EPOXIDE MIGRATION AND PSEUDO-EPOXIDE MIGRATION OF 1,6:2,3- AND 1,6:3,4-DIANHYDRO-β-D-HEXOPYRANOSES. SYNTHESIS OF SOME DEOXY HALO DERIVATIVES OF 1,6-ANHYDRO-β-D-HEXOPYRANOSES

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Dedicated to Professor Antonín Holý on the occasion of his 70th birthday.

Epoxide or pseudo-epoxide migration of 1,6:2,3-dianhydro- and 1,6:3,4-dianhydro-β-D-hexopyranoses was effected by treatment with aqueous sodium hydroxide or sodium iodide in acetone to give equilibrium mixtures. Various iodo derivatives of 1,6-anhydro-β-D-hexopyranoses were prepared as potential intermediates for pseudo-epoxide migration. NMR was used for following the reaction mechanism of epoxide and pseudo-epoxide migrations and analysis of reaction mixtures. Experimental data were compared with DFT calculations. Chair–boat equilibration of 1,6-anhydro-3-deoxy-3-halo-β-D-glucopyranoses was discussed.
Keywords: Carbohydrates; Anhydro sugars; Epoxides; Epoxide migration; Pseudo-epoxide migration; NMR spectroscopy; DFT calculations; Conformation analysis.

Epoxide migration[1], also called Payne rearrangement[2,3] is a well-known phenomenon related to α-hydroxy epoxides which, under favorable steric conditions, undergo isomerization in alkaline solution at room temperature to give an equilibrium mixture of two isomeric α-hydroxy epoxides. This rearrangement was first observed by Newth[1] and was later studied in detail[4,5] with 1,6:2,3-dianhydro-β-D-mannopyranose[4] (**1**) and 1,6:3,4-dianhydro-β-D-galactopyranose[5] (**2**) which are converted into 1,6:3,4-dianhydro-β-D-altropyranose (**3**) and 1,6:2,3-dianhydro-β-D-gulopyranose (**4**), respectively (Schemes 1 and 2). Several authors investigated also migration

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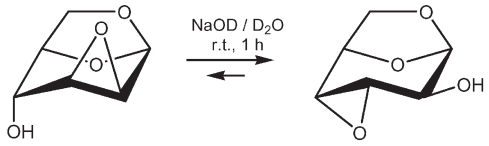
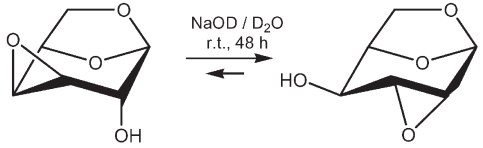
of other sugar epoxides[6–12] and inositol epoxides[13] (see also review[1c]) since these epoxides are readily available, and therefore valuable starting material for organic synthesis.



1 (1.5%) **3** (98.5%)

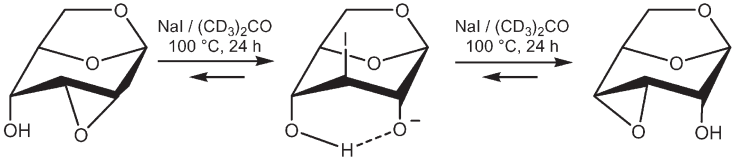
SCHEME 1



2 (17%) **4** (83%)

SCHEME 2

Another type of isomerization, so called pseudo-epoxide migration[1c], was first mentioned by Elbert et al.[14] with 1,6:2,3-dianhydro-β-D-allopyranose (**5**) and 1,6:3,4-dianhydro-β-D-allopyranose (**6**). This reaction was catalyzed by the action of sodium iodide in acetone at elevated temperature (Scheme 3). However, detailed experimental data are not available. As predicted, base-catalyzed epoxide-migration conditions are not effective in pseudo-epoxide migration (see below).

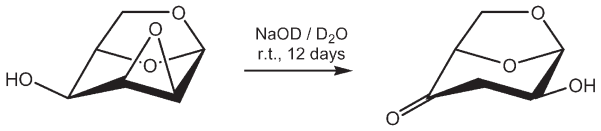


5 (26%) **6** (74%)

SCHEME 3

We present here our study of epoxide and pseudo-epoxide migration of all eight possible 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses using mainly NMR spectroscopy for examining the reaction course in more detail. Starting dianhydrohexoses **1**–**8** were prepared from 1,6-anhydro-β-D-gluco-pyranose according to the following literature: D-manno-[4,15] (**1**), D-altro-[4,15] (**3**), D-galacto-[5,16] (**2**), D-gulo-[5] (**4**), D-allo-[17] (**5**, **6**), D-talo-[18,19] (**7**, **8**).

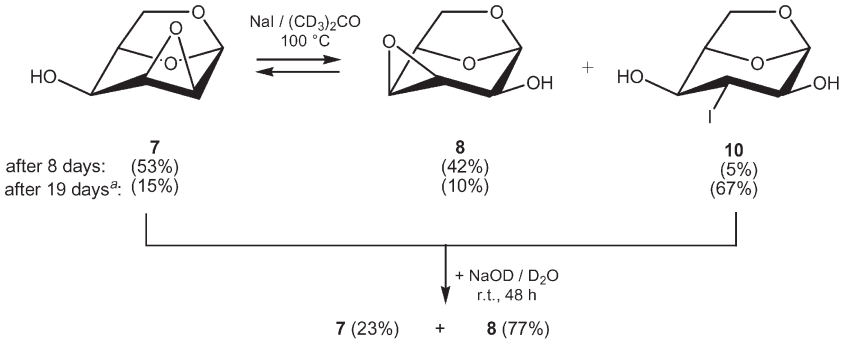
Epoxide migration of dianhydrohexoses **1**–**4** was investigated at ambient temperature (20–25 °C) in D_2O solutions containing NaOD. Equilibria were achieved starting from all pure isomers within several hours (Schemes 1 and 2). As expected, epoxides **5**, **6**, and **8** did not show any change within 24 h under the same reaction conditions. Conversely, when epoxide **7** was subjected to the same conditions, a slow steadily increasing conversion to the known[20] 1,6-anhydro-3-deoxy-β-D-*threo*-hexopyranos-4-ulose (**9**) was observed (Scheme 4).



