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Evidence for a nucleophilic *anti*-attack on the cleaved C(2)–oxygen bond in Cl_2AlH-catalyzed ring-opening of 2-substituted 1,3-dioxolanes

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Abstract—The Cl_2AlH-mediated ring-opening of 2-substituted *cis*-4-methyl-5-trifluoromethyl-1,3-dioxolanes was found to occur with regioselective cleavage of the O1–C2 bond by attack of the aluminum hydride from the direction *anti* to the departing oxygen. This stereochemical outcome, which appears to be unprecedented in the reductive cleavage of chiral acetals by aluminum reagents, is interpreted on the basis of theoretical calculations.
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1. Introduction

The utility of chiral acetals as templates for asymmetric synthesis is well recognized.[1] The mechanism and the stereochemical outcome of nucleophilic substitutions at the acetal carbon have been widely investigated.[1b,d,2a] It is well established that the C2-configuration resulting from a Lewis acid (L.a.)-promoted ring-opening of chiral 2-substituted 1,3-dioxanes and 1,3-dioxolanes is related to the following factors: (i) the regioselectivity in the attachment of the L.a. molecule to the oxygen atom of constitutionally asymmetric acetals or the predominance of one conformer when the ring-forming chiral diol is constitutionally symmetric;[1] (ii) the nature of electrophilic/nucleophilic reagent system and the consequent stereoselectivity of the ring-opening substitution reaction. Generally, with TiCl₄/silanes the attack of the nucleophile occurs from the direction *anti* to the departing oxygen (S_N2-like reaction), while the retentive substitution has been observed in all reactions performed with ambiphilic aluminum reagents (Scheme 1).[1b,d,3,4]
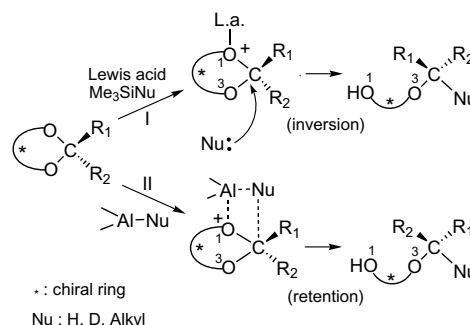

Scheme 1. Mechanisms and related stereochemistry of nucleophilic ring-opening of chiral cyclic acetals.

Recently we found that TiCl₄-mediated reduction of both diastereomers of 2-substituted (4*S*,5*S*)-4-methyl-5-trifluoromethyl-1,3-dioxolanes (*syn*-**3** and *anti*-**3**) with Et₃SiD furnished the same monodeuterated hydroxy ethers in good yields (route 'a' of Scheme 2).[2] A mechanistic rationale was proposed, and supported by theoretical calculations, for explaining the almost complete regioselectivity (ca. 100%) and the high diastereoselectivity (88–97%).[2,5] Considering the possibility to control the stereochemical course of the dioxolane ring cleavage by the choice of the catalyst/nucleophile couple, as mentioned above, deuteride addition to acetals *syn*- and
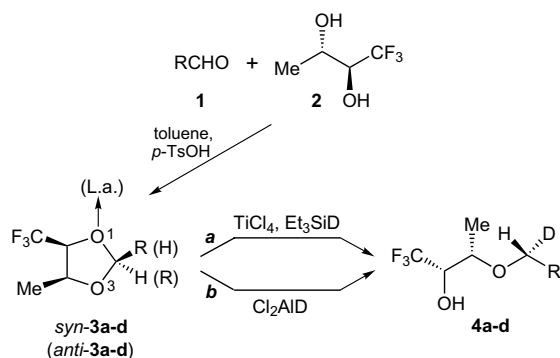
Scheme 2. See Table 1 for the substituent R.

anti-**3a**–**d** was performed using Cl_2AlD instead of $TiCl_4$/Et_3SiD. The results obtained and their interpretation are reported here.

