Tetrahedron Vol. 37, pp. 2149 to 2151, 1981
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0040-4020/81/112149-03$02.00/0
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STUDIES ON THE CONVERSIONS OF DIOLS AND CYCLIC ETHERS—49[1]

STEREOCHEMISTRY OF CYCLODEHYDRATION OF 1,4-DIOLS ON THE ACTION OF BRÖNSTED AND LEWIS ACIDS: A COMPREHENSIVE STUDY

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(*Received in UK* 11 *November* 1980)

Abstract—The stereochemistry of the cyclodehydration of (±)- and *meso*-2,5-hexanediol on the action of various dehydrating agents was investigated. The earlier assumed and confirmed intramolecular S_N2 mechanism for acid-catalysed ring-closure was found to hold in most cases. Various extents of racemisation can be observed on the action of certain Lewis acids, and the solvents concentrated H_2SO_4 and HMPT (hexamethyl phosporic acid triamide) under previously unexamined reaction conditions.

The stereochemistry of the cyclodehydration of (±)- and *meso*-2,5-hexanediol was studied by Mihailović *et al.*[2,3] on the action of H_2SO_4, H_3PO_4, Al_2O_3 and a large excess of dimethyl sulphoxide (DMSO). In the present work we have studied the sterochemistry of this process, in the presence of some other long known and long-used dehydrating agents, and yet others that had no' previously been utilized with diols, with a view to making a comparison of the stereochemistry observed by Mihailović *et al.*[2,3]

RESULTS AND DISCUSSION

The majority of the results (Table 1) obtained with the dehydrating agents employed support the intramolecular S_N2 mechanism proposed by Mihailović *et al.*[2,3] for dehydration under acidic conditions. The Lewis acids used similarly exert their effects primarily as proton-donor catalysts, i.e. they form a bond of donor-acceptor type with one of the OH-groups, and induce the synchronous elimination of water. (It should be noted that, because of the water formed in the dehydration, proton-catalysis too may occur.) The transformation is outlined in Scheme 1 (X denotes a proton originating from the acid, or a Lewis acid containing a negatively charged central atom in a donor-acceptor bond). The ring-closure proceeds with inversion: the *meso*-diol affords *trans*-oxolane while the (±)-diol is converted into *cis*-oxolane.

Thus, the above results mean the extension and the generalisation of the mechanism put forward and confirmed by Mihailović *et al.*,[2,3] to the much wider sphere of Brönsted and Lewis acids used in catalytic quantities.

However, it must be pointed out that with certain Lewis acids (I_2, $AlCl_3$, $PdCl_2$, $RuCl_3$, $RhCl_3$) the process is not fully stereospecific. The data in Table 2 show clearly that the cyclic ethers formed are stable under the diol-transformation conditions, i.e. the phenomenon is not caused by the isomerisation of the cylic ethers, but the different ionising abilities of Lewis acids.[4] Thus the ring-closure proceeding with inversion (Scheme 1) is accompanied by a process occurring via a carbonium ion, i.e. racemisation too is to be observed.

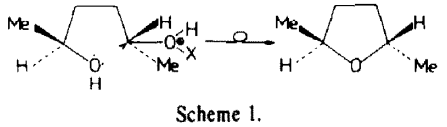
As pointed out previously,[1] during cyclodehydration in a diol excess, i.e. on the action of a small quantity of DMSO, the latter in part exerts its effect directly (by means of the formation of an alkoxy-sulphonium salt or the cyclic structure proposed by Mihailović *et al.*[2]), and in part indirectly (by means of the strong acids resulting from decomposition of the reagent). The action of DMSO is shown in Scheme 2, on the example of the transformation of the alkoxy-sulphonium salt, while the acid-catalysed process occurs as in Scheme 1 (X = H).

The process in 96% H_2SO_4 gives rise to the formation of both stereoisomeric oxolanes. This is brought about by the strong acidity of the H_2SO_4 present as solvent under the given reaction conditions (for 96% H_2SO_4 the Hammett acidity function is $H_0 = -8.98$).[5] Consequently, after rapid protonation of one of the OH-groups a carbonium cation is formed. In this way the chirality of this C atom is lost, and accordingly the isomeric cyclic ethers are produced as a result of cyclodehydration.

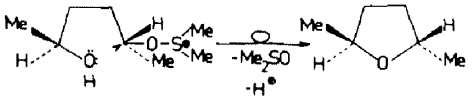
Ring-closure in HMPT likewise displays a very low stereospecificity. There are two possibilites as regards an explanation of the phenomenon: (1) the process takes place via an open carbonium cation; (2) the observed stereochemistry is the result of a mixed mechanism: ring-closure takes place by retention and inversion parallel.

The first assumption can be excluded on the basis of the results of observations with monoalcohols under similar conditions.[6,7]

The second possibility, the process involving retention, may be interpreted by setting out from observations by Arimatsu *et al.*[8] who succeeded in isolating the intermediate (I) assumed by Monson.[7] Accordingly, in the case of the diol the reagent yields the cyclic transition



Scheme 1.



Scheme 2.