7 **9**

SCHEME 4

Pseudo-epoxide migration of *allo*-epoxides **5** and **6** was performed at 100 °C in acetone or hexadeuterated acetone solution of sodium iodide to give within 24 h an equilibrium mixture containing epoxides **5** and **6** in the 26:74 ratio (Scheme 3). It is worth mentioning that the pseudo-epoxide migration also occurs with 1,6:2,3- (**7**) and 1,6:3,4-dianhydro-β-D-talopyranose (**8**) (Scheme 5). Nevertheless, the rate of this reaction is markedly slower compared to the reaction rate of *allo*-epoxides **5** and **6**, and a significant amount of 1,6-anhydro-3-deoxy-3-iodo-β-D-idopyranose (**10**) is continually formed. Thus, an equilibrium mixture was not reached and only the composition of the reaction mixture indicates the trend of the isomerisation. The treatment of **10** with aqueous NaOD gave only small amounts

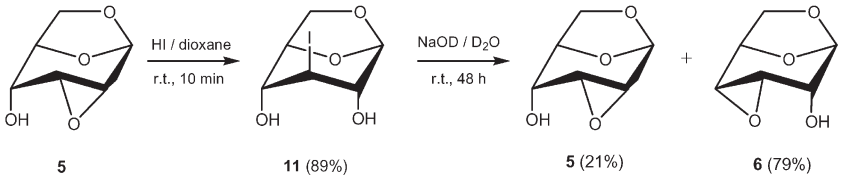


[a] Formation of two unidentified products (8% total) was observed by NMR.

SCHEME 5

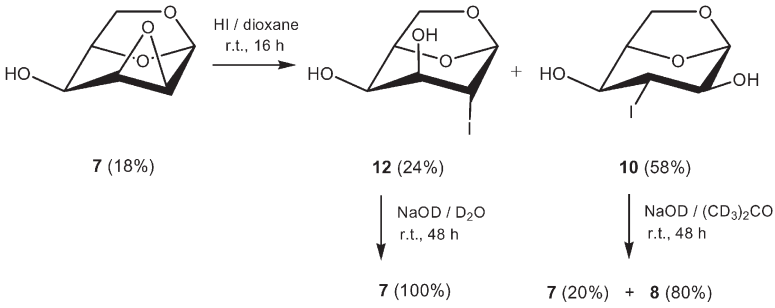
of *talo*-epoxides **7** and **8**. However, when water was replaced with acetone, a rapid reaction took place and epoxides **7** and **8** were formed in the 20:80 ratio.

The epoxide-migration mechanism of epoxides **1**–**4** is understood as an intramolecular SN2 reaction of the deprotonated α-hydroxy group attacking the adjacent oxirane ring. Possible cooperation of Na^+ in the cleavage of the oxirane ring by I^- in acetone cannot be excluded. This follows from the fact that the pseudo-epoxide migration proceeded slower in an aqueous or dimethylformamide solution. On the other hand, a plausible mechanism of the pseudo-epoxide migration of epoxides **5**–**8** is a two-step process involving intermediates, potentially deprotonated deoxy iodo derivatives of the corresponding 1,6-anhydro-β-D-hexopyranoses.



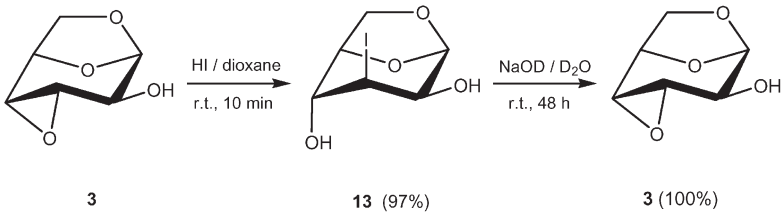
SCHEME 6

In order to identify these intermediates, we prepared 1,6-anhydro-3-deoxy-3-iodo-β-D-glucopyranose (**11**) by oxirane-ring cleavage in 1,6:2,3-dianhydro-β-D-allopyranose (**5**) with hydrogen iodide in dioxane at room temperature (Scheme 6). In a similar way, 1,6-anhydro-2-deoxy-2-iodo-β-D-galactopyranose (**12**) and iodo derivative **10** were formed from *talo*-epoxide **7**, but the iodo derivative **12** was not isolated (Scheme 7). 1,6-Anhydro-3-deoxy-3-iodo-β-D-mannopyranose (**13**) was prepared from



SCHEME 7

altro-epoxide **3** (Scheme 8). Iodo derivatives **10**–**13** were converted into the corresponding epoxides (1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses) by treatment with NaOH in aqueous or acetone solution (Schemes 6–8).



3 **13** (97%) **3** (100%)

SCHEME 8

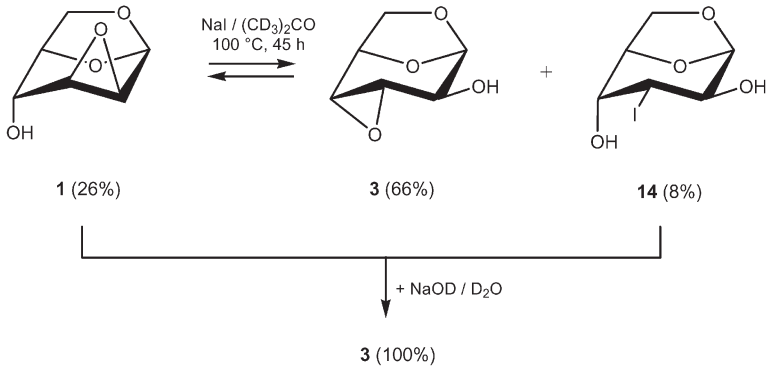
Treatment of the iodo derivative **11** with a dilute aqueous sodium hydroxide solution at room temperature resulted in the formation of a mixture of both *allo*-epoxides **5** and **6** in the 21:79 ratio, respectively (Scheme 6). This is in acceptable agreement with the result of the pseudo-epoxide migration of *allo*-epoxides **5** and **6** by the action of sodium iodide (Scheme 3). Even though the presence of **11** in the reaction mixture was not observed during the isomerization, this is not out of keeping with the suggested mechanism involving the deprotonated form of the iodo derivative **11** as a reaction intermediate.

