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Conformational analysis and selective hydrolysis of 2,5-disubstituted-1,3-dioxane-2-carboxylic acid esters

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Abstract—5-Alkyl-2-methyl-2-carbomethoxy-1,3-dioxanes were found to have a cis preferential configuration in the equilibrium state, and the ester hydrolysis rate of the trans-isomers was faster than that of the cis-isomers. Conformational analysis and charge calculation of the carbomethoxy group in both dioxanes elucidated this selectivity.

Axial preference of the carboalkoxy group in various 2-carboalkoxy-1,3-dioxane compounds is now well recognized as an anomeric effect.[1] For example, 2,4-dimethyl-2-carboethoxy-1,3-dioxane can open the ring and equilibrate the isomers **A** and **E** in the presence of acid with axial preference of the 2-carboethoxy group due to the large free energy difference between the isomers ($\Delta G^0 > 3$ kcal/mol),[2] as shown in Figure 1.

In the meantime, 2,5-disubstituted-2-carbomethoxy-1,3-dioxanes can also have cis and trans-isomers **1**, though the substituent effect of these compounds on the preference of their isomers is not well known.[3] In the case of this type of 1,3-dioxanes, the substituent effect of 5-position on cis/trans ratio as well as on the reactivity of the carboalkoxy group is an interesting subject to attain a selective synthesis of some challenging chemicals.[3,4]

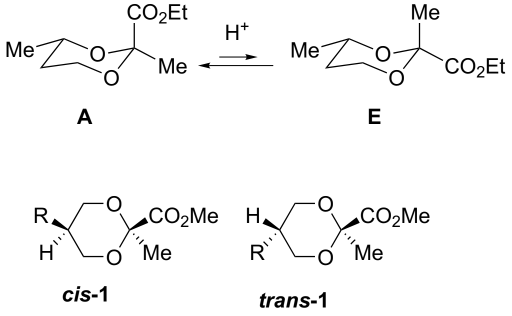

Figure 1. 2-Carboalkoxy-2,4- and 2,5-disubstituted dioxanes.

Four kinds of dioxane compounds **1a**–**d** were straightforwardly obtained from diols **3a**–**d**, which were prepared by reduction of the corresponding diethyl malonates **2** with LiCl–$NaBH_4$, as shown in Scheme 1. Conversion of the diols **3** into the dioxanes **1** was accomplished by the reaction with 1 equiv of methyl pyruvate in the presence of 1 equiv of $BF_3{\cdot}Et_2O$. This reaction proceeded under 15 °C to give a 1/1 ratio of the cis/trans mixture, then the ratio reached equilibrium at 25 °C. The obtained dioxanes **1a**–**d** were found in preference to the cis-isomers within the ratio of 2.1–6.8. The results of the conformational analysis using RHF/STO-3G[5] were in good agreement with those of the experiments (Table 1).

The cis and trans configurations of the dioxane derivatives **1** together with their conformations were determined by the ^1H NMR spectral studies. The observation of a higher δ value (ppm) of the C_5-proton and larger coupling constant between the $C_{4,6}$-axial protons and C_5-proton of the cis-isomer shows that the C_5-proton of the cis-isomer is axial and that of the trans-isomer is equatorial (Table 2). To ensure the assignments of the cis/trans configurations, we analyzed the alcohol derivatives *cis*-**4** and *trans*-**4** obtained by the $NaBH_4$–LiCl reduction of *cis*-**1** and *trans*-**1**, respectively. The C_5-protons of both alcohols can be identified as the

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Keywords: 1,3-Dioxane derivative; Conformational analysis; Selective hydrolysis; Charge calculation.

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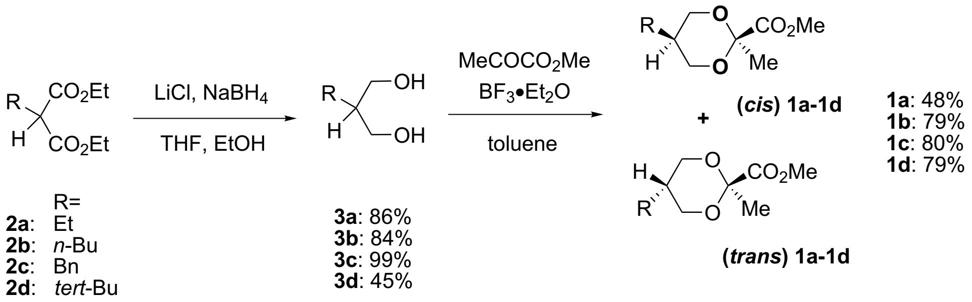


Scheme 1.

