δ=6.03 (ddt, $J_{1,2}$=9.9, $J_{1,5'qa}$=$J_{1,3}$=2.3, $J_{1,5'qe}$=4.6 Hz, 1H, H-1), 5.71 (bd, 1H, H-2), 5.29 (m, 1H, $J_{2,3}$=$J_{3,5'qa}$=$J_{3,5'qe}$=2.3, $J_{3,4}$=10.9 Hz, H-3), and 4.48 (dd, 1H, $J_{4,5}$=8.9 Hz, H-4). Compound **10**, m.p. 127-129°C, [α]$_D$ -10.0° (c 1.0, CHCl$_3$).; ^{1}H-NMR (C$_6$D$_6$) δ=3.42 (dd, 1H, $J_{1a,1e}$=12.4, $J_{1a,2}$=2.5 Hz, H-1a), 4.02 (ddd, 1H, $J_{1e,2}$=1.3 Hz, $J_{1e,3e}$=2.0 Hz, H-1e), 3.32 (m, 1H, $J_{2,3a}$=4.3, $J_{2,3e}$=2.0 Hz, H-2), 1.91 (ddd, 1H, $J_{3a,3e}$=13.2, $J_{3a,4}$=11.0 Hz, H-3a), and 2.47 (ddd, 1H, $J_{3e,4}$=4.3 Hz, H-3e). Compound **13**, m.p. 107-109°C, [α]$_D$ +22.0° (c 1.1, CHCl$_3$); ^{1}H-NMR (CDCl$_3$) δ=3.47 (t, 1H, $J_{1a,1e}$=$J_{1a,2}$=11.0 Hz, H-1a), 4.06 (ddd, 1H, $J_{1e,2}$=4.0 Hz, $J_{1e,3e}$=1.7 Hz, H-1e), 3.35 (m, 1H, $J_{2,3a}$=12.0, $J_{2,3e}$=4.0 Hz, H-2), 1.73 (q, 1H, $J_{3a,3e}$=$J_{3a,4}$=12.0 Hz, H-3a), and 2.52 (ddt, 1H, $J_{3e,4}$=4.0 Hz, H-3e).