A similar mixture of *allo*-epoxides **5** and **6** is formed[21] by the treatment of 1,6-anhydro-3-*O*-tosyl-β-D-glucopyranose and its 2,4-dibenzoate[17] with sodium methoxide, or by deamination of 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose with nitrous acid[14].

In connection with the above described pseudo-epoxide migration of *allo*-epoxides **5** and **6** controlled by the sodium iodide catalysis, we were interested in determining whether this catalyst was also effective in the epoxide migration. Thus, we treated *manno*-epoxide **1** with sodium iodide in acetone under the same reaction conditions. A typical product of the epoxide migration, *altro*-epoxide **3**, was found in the reaction mixture together with the starting *manno*-epoxide **1** and a small amount of 3-deoxy-3-iodo-β-D-altropyranose (**14**) (Scheme 9). The formation of *altro*-epoxide **3** may be rationalized by the effect of base catalysis of the iodide anion in an aprotic solvent such as acetone. However, a similar reaction with *gulo*-epoxide **4** did not proceed.

The above mentioned different behavior of *allo*- and *talo*-epoxides **5**, **6** and **7**, **8**, respectively, in the reaction with an acetone solution of sodium

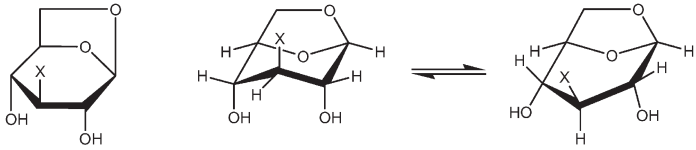
iodide can possibly be accounted for on the basis of conformational considerations. When the oxirane-ring cleavage takes place according to the Fürst–Plattner rules (*trans*-diaxial oxirane-ring cleavage), the resulting iodo derivatives (and their corresponding oxide ions) are readily formed. These intermediates are also prone to regenerate promptly starting epoxides or, if it is sterically favored, the corresponding isomeric epoxides. This is the case of *allo*-epoxides **5** and **6** where the attacking iodide ion opens the oxirane ring at C-3 to give oxide ion derived from iodo derivative **11** (Scheme 3). An alternative attack of the iodide ion at positions C-2 or C-4 is sterically hindered by the 1,6-anhydride bond, and is conformationally disfavored. On the other hand, *talo*-epoxides **7** and **8** are preferentially attacked at C-2 or C-4 to give diaxial 2-iodo- and 4-iodo derivatives, respectively. However, both these iodo derivatives are expected to give the starting epoxides. The approach of the iodide ion to position C-3 in *talo*-epoxides **7** and **8** is not hindered; nevertheless, the diequatorial cleavage of the oxirane ring is expectably slow and the resulting 3-iodo derivative **10** is relatively stable to be identified in the reaction mixture (Scheme 5). The formation of 1,6:2,3- and 1,6:3,4-dianhydro-β-D-talopyranoses **7** and **8** from 3-iodo derivative **10** requires an antiplanar orientation of the oxide ion and leaving iodide group which is realised in $B_{O,3}$ conformation. The passing-by effect plays an important role in this interconversion and consequently, disfavors the accomplishment of the reaction[7].



SCHEME 9

The structure of iodo derivatives **10** and **14** (see Schemes 5–9) found in the reaction mixtures was proved by NMR measurements, see below, and by converting each among them into the corresponding epoxides **7**, **8** and **1**, **3**, respectively. In addition to iodo derivative **11**, the corresponding chloro

and bromo derivatives **15** and **16** were prepared by treatment of *allo*-epoxide **5** with hydrogen chloride and hydrogen bromide, respectively. Their chair–boat populations were calculated and compared with fluoro derivative **17**.



11 X = I
15 X = Cl
16 X = Br
17 X = F

$^1C_4$ $B_{O,3}$

NMR SPECTRA AND THEORETICAL CALCULATIONS

NMR Characterization of Prepared Iodo Derivatives

The structures of the prepared iodo derivatives **10**–**14** were confirmed by ^{1}H and ^{13}C NMR spectra (Tables I–III). The presence and position of iodine atom is not well indicated in ^{1}H NMR spectra but is clearly manifested by characteristic upfield shifts of carbon atom bearing iodine (δ 22–38). Vicinal proton coupling *J*(2,3) in **12** and **14**, *J*(3,4) in **13** and both *J*(2,3) and *J*(3,4) in **10** and **11** are sensitive to the populations of chair and boat forms of pyranose ring. Using of the observed *J*-values and the generalized Karplus equation[22] shows the high preference (80–97%) of a chair form in all prepared iodo derivatives **10**–**14**.

Conversion of Iodo Derivatives to Epoxides in Alkaline Water Solution

About 5 mg of an iodo derivative **10**–**14** was dissolved in D_2O (0.5 ml) and its ^{1}H NMR spectrum recorded. The chemical shifts and coupling constants are summarized in Tables I and II. Then one drop of 10% NaOD in D_2O was added and ^{1}H NMR spectra were recorded after 48 h standing at room temperature. In the case of compound **10** the conversion was achieved only in acetone-d_6 solution with NaOD. The structure and relative amounts of the present components were determined by detailed analysis of NMR spectra. Results are discussed in theoretical part and summarized in Schemes 5–9.

