Inverted Stereoselectivity in Grignard Additions to Chiral Aldehydes by Use of Polyethers

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Reitstøen, Bjørn, Kilaas, Lars and Anthonsen, Thorleif, 1986. Inverted Stereoselectivity in Grignard Additions to Chiral Aldehydes by Use of Polyethers. – Acta Chem. Scand. B 40: 440–443.

The stereoselectivity of organimetallic additions to aldehydes and ketones with an alkoxy function at a chiral α carbon is usually explained on the basis of a chelation mechanism. The reaction of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose(*1*) with CH_3MgI is an example of this. Addition of polyethers, including crown ethers, to the reaction mixture inverted the stereoselectivity and the unchelated product was formed. This observation is probably due to a complexation between the Grignard reagent and the polyether which prevents the chelation mechanism from operating.

The synthesis of branched chain carbohydrates, which has been reviewed recently,[1] offers challenging problems in asymmetric synthesis. A common way to create R-C-O-branching is by nucleophilic addition to the oxo group in uloses. We have in particular been interested in addition of diazomethane, sulfur ylids and Grignard reagents[2] and in order to study the stereoselectivity of the reactions, we have included dialdo sugars, although the products do not contain a branching point. The stereoselectivity of such reactions is often difficult to control. For aldehydes and open chain ketones with chiral α carbons, the pioneering work was done by Cram and Abd Elhafetz.[3] Later, theoretical work[4] and *ab initio* calculations of transition states[5] have also contributed to the understanding of such addition reactions. For ketones and aldehydes carrying an alkoxy group at the chiral α carbon, the stereochemical course of the reaction is to a large extent a matter of chelation or non-chelation prior to the addition.[6] The reaction of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose (*1*) with CH_3MgI gave a mixture of 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (*2*) and 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-idofuranose (*3*) in a ratio of 30:70. The furanoses were identified as the corresponding pyranoses after hydrolysis.[7] This stereoselectivity may be explained on the basis of a preferred chelation between the carbonyl group, the ring oxygen and magnesium, since best access will then be from the side away from the ring thereby leading to a predominance of *3*. Oxidation of the mixture of *2* and *3* with RuO_2 and $NaIO_4$ gave 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-5-hexulofuranose (*4*) which on reduction with $LiAlH_4$ gave *2* and *3* in approximately inverse ratio (78:22) of that above. This result is also best accounted for on the basis of a chelation model.

Polyethers, including crown ethers, are known to complex cations. Among other factors, complexation constants depend on the the size of the cavity of the crown ether. We have investigated the influence of polyethers on the reaction of *1* with CH_3MgI. The stereoselectivity was inverted from being *2*:*3* = 30:70, to *2*:*3* = 65:35 on the addition of the smallest crown, 12-crown-4. The effect was even more pronounced as the size of the crown was increased (see Table 1). The following ratios were obtained when the reactions were carried out in the presence of 15-crown-5, 18-crown-6 and dibenzo-18-crown-6 respectively: 76:24, 83:17 and 95:5. Surprisingly, the greatest stereoselectivity was obtained with the acyclic 2,5,8,11,14-pentaoxapentadecane. In this case, the chelation product (the L-idofuranose *3*), was

Table 1. Reaction conditions, molar ratios of the epimeric products *2* and *3* and diastereomeric excess (% *de*) of reactions of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose with CH_3MgI in THF solutions under influence of various polyethers. Reaction mixtures were analyzed by GLC and ^{13}C NMR

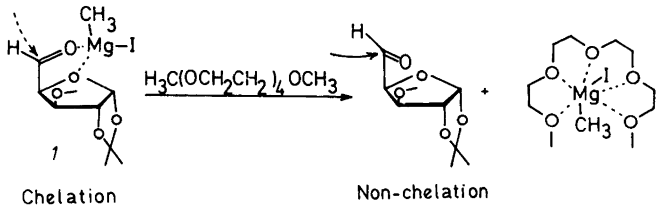
Polyether	Ratio *2:3*	% *de*	Unreacted aldehyde (%)	Temperature (°C)	Time (h)
No additive	30:70	−40	0	22	0.5
12-Crown-4	67:33	34	0	22	66
15-Crown–5	76:24	52	0	22	86
18-Crown-6	83:17	66	18	22	68
Dibenzo-18-C-6	95:5	90	17	Refl.	5
Dibenzo-24-C-8[a]	39:61	−22	4	22	19
2,5-Dioxahexane	91:9	83	20	22	168
Pentaoxapentadecane		>99	41	22	168

[a] Et_2O solution.