2. Results and discussion

When *syn*-**3a**[2a] was added to a diethyl ether solution of Cl_2AlD[6] at 0 °C (see General procedure below), compound **4a** was obtained as the only product of the reductive ring-opening. Its structure was confirmed by direct comparison with a sample prepared by treatment of *syn*-**3a** with $TiCl_4$–Et_3SiD.[2] The formation of the regioisomer resulting from cleavage of the O3–C2 bond[2a] was not detected by GC analysis of the reaction mixture. A number of Cl_2AlD-promoted deuteride substitutions at the acetal carbon of 1,3-dioxolanes prepared from different aldehydes (**1**) and (2*S*,3*S*)-1,1,1-trifluoromethylbutane-2,3-diol (**2**, 95% ee)[7] were carried out with both *syn*- and *anti*-isomers (Table 1). Data of Table 1 indicate that the same regio- and stereoselectivity as well as a rapid *anti*–*syn* conversion occur in the reductive ring-opening of *cis*-4-methyl-5-trifluoromethyl-1,3-dioxolanes by catalysis of either $TiCl_4$–Et_3Si(H)D or Cl_2Al(H)D (Scheme 2). This unexpected result could be interpreted in terms of geometry/energy factors favoring the S_N2-like substitution versus the retentive collapse[1d] of the oxygen-bound ambiphilic L.a.[4] in Cl_2Al(H)D-complexes of dioxolanes **3a**–**d**.

To support this explanation, theoretical calculations of energies and geometries of *syn*-**3a** and of the analog having the CH_3 group in place of CF_3 (Fig. 1) were per-

formed; the latter compound was chosen as a reference model to evaluate steric and/or electronic effects of the trifluoromethyl group.

Calculations were carried out on both complexes using the Gaussian 98 package[8] at the DFT level with the B3LYP[9] functional and the standard 6-31G**basis set. The conformational search performed by systematically varying the dihedral angles about Al–O1 and C2–C1′ bonds yielded three different minima for each species, which were subsequently confirmed through vibrational analysis. As one can see in Figure 1, these structures differ mainly in the torsion about Al–O1 bond, while the orientation of the benzene ring and the conformation of the dioxolane ring remain almost unchanged (see also Table 2 for selected geometric data).

Figure 1 and Table 2 reveal that among the three conformations assumed by the Cl_2AlH complex of the dimethyldioxolane, the thermodynamically most stable one, that is **C′**, has the shortest (Al)H–C2 distance and the most favorable orientation of the Al–H bond for intramolecular and retentive H-transfer. Such internal reductions[6] have been proposed to occur at the level of $O3^+$=C2//$HAlCl_2$–O1 separate ion pair in 2-substituted 4,5-dimethyldioxolanes.[1d,10] On the contrary, in the case of the Cl_2AlH complex of *syn*-**3a** the corresponding conformer **C**, showing the most favorable orientation and the shortest (Al)H–C2 distance, is characterized by the highest energy level.

Therefore, on the basis of the relative population/reactivity, the low abundance of conformer **C** and the geometry of the most abundant conformer **A** that makes the internal H-transfer rather difficult, may explain the almost exclusive occurrence of the S_N2-like mechanism (path I, Scheme 1) observed in the Cl_2AlH-catalyzed reductive ring cleavage of 5-trifluoromethyl substituted 1,3-dioxolanes (*syn*- and *anti*-**3a**). This interpretation is further supported by inspection of Figure 2, where the molecular electrostatic potential (MEP) generated by charge distribution is mapped onto an electronic isodensity surface for the two most abundant conformers **A** and **C′**. It is evident that the potential in the region close to the acetalic carbon and opposite to the complexed oxygen is more positive in **A** than in **C′**, as expected from the electron-withdrawing character of the CF_3 group. This fact would favor (in the trifluoromethyl

Table 1. Reaction of compounds *syn*-**3** (or *anti*-**3**) with Cl_2AlD or $TiCl_4$/Et_3SiD to give compounds **4**