TABLE I
^{1}H NMR chemical shifts of compounds **1**–**16**

Compd	Solvent	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	OH
1	D_2O	5.83	3.64	3.24	4.06	4.52	3.74	3.74	–
	$(CD_3)_2CO$	5.67	3.44	3.085	3.93	4.43	3.64	3.60	
2	D_2O	5.29	3.83	3.24	3.82	5.03	3.98	3.55	–
	$(CD_3)_2CO$	5.11	3.64	3.035	3.63	4.895	3.87	3.43	2-OH: 4.60
3	D_2O	5.365	3.90	3.12	3.45	4.87	4.17	3.885	–
	$(CD_3)_2CO$	5.21	3.67	2.88	3.20	4.71	4.07	3.78	2-OH: 4.04
4	D_2O	5.70	3.26	3.21	4.25	4.51	4.16	3.85	–
	$(CD_3)_2CO$	5.51	2.95	3.01	4.175	4.41	4.14	3.68	4-OH: 4.90
5	D_2O	5.71	3.285	3.50	3.90	4.47	3.805	3.92	–
	$(CD_3)_2CO$	5.61	3.16	3.45	3.93	4.46	3.805	3.87	
6	D_2O	5.255	3.74	3.43	3.47	4.86	4.09	3.78	–
	$(CD_3)_2CO$	5.18	3.68	3.35	3.43	4.81	4.06	3.73	
7	D_2O	5.81	3.76	3.45	4.35	4.53	3.99	3.63	–
	$(CD_3)_2CO$	5.625	3.535	3.24	4.24	4.38	4.05	3.465	
8	D_2O	5.35	3.96	3.43	3.94	5.01	3.96	3.58	–
	$(CD_3)_2CO$	5.26	3.87	3.33	3.86	4.95	3.94	3.48	
9	$CDCl_3$	5.59	4.16	2.95	–	4.50	3.97	3.94	2-OH: 2.07
				2.31					
10	$CDCl_3$	5.24	3.83	3.80	4.13	4.41	4.06	3.75	2-OH: 2.08; 4-OH:2.36
	D_2O	5.27	3.88	3.77	4.14	4.485	4.055	3.76	–
11	$CDCl_3$	5.48	4.07	4.04	4.12	4.58	4.48	3.85	2-OH: 2.90; 4-OH:2.90
	D_2O	5.47	4.035	3.87	4.17	4.65	4.28	3.81	–
	$(CD_3)_2CO$	5.37	4.05	4.08	4.19	4.62	4.37	3.72	
12	$CDCl_3$	5.61	4.25	4.29	4.37	4.48	4.36	3.73	3-OH: 2.94; 4-OH:2.99
	D_2O	5.70	4.26	4.38	4.41	4.53	4.47	3.74	–
13	$CDCl_3$	5.43	3.15	4.55	4.38	4.53	4.51	3.87	2-OH: 2.32; 4-OH:2.80
	D_2O	5.45	3.33	4.455	4.54	4.63	4.58	3.86	–
14	$(CD_3)_2CO$	5.35	3.88	4.36	3.97	4.61	3.915	3.73	
15	$(CD_3)_2CO$	5.32	3.81	3.63	3.81	4.55	4.09	3.70	
16	$(CD_3)_2CO$	5.32	3.77	3.84	3.94	4.55	4.13	3.70	

TABLE II
^{1}H NMR coupling constants of compounds **1**–**16**

Compd	Solvent	6en, 6ex	1,2	2,3	3,4	4,5	5,6en	5,6ex	1,3	1,5	1,6en	1,6ex	2,4	3,5	4,6ex
1[a]	D_2O	[a]	3.2	3.9	0.8	1.3	[i]	[i]			0.6	0.6	0.85	1.6	
	$(CD_3)_2CO$	7.1	3.2	3.8	0.7	1.2	2.15	6.6			0.5	0.4	0.9	1.5	
2[b]	D_2O	7.0	1.1	0.7	4.15	5.0	0.7	4.8	1.6		0.5	0.5	0.9	0.7	
	$(CD_3)_2CO$	6.4	1.0	≤0.5	4.3	5.0	0.8	4.9	1.5		0.5	0.5	0.9	≤0.5	
3[c]	D_2O	7.8	3.05	0	4.1	1.7	0.8	4.6	2.3	0.6		<0.3	0.9	0.7	
	$(CD_3)_2CO$	7.4	3.1	0	4.0	1.6	0.7	4.5	2.3	0.55	≤0.5		1.0	0.7	
4	D_2O	8.5	1.2	4.0	0	5.25	2.1	6.3	0.7	0.4	0.65	<0.3	1.0	2.1	0.8
	$(CD_3)_2CO$	7.9	1.0	3.9	0	5.3	2.1	6.2	0.6	0.4	0.6	~0.3	1.0	2.1	0.8
5	D_2O	8.45	1.3	4.15	4.9	1.0	2.3	6.8	0.7		0.55	0.45		2.0	
	$(CD_3)_2CO$	8.2	1.3	4.0	4.8	1.1	2.4	6.7	0.75		0.5	0.5		1.9	
6	D_2O	7.7	0.9	4.5	4.3	1.8	0.7	4.6	2.1	0.6	<0.3	<0.3		0.8	
	$(CD_3)_2CO$	7.5	0.7	4.8	4.1	1.7	0.7	4.5	2.1		~0.4	~0.4		0.75	0.4
7	D_2O	7.6	3.0	4.25	3.1	6.2	1.65	6.2			0.5	0.5		1.0	0.6
	$(CD_3)_2CO$	6.9	3.0	4.1	3.0	6.0	1.7	6.2			0.6	0.6		1.0	0.6
8	D_2O	7.0	3.8	3.5	4.5	4.7	0.75	4.9	1.2		0.5	0.6			
	$(CD_3)_2CO$	6.6	3.8	3.5	4.35	4.7	0.7	4.7	1.2			0.6			
9[d]	$CDCl_3$	8.4	2.8	7.0	–	–	1.5	4.9	1.0	0.4				1.6	
				7.7											
10[e]	$CDCl_3$	8.1	1.5	9.0	9.0	4.1	0.5	5.0							0.8
	D_2O	8.3	1.8	9.7	9.95	4.1	1.0	5.0				0.3			1.0
11[f]	$CDCl_3$	8.0	1.8	2.4	2.6	1.9	0.9	5.4	1.2	0.3	0.3	0.5	1.0	1.6	
	D_2O	8.1	1.2	4.6	4.6	1.5	1.1	5.55	0.9		0.3	0.5		1.0	
	$(CD_3)_2SCO$	7.9	1.6	3.3	3.3	1.75	1.0	5.4	1.0			0.5	0.8	1.3	
12[g]	$CDCl_3$	7.8	1.4	1.4	5.0	4.2	0.7	4.8	1.3	0.4		0.4	0.6	1.2	1.1
	D_2O	7.7	1.5	1.3	4.8	4.0	0.7	5.2	1.2		0.4	0.5	0.5	1.3	1.2
13[h]	$CDCl_3$	8.1	2.2	6.1	2.4	1.9	0.8	5.4	1.0	0.3		0.4	0.9	1.6	
	D_2O	8.3	1.95	6.35	1.9	1.8	0.9	5.6	1.0			0.3	0.9	1.5	
14	$(CD_3)_2CO$	8.1	1.6	10.3	4.1	2.5	0.9	5.4							
15	$(CD_3)_2CO$	7.7	1.0	4.0	4.2	1.6	1.0	5.5	0.8			0.3	0.8	1.1	
16	$(CD_3)_2CO$	7.6	1.2	4.65	4.8	1.45	1.0	5.4	0.8			0.5	0.5	0.9	

