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CHLORINATION OF 1,5-ANHYDRO-3-NITRO-1-ENITOL DERIVATIVE IN VARIOUS ETHERS AND ITS MNDO STUDY

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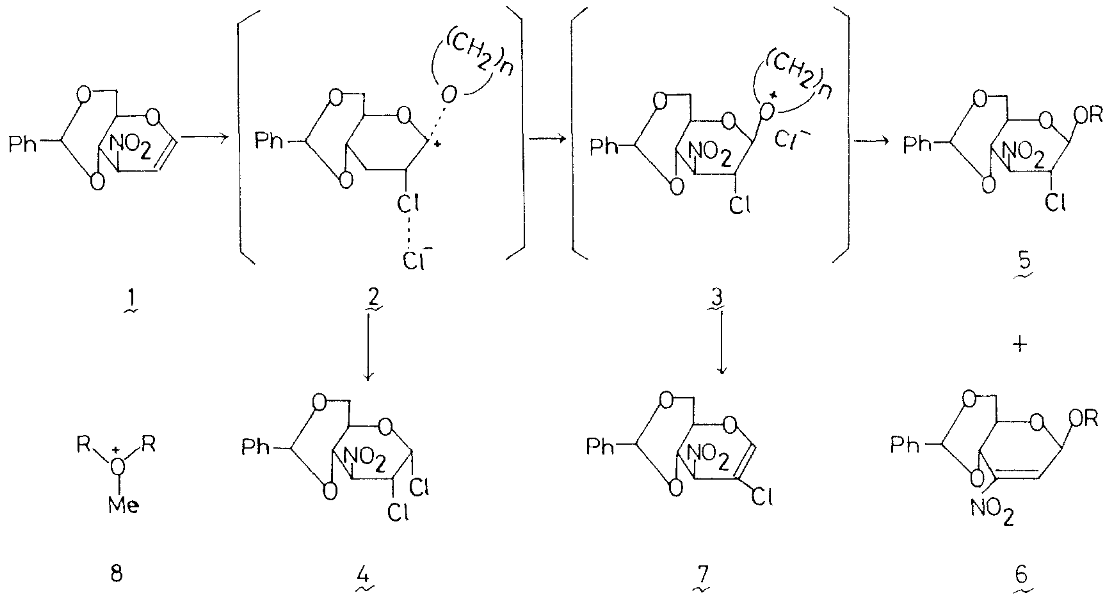
Abstract: Chlorination of 3-nitro-D-glucal derivative in ethylene oxide and in hexamethylene oxide is described and compared with those in p-dioxane, tetrahydrofuran, tetrahydropyran, trimethylene oxide, and diethyl ether; a fairly good correlation is observed between the yield of D-glucopyranosyl chloride (**4**) and methyl cation affinity.

Semiempirical molecular orbital procedure established by Dewar continues to serve as an economical and often surprisingly successful tool, for example, for the study of cations.[1] To our knowledge, however, this procedure has hardly been applied in the sugar realm.[2] In this communication we wish to report an example, showing the usefulness of MNDO method[3] for interpreting a reaction by the use of a suitable model even in the field of carbohydrate chemistry.

Recently we have reported that chlorination of 3-nitro-D-glucal **1** in various ethers afforded the α-D-glucopyranosyl chloride **4** and/or ω-chloroalkyl β-D-hexopyranosides(**5** and **6**)[4], in which the ratios of the former to the latter were strongly affected by the ether used.[5] For example, in p-dioxane compound **4** was isolated in 92% yield, whereas in tetrahydrofuran (THF) a mixture of **5a** and **6a** in 93% yield (Table, Entries 1 and 5).

It is of interest to clarify why the reaction way depends on the ether employed as a solvent. For this purpose, it is desirable to improve the total yields. Therefore, we reinvestigated chlorination of **1** in trimethylene oxide and isolated 3-(3-choloropropoxy)propyl β-D-glucopyranoside **5c** (10.4%), mp 103-104°C, $[\alpha]_D^{30}$ -33.2° (c 0.94, acetone) besides **5b** (78%)(Entry 7). In diethyl ether and tetrahydropyran(THP), 2-chloro-1-enitol **7**, mp 102-104°C, $[\alpha]_D^{15}$ -31.6° (c 1.14, acetone) was isolated in 12.4 and 7.6% yields besides the β-D-glucopyranosides **5d** and **5e**, respectively (Entries 2 and 4).