1,3-Dioxolanes *syn*-**3** (or *anti*-**3**)[a]		Compound **4**[a]			
		Cl_2AlD		$TiCl_4$/Et_3SiD	
Entry	R	Isolated yields (%)	Diastereomeric ratio (1*R*:1*S*)[b]	Isolated yield (%)	Diastereomeric ratio (1*R*:1*S*)[b]
1	C_6H_5 (**3a**)	80 (75)	92:8 (92:8)	95 (75)[c]	94:6 (93:7)[c]
2	*p*-Me–C_6H_4 (**3b**)	70 (68)	88:12 (88:12)	93 (81)[c]	93:7 (92:8)[c]
3	C_6H_5–$(CH_2)_2$ (**3c**)	75	96:4	84[d]	97:3[d]
4	CH_3–$(CH_2)_6$ (**3d**)	78	95:5	86[d]	96:4[d]

[a] Data from *anti*-**3** are in parentheses.
[b] Determined by integration of the two C1′-proton signals in ^1H NMR on the assumption that the upfield singlet was due to Hs (as in **4**)[2a] and the isotopic abundance of the examined compound was >99%D.
[c] Ref. 2a.
[d] Ref. 2b. No *anti* isomer was detected in preparing the dioxolane.
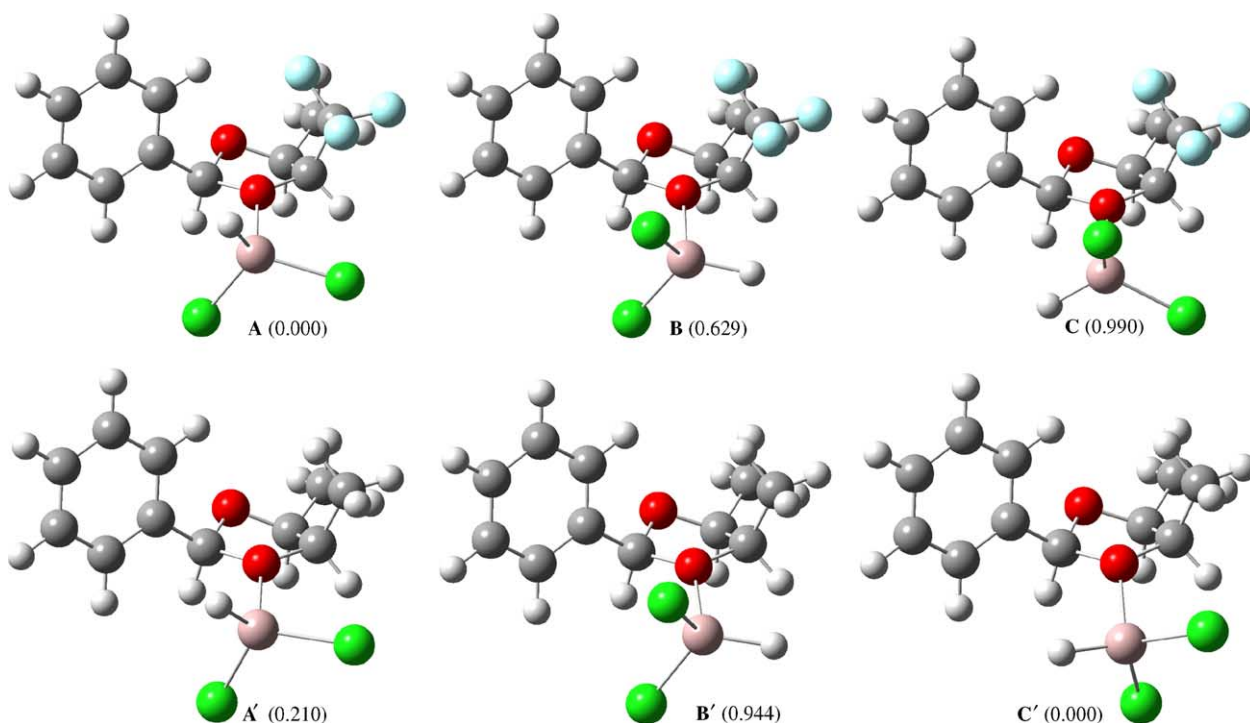
Figure 1. Calculated geometries and relative energies (in parentheses, in kcal/mol) for conformational minima of Cl₂AlH complexes of *syn*-**3a** (**A,B,C**) and of the analog having a methyl group in place of CF₃ (**A′,B′,C′**).