[a] J(1,4) = 0.7. [b] J(2,OH) = 6.6. [c] J(2,OH) = 9.3. [d] J(2,OH) = 9.9, J(3eq,3ax) = 17.2. [e] J(2,OH) = 7.3, J(4,OH) = 3.2. [f] J(1,4) = 0.6, J(2,5) = 0.5. [g] J(3,OH) = 7.5, J(4,OH) = 8.8, J(2,5) = 0.7. [h] J(2,OH) = 11.4, J(4,OH) = 9.0, J(1,4) = 0.5. [i] Coupling constants could not be resolved.

Epoxide Migration in Alkaline Water Solution Followed by ^1H NMR

About 5 mg of an epoxide **1**–**8** was dissolved in D_2O (0.5 ml) and its ^1H NMR spectrum recorded. Proton chemical shifts and coupling constants are summarized in Tables I and II. Then 1 drop of 10% NaOD in D_2O was added and ^1H NMR spectra were recorded repeatedly at defined time intervals during 3 days standing at room temperature. The structure and relative amounts of present components were determined from the detailed analysis of NMR spectra. Results are discussed in theoretical part and summarized in Schemes 1, 2, and 4.

Reaction of Epoxides in Acetone with Sodium Iodide (Pseudo-Epoxide Migration)

The each epoxide **1**, **4**, **5**, **7**, and **8** was dissolved in acetone, freshly powdered NaI (1.5–1.8 eq.) was added and heated to 100 °C in sealed ampule. After 24 h heating the NMR spectrum was recorded and the structure and relative amounts of present components were determined from the detailed analysis of NMR spectrum. In some cases a much longer heating was used. To the reaction mixtures of epoxide **1**, **7**, and **8**, where some amount of iodo derivative was present, 1 drop of 30% NaOD in D_2O was added and NMR spectrum recorded. Results are discussed in theoretical part and summarized in Schemes 5–9.

TABLE III
^{13}C NMR chemical shifts of compounds **9**–**16**

Compd	Solvent	C-1	C-2	C-3	C-4	C-5	C-6
2	$(CD_3)_2CO$	101.82	66.68	50.60	53.34	72.59	65.01
3	$(CD_3)_2CO$	100.38	66.62	51.81	50.75	70.60	57.80
9	$CDCl_3$	101.33	69.56	43.15	202.52	77.93	66.77
10	$CDCl_3$	101.00	76.96	38.05	73.96	75.07	64.79
11	$CDCl_3$	101.90	73.78	22.77	73.31	77.07	66.38
	$(CD_3)_2CO$	103.82	74.93	26.64	74.18	79.11	67.77
12	$CDCl_3$	102.03	27.38	73.74	62.73	75.50	65.21
13	$CDCl_3$	101.66	65.43	34.74	74.73	76.93	67.00
14	$(CD_3)_2CO$	103.40	74.20	36.85	72.19	77.19	66.64
15	$(CD_3)_2CO$	103.68	74.32	62.27	74.03	78.28	66.93
16	$(CD_3)_2CO$	103.88	75.14	53.95	74.62	78.66	67.32

Theoretical Calculations of Isomeric Epoxides Population in Equilibrium Mixtures

The populations of isomeric epoxides in equilibrium mixtures, determined from NMR spectra, are summarized in Table IV. They should correspond to the free energy difference ΔG between pair of epoxides. Therefore we have tried to estimate those populations using theoretical calculations of the energy of individual epoxides **1**–**8** by: (1) simple molecular mechanics (MM+ force field)[23] and (2) ab initio calculation (DFT method with B3LYP/6-31** basis set)[24]. The geometry of each staggered OH-rotamer was obtained by energy minimization. The values of the lowest energy OH-rotamers are in bold and those which can form intramolecular H-bonds are underlined. The search for energy minima for OH staggered rotamers using DFT method led in some cases to the result that the expected rotamer was not found and the optimization ended with the geometry corresponding to another rotamer (see arrows in Table IV). The vibration and thermochemical analysis was made for all optimized rotamer structures that allowed to obtain values of Gibbs energy *G*. For calculation of the theoretical population of isomeric epoxide pairs, three attempts were used: (A) energy difference between the calculated lowest energy rotamers, (B) all calculated staggered OH-rotamers taken with populations calculated from their relative energy values, (C) energy differences between *trans*-OH rotamers (not able to form intramolecular H-bonds) were used.

(1) MM+ results: All three attempts (A–C) provided very similar results and correct prevailing epoxide in pairs **1**⇔**3** and **2**⇔**4**, but the opposite prevailing rotamer than NMR experiment in pairs **5**⇔**6** and **7**⇔**8** (see Table IV). It seems obvious that simple MM+ force-field fails in this type of application. Therefore we have turned our attention to higher level of theoretical calculations based on the DFT method.

(2) DFT results: The approaches (A) and (B) show rather similar results and give right prevailing epoxide in pairs **1**⇔**3**, **5**⇔**6** and **7**⇔**8** but the wrong one in **2**⇔**4**. It is only attempt (C) based on comparison of *trans*-OH-rotamers that predicts right prevailing epoxide in all four pairs (see Table IV). This could be explained by the fact that solvation in a water solution destabilizes the OH-rotamers which can form intramolecular H-bonds and consequently, *trans*-OH-rotamers (most easily accessible to form intermolecular H-bonds with water) are most stable.