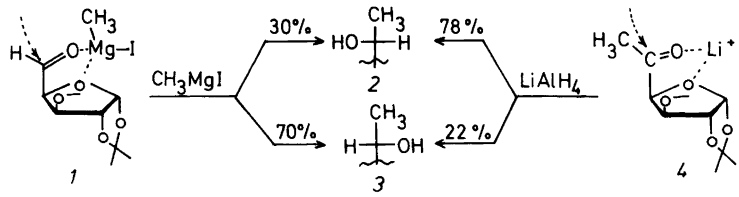
hardly detectable by GLC. This means that the diastereomeric excess was higher than 99%. A similar predominance of *2* was also obtained in the reaction of *1* with methyltriisopropoxytitanium. The preference of this reagent to yield unchelated products is well documented.[8] It was also noticeable that dibenzo-24-crown-8 was not capable of inverting the stereoselectivity. The effect of polyether addition can be understood on the basis of the mechanism of the Grignard reaction. Although the mechanism is not fully elucidated, it seems to be generally accepted that the so-called Schlenk equilibrium plays an important part.[9] According to this, solvated species of RMgX are present in solution in equilibrium with R_2Mg and MgX_2. The solvation number is 2 in diethyl ether and 2–4 in THF. It has been determined that R_2Mg is about ten times more reactive than RMgX, but the latter is present in about ten times the concentration of R_2Mg. Therefore, it would appear that the reaction takes place with both species. Moreover, complexation of Grignard reagent with ketones is also important. In diethyl ether of complexation constants in the range 1–20, depending on nature of the ketone and the magnesium compound, have been determined. When the ketone carries an α alkoxy group, there is good reason to believe that the complexation constants are considerably higher.

Such complexation, and also the effect of the addition of 2,5,8,11,14-pentaoxapentadecane, is depicted in Scheme 1. The complexation constant for the Grignard reagent-polyether complex is supposed to have greater value than that for the Grignard reagent-aldehyde complex. It is likely that both RMgX and R_2Mg may be capable of forming complexes. Other effects of polyether additions besides inversion of stereoselectivity, are higher diastereomeric excesses and lower reaction rates. Both of these observations probably reflect the bulkiness of the solvated Grignard reagent.

Through the series of crown ethers with increasing size, the inversion effect was found to be at a maximum with dibenzo-18-crown-6 (Table 1). Dibenzo-24-crown-8 seemed to be too large and was not an efficient complexation agent. The



Scheme 1.



question of why the open chain polyether was the most efficient additive in spite of the negative entropy effect that the complexation includes, is left unanswered so far.

We also added polyethers to the $LiAlH_4$ reduction reaction of *4*. The reduction, which yielded *2* and *3* in the ratio 78:22 was influenced by the addition of 12-crown-4 to give *2*:*3* = 69:31. When 2,5,8,11,14-pentaoxapentadecane was added the ratio was changed to 60:40, but there was no inversion of the stereoselectivity. It has been reported that $LiAlD_4$ reduction of the benzyl ether that corresponds to the aldehyde *1*, gave the unchelated product in 30 % excess.[10] It seems that the ketone gives the chelation product preferably, while the aldehyde has the opposite stereoselectivity. Moreover, the reaction with the ketone is only influenced to a negligible extent by the addition of polyethers.

Addition reactions to the carbonyl group in 2,3-*O*-isopropylidene-D-glyceraldehyde are difficult to control stereochemically.[2] In our hands, the addition of MeMgI in diethyl ether at 20 °C gave 58 % excess of the unchelated product (the erythro alcohol). Similar results have been obtained by other workers[11] and tridentate complexation has been suggested as a possible explanation for this result. Addition of crown ethers and 2,5,8,11,14-pentaoxapentadecane did not alter the stereoselectivity significantly (*de* = 50 %). On this basis, it seems unlikely that a complexation mechanism was operative. The stereoselectivity in this case consists of a non-chelation mechanism. This is also in accord with the fact that the oxygen atoms in the 1,3-dioxolane ring are less prone to complexation than the ring oxygen of *1*. Stereoselectivities of the addition of diazomethane to 2,3-*O*-isopropylidene-D-glyceraldehyde[2] and related ketones[12] have been explained on the basis of a dipolar model.

Recently, it has been found that ordinary chiral aldehydes which have no ability to be chelated give enhanced Cram addition of Grignard reagents when crown ethers are added to the reaction mixtures.[13] As was the case for our reactions, the rates decrease markedly.

We are continuing our studies on other substrates and with other hosts. We hope that NMR studies will reveal details of interaction between hosts and Grignard reagents which are sufficient to shed light on the influence of the solvent on the mechanism and the stoichiometry of transition states.

Experimental

A Varian 3400 instrument equipped with FI detector was used for GLC (inj. temp. 250°, detect. temp. 300°) and the VISTA 402 data system. The column was fused silica packed with cross-linked methyl silicone (25 m × 0.33 mm, 0.25 mm). NMR spectra were recorded on a Jeol FX-100 at 99.6 MHz for ^1H and 25.1 MHz for ^{13}C. The solvent was $CDCl_3$. Et_2O was dried over sodium and THF over molecular sieve (4 Å).

General procedure. A solution of polyether (0.01 mole) in Et_2O (5 ml) was added under vigorous stirring at room temp. to a freshly prepared solution of CH_3MgI prepared from Mg (0.25 g, 0.01 mole) and CH_3I (1.45 g, 0.01 mole) in Et_2O. The mixture was stirred for 30 min and then a solution of aldehyde (1.23 mmole) in Et_2O (5 ml) was added dropwise. The reaction was monitored by GLC. When practically all the starting material had reacted, water (5 ml) was added and the solution neutralized with M HCl. The solution was extracted with Et_2O (5 × 25 ml), the combined extracts washed with water (2 × 10 ml), dried over Na_2SO_4 and concentrated *in vacuo*. This furnished an oily mixture of the two epimeric alcohols. Quantitative analyses of the mixtures were performed by GLC and ^{13}C NMR. Special reaction conditions and results for each reaction are shown in Table 1.

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Received November 18, 1985.