Table 2. Selected interatomic distances (Å) and dihedral angles (degrees) of conformers represented in Figure 1[a]

Conformer	Al–H···C2	O1–C2	Al–H	H–Al–O1–C2
A	3.789	1.557	1.567	−87.3
B	4.162	1.562	1.574	148.8
C	3.026	1.548	1.574	11.9
A′	3.625	1.529	1.568	−73.8
B′	4.144	1.529	1.577	152.0
C′	3.326	1.528	1.569	−47.6

[a] See Scheme 2 for atom numbering.

dioxolane **A** more than in **C′**) the approach of the external nucleophile to C2 on the side of the complex opposite to the Lewis acid.

It can be noted that each couple **A/A′** and **B/B′** shows striking similarities both in the torsional angle of Al–O1 bond and in the relative energy. On the contrary, marked differences in these features are apparent between **C** and **C′**: thus, **C′** corresponds to the lowest energy minimum while **C** to the highest, each in the respective set of conformers. This fact can be interpreted as due to destabilizing interactions in **C** between a chlorine atom and the trifluoromethyl group. In a rotamer obtained from **C** by rotation about the Al–O1 bond in order to have the same torsional angle as in **C′**, the calculated energy was ca. 2.0 kcal/mol higher than that of **C**, and the distance between the two closest F and Cl atoms was found to be 0.25 Å shorter than the sum of the van der Waals radii of these atoms (Cl: 1.75 Å and F: 1.47 Å).[12]
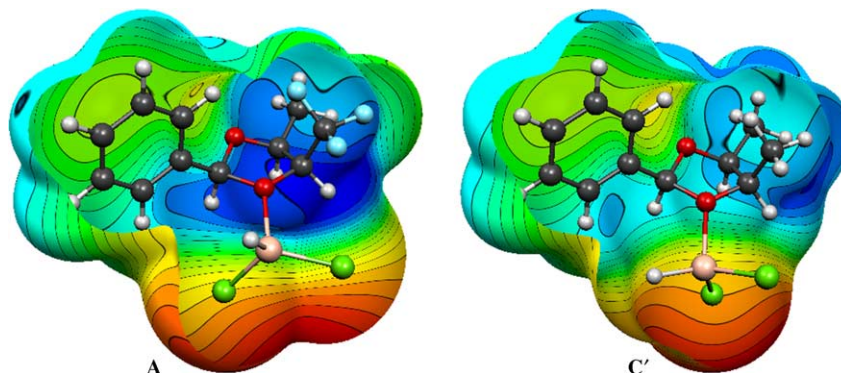
Figure 2. The molecular electrostatic potential (MEP) of conformers **A** and **C′** is mapped onto a 'clipped' electronic isodensity surface (ρ = 0.0004 a.u.) through a color code (the most negative and positive values are represented in red and blue, respectively, while isopotentials contours are visible in black). Illustration prepared with Molekel 4.3 (Ref. 11).

3. Experimental

3.1. General procedure

AlCl$_3$ (200 mg, 1.5 mmol) was dissolved in diethyl ether (2 mL, precooled in a refrigerator for at least 20 min) under a stream of dry nitrogen at 0 °C. A solution of LiAlD$_4$ (15 mg, 0.37 mmol) in diethyl ether (0.4 mL) was then added dropwise. After stirring at 0 °C for 30 min, a solution of the dioxolane (0.5 mmol) in diethyl ether (1 mL) was added dropwise and the mixture was stirred at the same temperature for 3 h. The reaction mixture was diluted with diethyl ether (5 mL) and quenched by cautious addition of 1 M HCl (5 mL); the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried (Na$_2$SO$_4$) and the solvent was evaporated under reduced pressure. The product was then purified by flash column chromatography as described elsewhere.[2a]

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