Table 1. Observed and calculated results of cis/trans ratio of 1,3-dioxane derivatives **1**

Dioxane	*R*	Experimental ratio (cis/trans)	Calculated ratio (cis/trans)	$\Delta E_{\text{Experiment}}$ (kcal/mol)	$\Delta E_{\text{Calculation}}$[a] (kcal/mol)
1a	Et	3.7[b]	4.1	0.775	0.840
1b	*n*-Bu	3.7[b]	4.3	0.775	0.870
1c	Bn	2.1[b]	2.0	0.440	0.420
1d	*tert*-Bu	6.8[c]	6.0	1.062	1.060

[a] $\Delta E_{\text{Calculation}} = \Delta E_{\text{trans}} - \Delta E_{\text{cis}}$.

[b] Determined by GC.

[c] Determined by ^{1}H NMR.

Table 2. ^{1}H NMR spectral data of **1a–d**

Dioxane[a]		δ (ppm) 4,6-H$_{\text{equatorial}}$	4,6-H$_{\text{axial}}$	5-H
1a	Cis[b]	3.97 dd	3.39 dd	1.94m
		(11.8, 4.4)[d]	(11.8, 11.8)	
	Trans[c]	3.96 dd	3.81 dd	1.29m
		(12.0, 3.3)	(12.0, 2.4)	
1b	Cis[b]	3.95 dd	3.39 dd	2.00m
		(10.9, 4.8)	(10.9, 10.9)	
	Trans[c]	3.96 dd	3.79 dd	1.34m
		(10.8, 2.0)	(10.8, 2.4)	
1c	Cis[b]	3.90 dd	3.49 dd	2.35m
		(12.2, 4.4)	(12.2, 12.2)	
	Trans[c]	3.94 dd	3.78 dd	1.61m
		(10.5, 2.7)	(10.5, 1.5)	
1d	Cis[b]	4.02 dd	3.64 dd	1.82m
		(10.6, 4.4)	(11.0, 10.6)	
	Trans[b]	4.03 dd	3.92 dd	1.38m
		(12.2, 4.8)	(12.2, 4.8)	

[a] Each isomer was separated from a 1/1 mixture by column chromatography.

[b] Measured by 200 MHz in CDCl$_3$.

[c] Measured by 300 MHz in CDCl$_3$.

[d] *J* Values (in Hz) in parentheses.

axial position on the basis of their large diaxial coupling constants (*cis*-**4**: $J = 7.5$ Hz, *trans*-**4**: $J = 10.4$ Hz) and the strong NOE from the C$_{4,6}$-equatorial protons. They are also supported by the strong NOE between the C$_{4,6}$-axial protons and 2-hydroxymethyl protons in *cis*-**4** and 2-methyl protons in *trans*-**4**, respectively (Fig. 2).

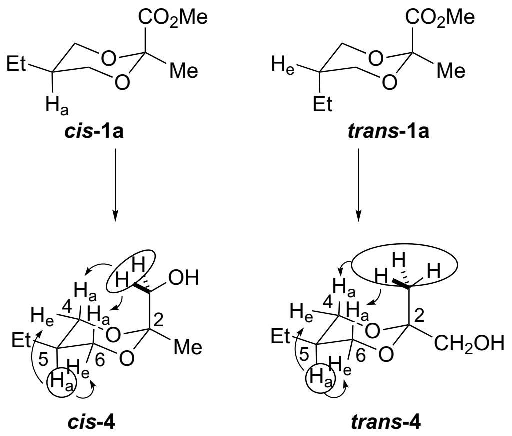
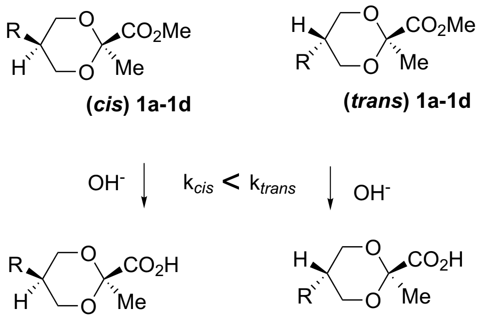


Figure 2. NOE correlations of *cis*-**4** and *trans*-**4**.

Due to the difficulty to attain high cis-ratio of **1** in the ring formation reaction, we challenged selective hydrolysis of the cis and trans mixture to obtain pure cis-isomer. The initial hydrolysis attempts seemed to be promising and detailed studies revealed that trans-isomers were hydrolyzed with base approximately ten-times faster than cis-isomers based on pseudo first order kinetics. 1,3-Dioxanes **1a–d** obtained as a mixture of cis/trans-isomers were subjected to the selective hydrolysis of trans-isomers to give rise to over 90% diastereomeric excess of cis esters (Scheme 2, Fig. 3).