As proposed in halogenation of simple alkenes[6] and α, β-unsaturated carbonyl derivatives,[7] compound **5** should be formed *via* the oxonium intermediate **3**. The basicity of ether employed, therefore, seems to be important for product determination. Although the basicity order of ether sometimes contradicts by a method[8] used and the basicity of all ethers employed here is not determined by the same method, it might be valid that oxirane is less basic than p-dioxane according to the papers of Searles[9] and Kagiya.[10] We expected, therefore, that chlorination of **1** in ethylene oxide gave dichloro-derivative **4** exclusively. The reaction, however, almost exclusively gave the β-D-glucopyranosides **5f**,



1 **2** **3** **5** **6** **8** **4** **7**

a; R=$(CH_2)_3CH_2Cl$, b; R=$(CH_2)_2CH_2Cl$, c; R=$(CH_2)_2CH_2O(CH_2)_2CH_2Cl$, d; R=Et,
e; R=$(CH_2)_4CH_2Cl$, f; R=CH_2CH_2Cl, g; R=$CH_2CH_2OCH_2CH_2Cl$,
h; R=$CH_2CH_2OCH_2CH_2OCH_2CH_2Cl$, i; R=$(CH_2)_5CH_2Cl$,

mp 149-150°C, $[\alpha]_D^{15}$ -31.1° (*c* 1.08, acetone) and **5g**, syrup, $[\alpha]_D^{28}$ -41.6° (*c* 1.26, acetone), in high yields(Entry 6); the latter should be formed by the attack of ethylene oxide to **3**, followed by ring opening through the attack of a chloride ion.

Since ethylene oxide and trimethylene oxide exclusively gave the β-D-glucopyranosides **5**, more strained the oxonium ion **3**, the larger the amounts of **5**. Because the parameter of a trivalent oxygen atom is not given by molecular mechanics, strain energies of ethers instead of the oxonium ions are calculated by MM2 method[3](Table). Since the strain energy of hexamethylene oxide is larger than that of THF, smaller amount of dichloro derivative **4** should be formed in the former than in the latter. Chlorination in hexamethylene oxide, therefore, was investigated, but the results were inconsistent with the prediction (Entry 3 vs. 5).

The energy levels of the highest occupied molecular orbitals of the ethers calculated by MNDO method with optimization of all independent bond length, bond angles, and dihedral angles (full optimization), can not account for the above experimental results.

Empirical parameters measured by spectroscopy also do not give a rationale for the present results.

Difference in heat of formation ΔH_f between the ether and its oxonium intermediate **3** was next considered as a potential index to relative stability of **3**. Intermediate **3**, however, seems to be too large molecule for the calculation; we chose the methyl oxonium ion **8** as a simplified model compound of **3**. From the equation (1), we derive ΔH_f,[11] in which $H^{+}_{ROR(Me)}$, H_{ROR}, and H^{+}_{Me}[12] are calculated by MNDO method with full optimization (Table).

$$ROR + Me^{+} \longrightarrow ROR(Me) \qquad \Delta H_f = -[\,H^{+}_{ROR(Me)} - H_{ROR} - H^{+}_{Me}\,] \qquad (1)$$

Considering such a simple model and experimental errors, we could state that the yields of **4** or total yields of **5**+**6**+**7** surprisingly well correlate with ΔH_f.

Most reasonable reaction mechanism is likely to be as follows. Chlorine attacks the double bond of **1** to form an ion pair **2**, of which cation might be stabilized by interacting with an ether. Conversion of **2** into the oxonium ion **3** should be a crucial step for product distribution, i.e., **4** vs. **5**+**6**+**7**. Facility of conversion of **2** into **3** depends on the stability of **3**, i.e., ΔH_f ; in an ether having a large ΔH_f such as trimethylene oxide, **3** would readily form before collapse of **2** into the dichloro-derivative **4**. In **3**, a chloride ion attacks the oxonium ring or abstracts the hydrogen atom at C-2 to give the β-D-glucopyranosides **5** or the 2-chloro-1-enitol **7**, respectively. However, the attack by the chloride ion on the anomeric carbon atom of **3** affording **4** is not likely to be the case by considering steric hindrance and the fairly good correlation between the yield of **4** and ΔH_f.

Thus the present work demonstrates the versatility of MNDO method for interpreting a reaction. Furthermore it is noteworthy that molecular orbital calculation provides us a clue for discussing relative stability of methyloxonium ions **8** which seems not to be determined experimentally with ease.

TABLE

Entry	Ether[a]	Yield (%)				Strain Energy[d]	ΔH_f[e]
		4	**5+6**	**7**	total	kcal/mol	kcal/mol
1	p-Dioxan	92	-	-	92	7.3	44.3
2	Et_2O	45	16.3	7.6	68.9	4.0	48.2
3	HO	14	49[b]	5.7	68.7	15.7	48.7
4	THP	20	58	12.4	90.4	7.6	48.8
5	THF	4.6	93	-	97.4	10.6	51.5
6	EO	-	82.5[c]	-	82.5[c]	-	52.8
7	TO	-	88	-	88	28.8	56.0

[a] HO, EO, and TO stand for hexamethylene oxide, ethylene oxide, and trimethylene oxide, respectively. [b] Compounds **5i**, mp 118-119°C, $[\alpha]^{28}_{D}$ -38.6°(c 1.03, acetone) and **6i**, mp 65.5-67.0°C, $[\alpha]^{28}_{D}$ -122° (c 1.0, acetone). [c] Isolated as crystals in 42.5% (**5f** + **5g**), besides these products, compound **5h** which is formed by participation of three molecules of ethylene oxide might be formed, but its purification have not been succeeded. [d] Calculated by MM2. [e] Calculated by MNDO.

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References and Notes

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