TABLE IV

The calculated values of the energy for OH-rotamers and equilibrium populations of isomeric epoxide pairs **1**⇔**3**, **2**⇔**4**, **5**⇔**6** and **7**⇔**8**

Compd	Energy, kcal/mol (MM+)[a]			Gibbs energy, Hartree (DFT, B3LYP/6-31g**)[a]			Equilibrium population, %						
	OH (g_+)	OH (g_-)	OH (t)	OH (g_+)	OH (g_-)	OH (t)	Calc. MM+			Calc. DFT			Obs.
							A	B	C	A	B	C	D
1	**167.088**	167.294	167.159	–534.161630	**–534.166011**	–534.161470	27	27	26	0	0	1	**1.5**
3	**166.504**	166.719	166.534	–534.165140	**–534.171119**	–534.166076	73	73	74	100	100	99	**98.5**
2	168.038	**167.686**	167.798	**–534.168413**	–534.164789	–534.164922	7	8	7	78	69	15	**17**
4	167.038	**166.162**	166.271	–534.165339	**–534.167230**	–534.166656	93	92	93	22	31	85	**83**
5	**165.784**	165.986	165.843	→	**–534.170598**	–534.161334	67	70	69	17	17	8	**26**
6	166.591	**166.210**	166.328	**–534.172103**	←	–534.163649	33	30	31	83	83	92	**74**
7	168.559	**167.791**	167.917	**–534.165614**	–534.163138	–534.161894	66	60	62	1	1	46	**20**[b]
8	**168.177**	168.369	168.219	–534.161716	**–534.170322**	–534.162035	34	40	38	99	99	54	**80**[b]

[a] The values for the lowest energy rotamers are typed in bold and those which can form intramolecular H-bonds are underlined. [b] Composition of the reaction mixture could not be determined by the same way as for other epoxides (see Scheme 5). The ratio of isomeric epoxides was obtained from the reaction of iodo derivative **10** with NaOD in acetone (see Scheme 7).

A, Calculated from the energy difference values of lowest energy OH-rotamers; B, calculated from the energy difference values and populations of all staggered OH-rotamers; C, calculated from the energy difference values of *trans*-rotamers; D, determined from ^{1}H NMR spectra of equilibrium mixtures of epoxides in D_2O + NaOD solution (for details see discussion above).

Conformation of Pyranose Ring in 1,6-Anhydro-β-D-Glucopyranose with Halogen Atom (F, Cl, Br, I) in Position 3

To estimate the effect of the type of halogen atom in position 3 on the conformation of pyranose ring in 3-halogluco derivatives we have synthesized, in addition to 3-iodo derivative **11**, also 3-chloro and 3-bromo derivatives **15** and **16**. Their NMR spectra were measured in $(CD_3)_2CO$ (for data see Tables I–III) to be fully comparable with partial NMR data for 3-fluoro derivative **17** described by Grindley[25].

The conformation of pyranose ring in 1,6-anhydro-β-D-glucopyranose derivatives is well reflected by vicinal coupling constants *J*(2,3) and *J*(3,4). In general, higher *J*-values indicate increasing population of the boat form. However, the differences in the observed *J*-values in our series of halogeno derivatives are influenced not only by the populations of the chair and boat form but also different electronegativities of halogen atoms and by solvent. Therefore we calculated first the expected *J*-values for the chair and boat form of each halo derivative using generalized Karplus equation[22] and torsion angles for chair and boat form derived by Grindley[25] (Table V). The calculated *J*(chair) and *J*(boat) values and the observed averaged *J*(2,3) and *J*(3,4) values were used for estimation of the equilibrium population of the chair form (X(chair)) using simple relation:

$$X(\text{chair}) = (J(\text{observed}) - J(\text{boat}))/(J(\text{chair}) - J(\text{boat})).$$

The results summarized in Table V show that the population of the chair form decreases with the bulkiness of halogen substituent: from fluoro (97% chair), to chloro (62% chair) and bromo derivative (55% chair) while it increases again for iodo derivative (74% chair). It seems that in the case of 3-iodo derivative *gauche* interactions between OH and bulky iodine atom can destabilize the boat form and lead to higher population of the chair form than in chloro and bromo derivative. The effect of solvent can be demonstrated on 3-iodo derivative which gives *J*(2,3) = 2.4 and *J*(3,4) = 2.6 Hz in $CDCl_3$, 3.3 Hz for both in $(CD_3)_2CO$ and 4.6 Hz for both in D_2O. According to these *J*-values, the calculated amount of chair form decreases from 84% in $CDCl_3$ to 74% in $(CD_3)_2CO$ and 59% in D_2O.

The above discussed chair–boat equilibrium of pyranose ring in halo derivatives **11**, **15**–**17** is determined by free energy of both conformers. Therefore we have tried to calculate corresponding energy values and compare the results with those obtained from *J*(H,H)'s.

TABLE V
Chair–boat conformation equilibrium of pyranose ring in 1,6-anhydro-3-deoxy-3-halo-β-D-glucopyranoses **11**, **15**–**17** derived from ^3J(H,H)

Compd	Halogen atom	Conf.	*J* calculated[a]		Solvent	*J* observed		Chair from calculated[b], %	
			J(2,3)	*J*(3,4)		*J*(2,3)	*J*(3,4)	*J*(2,3)	*J*(3,4)
17	F	$^1C_4$	1.53	1.48	$(CD_3)_2CO$	1.7	1.7	97	96
		$B_{O,3}$	7.15	7.36					
15	Cl	$^1C_4$	1.41	1.39	$(CD_3)_2CO$	4.0	4.2	63	61
		$B_{O,3}$	8.51	8.64					
16	Br	$^1C_4$	1.31	1.30	$(CD_3)_2CO$	4.65	4.8	56	55
		$B_{O,3}$	8.90	9.02					
11	I	$^1C_4$	1.14	1.14	$CDCl_3$	2.4	2.6	85	83
					$(CD_3)_2CO$	3.3	3.3	74	74
		$B_{O,3}$	9.48	9.60	D_2O	4.6	4.6	59	59

[a] Torsion angles for chair (< (H2,H3) = –79°, < (H3,H4) = 80°) and boat form (< (H2,H3) = –161°, < (H3,H4) = 164°) were taken from ref.[25]. Coupling constants for chair and boat form were calculated using the generalized Karplus equation[22]. [b] Population of the chair form was calculated using relation: X(chair) = (*J*(observed) – *J*(boat))/(*J*(chair) – *J*(boat)).