The steric effect on the hydrolysis of both isomers cannot explain the faster reaction rate of the trans-isomer, because both isomers are dominated by the axial conformation based on conformational analyses. Another possible factor that affects the different hydrolysis rates is the charge difference between the carbonyl carbons of the cis- and trans-forms (Fig. 4). The charge was calcu-



Scheme 2.

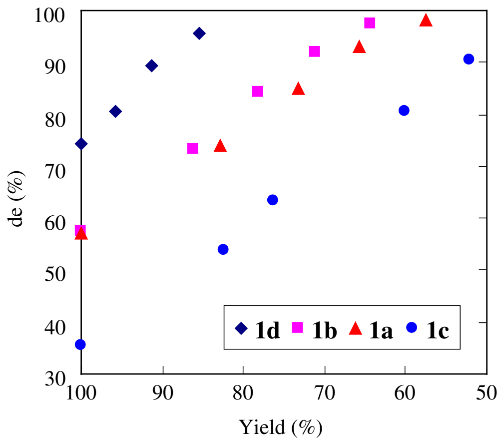


Figure 3. Diastereomeric excess (de) of the cis esters versus yield of the remaining esters after the hydrolysis of **1** by treatment with aq NaOH in MeOH at 298 K [**1** (100 mg) in MeOH (1 ml)].

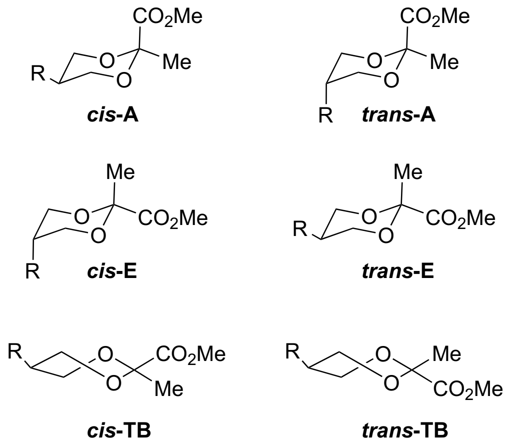


Figure 4.

lated using the RHF/STO-3G basis set, which can be applied to larger molecules with an efficient computational time cost. The distribution of each conformation and charges on the carbon in the carbonyl groups of both *cis*-**1** and *trans*-**1** are summarized in Tables 3 and 4.[6] The charge order was found to be as follows: *trans*-**A** group > *cis*-**A** group > *trans*-**E** and *trans*-**TB** group > *cis*-**E** and *cis*-**TB** group. This clearly explains the faster hydrolysis of the trans-isomers than that of the cis-isomers.

Table 3. Distribution of each conformer of **1** (unit: %)

Dioxane	Cis series			Trans series		
	cis-**A**	*cis*-**E**	*cis*-**TB**	*trans*-**A**	*trans*-**E**	*trans*-**TB**
1a	*74.39*	0.79	0.50	*21.73*	2.19	0.41
1b	*75.24*	0.66	0.50	*20.94*	2.22	0.43
1c	*61.89*	1.50	0.47	*34.19*	1.64	0.32
1d	*77.07*	0.36	2.15	*16.71*	2.14	1.57

Table 4. Weighted charge on the carbon atom in the carbonyl group of **1**

Dioxane	Cis series			Trans series		
	cis-**A**	*cis*-**E**	*cis*-**TB**	*trans*-**A**	*trans*-**E**	*trans*-**TB**
1a	*0.843*	0.671	0.694	*0.958*	0.747	0.757
1b	*0.835*	0.684	0.706	*0.960*	0.759	0.764
1c	*0.836*	0.684	0.713	*0.976*	0.796	0.767
1d	*0.842*	0.725	0.668	*0.977*	0.766	0.774

In conclusion, 1,3-dioxane derivatives **1a**–**d** were obtained as a cis and trans mixture with preferential equilibrium of the cis-isomer. The ratio from the experiments was in agreement with that from the conformational analysis. Selective hydrolysis of the cis and trans mixture combined with the preferential equilibrium to cis-isomer gave the over 90% de of cis-isomer. We believe the faster hydrolysis rate of the trans-isomers is caused by the higher charge and larger population of *trans*-**A**. Work is underway to elucidate the selective hydrolysis of 1,3-dioxane derivatives.

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