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On the Origin of the Distal vs. Proximal Regioselectivity in Di-*O*-alkylation of Calix[4]arenes

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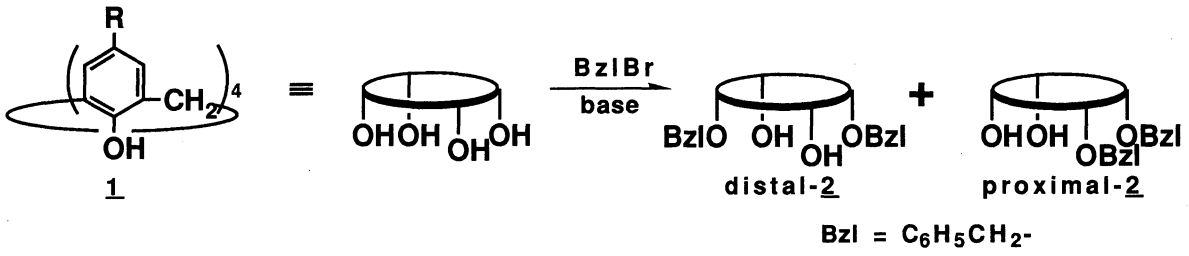
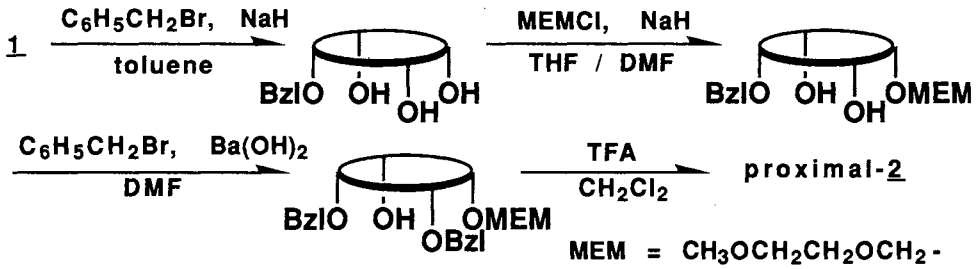
The mechanistic basis of the distal vs. proximal regioselectivity in di-*O*-alkylation of calix[4]arene was investigated through the detailed product analyses. It was found that (i) the regioselectivity is profoundly affected by the residual intramolecular hydrogen-bonds and (ii) the distal isomer is more reactive for further *O*-alkylation than the proximal isomer, resulting in the "apparent" proximal selectivity.

It is known that the oxygen-through-the-annulus rotation in calix[4]arene-25,26,27,28-tetrols(**1**), through which interconversion among conformers takes place, can be inhibited by *O*-substituents bulkier than the ethyl group.[1,2] Tetra-*O*-alkylation with propyl bromide, for example, affords four different conformers, namely, cone, partial cone, 1,2-alternate, and 1,3-alternate.[1,2] We previously found that the conformer distribution is profoundly affected by alkali and alkaline earth metal cations present as base in the reaction system.[2-4] The key intermediate is a di-*O*-substituted compound but the production mechanism is still a matter of serious controversy: in *O*-propylation in the presence of M_2CO_3 (M=K or Na) the major product is a 1,3-disubstituted (distal) compound[2,3] whereas in *O*-benzylation or *O*-(2-pyridyl)methylation in the presence of NaH the major products are 1,2-disubstituted (proximal) compounds.[5,6] What is the origin of the distal vs. proximal regioselectivity? To answer this question seems to be obligatory in order to understand the final conformer distribution in tetra-*O*-substituted calix[4]arenes. We thus synthesized the authentic samples, distal-**2** and proximal-**2** from 5,11,17,23-tetra-t-butylcalix[4]arene- 25,26,27,28-tetrol (R=t-Bu in **1**) and investigated the



influence of the reaction conditions on the distal vs. proximal regioselectivity in **2** in detail by using HPLC and ^{1}H NMR spectroscopy.

Distal-**2** (as an authentic sample) was synthesized from **1** and benzyl bromide in the presence of K_2CO_3 in DMF in a manner similar to that described previously.[2] Proximal-**2** (as an authentic sample) was synthesized by a protection-deprotection method as shown in the following scheme. The products were identified by IR and ^{1}H NMR spectral evidence and elemental analysis data.



We carried out dibenzylation according to the two different methods: (i) **1** (500 mg, 0.675 mmol) was treated with NaH in acetonitrile and the mixture was allowed to react with benzyl bromide (0.176 cm^3, 1.48 mmol) at 30 °C; (ii) **1** (500 mg, 0.675 mmol) was allowed to react with benzyl bromide (0.176 cm^3, 1.48 mmol) in the presence of K_2CO_3 in acetonitrile at 30 °C. The progress of the reaction was followed by an HPLC method using two columns simultaneously: **1**, distal-**2**, tri- and tetra-*O*-benzyl derivatives were separated by an ODS column (chloroform - methanol) and mono-*O*-benzyl derivative and proximal-**2** were separated by a silica-gel column (ethyl acetate - hexane).[7] The product distribution determined after the saturation of the reaction (about 19 h) is summarized in Table 1.