TABLE VI

The calculated values of energy (in Hartrees) for OH-rotamers and equilibrium chair–boat population in halogeno derivatives (DFT B3LYP/6-311+g** used for **15**–**17** and B3LYP/3-21g** for **11**)

2-OH, 4-OH rotamer	**17**		**15**		**16**		**11**	
	chair	boat	chair	boat	chair	boat	chair	boat
g_+, g_+	–634.948869	–634.945085	–995.302580	–995.300645	–3109.222748	–3109.221339	–7422.660917	–7422.653111
g_+, t	[a]	–634.945249	[a]	[a]	[a]	[a]	[a]	–7422.652199
g_+, g_-	–634.941297	–634.947029	–995.294831	–995.303101	–3109.215068	–3109.223779	–7422.641019	–7422.654292
t, g_+	–634.948629	[a]	–995.301845	[a]	–3109.221821	[a]	–7422.660250	[a]
t, t	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
t, g_-	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
g_-, g_+	[a]	–634.940961	[a]	–995.295677	[a]	–3109.216184	–7422.664019	–7422.649316
g_-, t	–634.948966	–634.942111	–995.302194	[a]	–3109.222171	[a]	[a]	[a]
g_-, g_-	–634.949258	–634.944072	–995.302912	–995.299725	–3109.223059	–3109.220383	–7422.661081	–7422.652368
Population calculated from ΔE	96%	4%	65%	35%	50%	50%	100%	0%
Population calculated from J's	96.5%	3.5%	62%	38%	55.5%	44.5%	74%	26%

[a] The energy minimum of given rotamer was not found and optimization resulted in the geometry that corresponds to another staggered rotamer.

The presence of two OH groups in these derivatives leads to nine combinations of possible staggered OH-rotamers. The geometry of each rotamer was obtained by energy minimization using molecular mechanics (MM+)[23]. It was then used as the starting geometry for geometry optimization by the ab initio DFT method[24] with B3LYP/6-311+g** for F, Cl and Br derivatives and B3LYP/3-21g** for I derivative. In some cases (indicated by *a* in Table VI) the energy minimum of given rotamer was not found and optimization resulted in the geometry that corresponds to another rotamer. The population of each chair- and boat-form rotamer was calculated from its energy and their sum was used to estimate the final chair and boat population. The calculated chair–boat equilibrium populations agree very well with those calculated from the observed averaged $J(2,3)$ and $J(3,4)$ values except for 3-iodogluco derivative **11**. It can be due to the lower accuracy of geometry optimization and energy calculated with B3LYP/3-21g** (higher basis set is not defined for iodine atom) and/or to the effect of solvation that is not present in the calculation.

EXPERIMENTAL

Melting points were determined with Boëtius micro melting-point apparatus and are uncorrected. The optical rotations were measured on an Autopol III (Rudolph Research, Flanders (NJ), U.S.A.) polarimeter at 25 °C, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were measured on a Bruker AVANCE-500 and/or Varian UNITY-500 instrument (^{1}H at 500 MHz; ^{13}C at 125.7 MHz) in $CDCl_3$ (^{1}H referenced to TMS; ^{13}C to solvent peak using $\delta_C(CDCl_3)$ 77.0), D_2O and/or D_2O + NaOD (a drop of dioxane added and used as reference: δ_H 3.76, δ_C 69.33) and $(CD_3)_2CO$ (referenced to the solvent peak: δ_H 2.09; δ_C 30.7). The structures of all synthesized compounds **1**–**16** were confirmed by ^{1}H and ^{13}C NMR spectra. Structural assignment of proton signals was obtained using H,H-COSY spectra, characteristic splitting patterns and chemical shifts. Coupling constants were derived from expanded resolution enhanced spectra. Homonuclear decoupling experiments were used to determine the values of some small coupling constants. Carbon signals were assigned from APT and 2D-H,C-HSQC spectra. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plates and visualized under UV light (254 nm) and/or by carbonization at high temperature. All solvents were dried and distilled; acetone with K_2CO_3, dioxane with $LiAlH_4$, chloroform with P_2O_5. Solvents were evaporated using vacuum rotary evaporator (water bath 45 °C). The samples for analysis were dried at 6.5 Pa at room temperature.

Isomerization of Epoxides by Sodium Iodide. General Procedure

A solution of epoxide and sodium iodide in dry acetone or acetone-d_6 was sealed into a glass ampule and heated at 100 °C for a given time. Then, the reaction mixture was cooled down to room temperature. The composition of the reaction mixture was determinated by NMR measurement, in case of used dry acetone the solvent was first evaporated.

Isomerization of 1,6:2,3-Dianhydro-β-D-mannopyranose (**1**)

Epoxide[4,15] **1** (8.8 mg, 0.06 mmol) and NaI (16.4 mg, 0.11 mmol) in dry acetone (0.4 ml); 1-h heating. The determined composition of the reaction mixture was **1**:**3**:**14** = 26:66:8.

Isomerization of 1,6:3,4-Dianhydro-β-D-galactopyranose (**2**)

Epoxide[5,16] **2** (7.9 mg, 0.05 mmol) and NaI (12.1 mg, 0.08 mmol) in dry acetone (0.8 ml). No reaction was observed after 24-h heating.

Isomerization of 1,6:2,3-Dianhydro-β-D-gulopyranose (**4**)

Epoxide[5] **4** (8.3 mg, 0.06 mmol) and NaI (16 mg, 0.08 mmol) in acetone-d_6 (0.8 ml). No reaction was observed after 4-day heating.