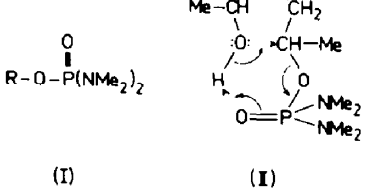
Table 1. Selectivities of cyclodehydration of (±)- and *meso*-2,5-hexanediol in the presence of various agents

Reagent	Reagent amount g Diol:reagent mole ratio	Method	Temp. °C	Time h	Diol[a]	Cis:trans-2,5-dimethyloxolane[b]
p-Toluene-sulphonic acid	0.0086 20:1	B	160	2	meso	2:98
Phtalic anhydride	0.74 1:1	B	200	2	meso	2:98
P_2O_5	0.0142 50:1	B	200	1	meso	5:95
48% HBr	0.015 50:1	B	110	1	± meso	97:3 4:96
Dowex 50 Wx8	0.2	B	130	1	meso	2:98
Iodine	0.0084 150:1	B	180	1	± meso	91:9 9:91
BF_3-etherate	0.0284 25:1	B	140	2	meso	2:98
$CuCl_2$	0.034 20:1	A B	150 120	1 1	meso meso	3:97 2:98
$AlCl_3$	0.0333 20:1	A	110	5	± meso	96:4 5:95
		A	100	5	meso	5:95
$PdCl_2$	0.0443 20:1	A	150	1 3	± meso	97:3 9:91
$RuCl_3 \cdot 3H_2O$	0.0163 80:1	B	110	4[c]	meso	7:93
$RhCl_3 \cdot 3H_2O$	0.0165 80:1	B	110	4[c]	± meso	85:15 20:80
$RhCl_3/PPh_3$	0.0657 80:1:1	B	120	4[c]	± meso	89:11 11:89
DMSO	0.025 16:1	A	190	18	± meso	98:2 2:98
96% H_2SO_4	0.98 1:1	C	20	1	meso	32:68[d]
	1.95 1:4	C	20	1	± meso	52:48 39:61
	4.9 1:10	C	20	1	meso	48:52
HMPT	2.23 1:2.5	B	220	3	± meso	77:23[e] 34:66

[a]Isomer purity: 98%. [b]Selectivity of cyclic ether formation and conversion 100%. [c]Reflux for 3 h under stirring, then distillation. [d]Yield of cyclic ethers: 45–55%. [e]Yield of cyclic ethers: 65%.

state (II), which results in the cyclic ether formed with retention, while the 2,5-dimethyloxolane is simultaneously produced with inversion too in the reaction corresponding to that outlined in Scheme 1.

To summarize, in the knowledge of the chemical properties of the diols,[9] the above results permit the finding that the mechanism and stereochemistry given by Mihailović *et al.*[2,3] are of general validity in the cyclodehydration of diols containing primary and secondary OH-groups and aliphatic substituents on the action of catalytic quantities of Brönsted and Lewis acids. This stereochemistry and reaction mechanism are not manifested in the cases of certain Lewis acids, and concentrated H_2SO_4 and HMPT employed in excess.



(I) (II)

EXPERIMENTAL

Gas chromatography. Carlo Erba Mod. GV instrument. Reoplex 400 column (1.2 m), hydrogen carrier gas (20 ml min^{-1}), 80°C. Retention times: *cis*-2,5-dimethyloxolane: 259 s; *trans*-2,5-dimethyloxolane: 304 s.

Separation of (±)- *and* meso-*2,5-hexanediol.* 4,7-dimethyl-1,3-dioxepan was prepared[10] from 2,5-hexanediol (Fluka) (yield: 68%). Rectified on a rotating spiral column with a theoretical plate number 30 (Abegg system, product of Büchi), the isomer mixture was separated into two components, boiling at 70° (73 mm Hg) and 82° (67 mm Hg), respectively (isomer purity: 99%). These isomers (77% of the starting dioxepan) were reconverted to diols (yield: 63%) by methanolysis in the presence of a catalytic quantity of HCl. The starting diol (118 g) yielded the (±)-2,5-hexanediol (b.p. 90–92° at 3 mm Hg; 14 g, 12%) and the

Table 2. Stabilities of stereoisomeric oxolanes under conditions of diol transformation

Reagent[a]	Method	Temperature °C	Time h	cis:trans ratio
	cis-2,5-Dimethyloxolane[b]			
Iodine[c]	A	150	3	98:2
$RuCl_3 \cdot 3H_2O$	Reflux	110	3	98:2
$RhCl_3 \cdot 3H_2O$	Reflux	110	2	98:2
	trans-2,5-Dimethyloxolane[b]			
$AlCl_3$[c]	A	100	6	2:98
$PdCl_2$[c]	A	150	3	3:97
$RhCl_3/PPh_3$	Reflux	120	3	2:98
96% H_2SO_4	C	20	1	3:97
	C	20	15	7:93

[a]Cyclic ether: reagent mole ratio same as diol: reagent mole ratio given in Table 1. [b]Isomer purity: 98%. [c]Reaction mixture also contained one drop of water [d]Cyclic ether: H_2SO_4 mole ratio = 1:4.

meso-2,5-hexanediol (b.p. 90–93° at 4.5 mm Hg; m.p. 38–39.5°, lit.[2] 40–41°; 24.4 g, 21%).

The purities of the resulting isomeric diols were found to be 98%.

Cyclodehydrations were carried out by the following methods:

Method A. The diol (0.59 g, 0.005 mole) and the appropriate amount of reagent was heated in a sealed ampoule (5 ml). After cooling, neutralisation and drying the mixture was chromatographed.

Method B. The diol (0.59 g, 0.005 mole) and the appropriate amount of reagent were measured into a flask (3 ml) and the product was continuously distilled out of the reaction mixture.

Method C. The diol (0.59 g, 0.005 mole) was slowly added under stirring and ice-cooling to the appropriate amount of ice-cooled 96% H_2SO_4; the mixture was homogenised and allowed to warm up to room temp. After 1 hr a five-fold volume of ice-water was added under cooling to the recooled mixture. The organic phase separating out was extracted into diethyl ether (1 ml), separated, neutralised, dried, and chromatographed.

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