Isomerization of 1,6:2,3-Dianhydro-β-D-allopyranose (**5**)

Epoxide[17] **5** (7.6 mg, 0.05 mmol) and NaI (11.8 mg, 0.08 mmol) in acetone-d_6 (0.8 ml); 24-h heating. The determined composition of the reaction mixture was **5**:**6** = 24:76.

Isomerization of 1,6:2,3-Dianhydro-β-D-talopyranose (**7**)

Epoxide[18,19] **7** (10.5 mg, 0.07 mmol) and NaI (16.8 mg, 0.11 mmol) in acetone-d_6 (1.1 ml). The determined composition of the reaction mixture was **7**:**8**:**10** = 53:42:5 after 8-day heating and **7**:**8**:**10**:unidentified products = 15:10:67:8 after 19-day heating.

Isomerization of 1,6:3,4-Dianhydro-β-D-talopyranose (**8**)

Epoxide[18,19] **8** (9.6 mg, 0.07 mmol) and NaI (14.9 mg, 0.1 mmol) in acetone-d_6 (1.1 ml). The determined composition of the reaction mixture was **7**:**8**:**10**:unidentified product = 11:79:7:3 after 8-day heating and **7**:**8**:**10**:unidentified product = 15:45:32:8 after 19-day heating.

Epoxide Migration of 1,6:2,3-Dianhydro-β-D-talopyranose (**7**) in Alkaline Water Solution

Epoxide[18,19] **7** (200 mg, 1.39 mmol) was dissolved in 4.3 ml D_2O and 0.6 ml of 30% NaOD in D_2O was added. The reaction mixture was allowed to stand at room temperature for 12 days. Alkaline solution was then neutralized with cooled 1 M HCl solution (2.5 ml, until pH 8) and with acetic acid (1 drop, until pH 7) and lyophilized. Extract from $CDCl_3$ was used for NMR measurement and the composition of the reaction mixture was determined as **7**:**9** = 40:60.

Synthesis of 1,6-Anhydro-3-deoxy-3-iodo-β-D-hexopyranoses. General Procedure

Dianhydrohexopyranose was dissolved in dry dioxane and the solution of 9% HI in chloroform was added. The reaction mixture was allowed to stand at room temperature for a given time, diluted with dichloromethane (20 ml), extracted with water (3 × 20 ml) and the aqueous layer was evaporated. The residue was chromatographed on a silica gel column in toluene–EtOAc (3:1).

1,6-Anhydro-3-deoxy-3-iodo-β-D-idopyranose (**10**)

Prepared from epoxide[18,19] **7** (0.5 g, 3.5 mmol) in dioxane (20 ml) and HI solution (3.9 ml) following the general procedure (standing overnight). Yield 150 mg (16%) of **10**; m.p. 125–126 °C; $[\alpha]_D$ –73 (*c* 0.35, MeOH). For $C_6H_9IO_4$ (272.0) calculated: 26.49% C, 3.33% H, 46.65% I; found: 26.57% C, 3.34% H, 46.36% I. The rest of the reaction mixture containing the iodo derivative **12** and the starting epoxide **7** (200 mg, 55:45) was not separated.

1,6-Anhydro-3-deoxy-3-iodo-β-D-glucopyranose (**11**)

Prepared from epoxide[17] **5** (0.2 g, 1.4 mmol) in dioxane (10 ml) and HI solution (1.4 ml) following the general procedure (10-min standing). Yield 0.33 g (89%) of **11** as a colorless oil; $[\alpha]_D$ –64 (*c* 0.15, H_2O). For $C_6H_9IO_4$ (272.0) calculated: 26.49% C, 3.33% H, 46.65% I; found: 26.54% C, 3.64% H, 46.29% I.

1,6-Anhydro-3-deoxy-3-iodo-β-D-mannopyranose (**13**)

Prepared from epoxide[4,15] **3** (0.2 g, 1.4 mmol) in dioxane (10 ml) and HI solution (1.4 ml) following the general procedure (10-min standing). Yield 0.37 g (97%) of **13**; m.p. 128.5–130.5 °C; $[\alpha]_D$ –121 (*c* 0.36, H_2O). For $C_6H_9IO_4$ (272.0) calculated: 26.49% C, 3.33% H, 46.65% I; found: 26.75% C, 3.41% H, 46.35% I.

1,6-Anhydro-3-chloro-3-deoxy-β-D-glucopyranose (**15**)

Epoxide[17] **5** (29 mg, 0.2 mmol) was dissolved in dry dioxane (1.5 ml) and 5.18 M solution of HCl in dioxane (0.2 ml) was added. The reaction mixture was allowed to stand at room temperature for 20 h. After evaporation of the solvent the residue was diluted with chloroform (10 ml), extracted with water (3 × 10 ml) and the aqueous layer was evaporated to give 27 mg (75%) of compound **15** as a white solid; m.p. 49–51 °C; $[\alpha]_D$ –83 (*c* 0.34, H_2O). For $C_6H_9ClO_4$ (180.0) calculated: 39.91% C, 5.02% H, 19.63% Cl; found: 39.98% C, 5.13% H, 19.70% Cl.

1,6-Anhydro-3-bromo-3-deoxy-β-D-glucopyranose (**16**)

To a solution of epoxide[17] **5** (29 mg, 0.2 mmol) in dry dioxane (1.5 ml) a saturated solution of HBr in dichloromethane (0.1 ml) was added and the reaction mixture was allowed to stand overnight at room temperature. TLC showed residual epoxide **5**, therefore more HBr in dichloromethane (2 × 0.1 ml) was added every 5 h. After that, the reaction mixture was worked up though it still contained starting compound. The solution was evaporated, the residue was dissolved in dichloromethane (10 ml) and extracted with water (3 × 10 ml). The aqueous layer was concentrated and purified by silica gel chromatography (toluene–EtOAc 2:1) to yield 17 mg (38%) of **16** as a colorless syrup; $[\alpha]_D$ –54 (*c* 0.29, H_2O). For $C_6H_9BrO_4$ (224.0) calculated: 32.02% C, 4.03% H, 35.51% Br; found: 33.15% C, 4.33% H, 34.02% Br.

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