It is clearly seen from Table 1 that (i) distal-**2** results selectively when K_2CO_3 is used as base and (ii) when 2 equiv. of NaH are used, proximal-**2** results selectively. As reported previously,[2,3] the product distribution of *O*-alkylcalix[4]arenes is affected by the metal template effect. In the present study, the difference between Na^+ and K^+ scarcely affects the distal vs. proximal ratio because when Na_2CO_3 is used instead of K_2CO_3, distal-**2** results selectively (although the reaction rate is much slower). The foregoing findings allow to conclude that the distal vs. proximal regioselectivity is primarily governed by the basicity and the quantity of the base.

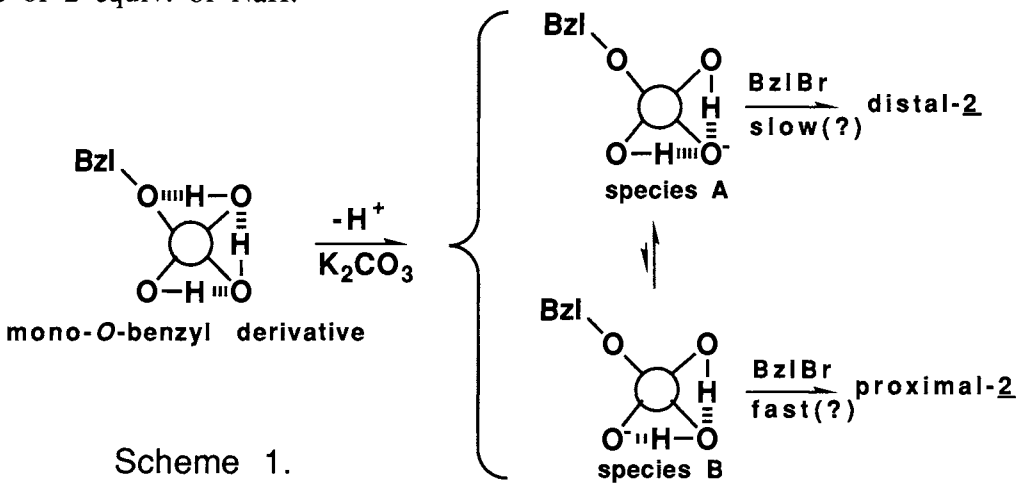
Why does the reaction in the presence of K_2CO_3 result in distal-**2** selectively? Judging from the pK_a values of calix[4]arenes,[8] the OH groups are only partly dissociated in the presence of K_2CO_3. The distal vs. proximal ratio is determined when the second benzyl group enters. In scheme 1, species A which has a phenoxide anion stabilized by two hydrogen bonds should exist in preference to species B which has a phenoxide anion stabilized only by one hydrogen bond. One can expect, in contrast, that species B may be more reactive than species A as a nucleophile. The high distal

Table 1. Product distribution [a]

Base(equiv.)	Yield / %				
	Distal-**2**	Proximal-**2**	Mono-*O*-Bzl	Tri-*O*-Bzl	Tetra-*O*-Bzl
NaH (2.0)	24	14	46	2	10
NaH (5.0)	0	58	0	1	22
K_2CO_3 (2.0)	86	5	5	0	0
K_2CO_3 (3.0)	93	0	3	2	0
K_2CO_3 (5.0)	88	0	1	2	0
Na_2CO_3(5.0)	11	0	4	0	0

a) When the sum of the products is less than 100%, the residue is unreacted **1**.

selectivity shown in Table 1 supports the view that actually, the difference in the nucleophilicity is rather small and the selectivity mainly stems from the equilibrium declined to species A. The similar explanation is applicable to the reaction in the presence of 2 equiv. of NaH.



Scheme 1.

The reaction in the presence of 5 equiv. of NaH gave proximal-**2**. We noticed, however, that the reaction also gives a considerable amount of a tetra-*O*-benzyl derivative. To totally explain the distal vs. proximal regioselectivity one must estimate from which this tetra-*O*-benzyl derivative comes. We treated a 1:1 mixture of distal-**2** and proximal-**2** (0.603 mmol each) with benzyl bromide (1.48 mmol) in the presence of NaH (1.80 mmol) in acetonitrile (15 cm^3) at 30 °C . As shown in Fig. 1, distal-**2** disappeared much faster than proximal-**2**; after 5 min, residual distal-**2** was 0.024 mmol while residual proximal-**2** was 0.446 mmol. The result indicates that the tetra-*O*-benzyl derivative mostly comes from distal-**2**. It is thus concluded that distal-**2** and proximal-**2** are produced in a 1:2 ratio and distal-**2** has disappeared because of further benzylation. As shown below, NaH is a base strong enough to produce a totally OH-dissociated mono-*O*-benzyl derivative which has two

phenoxide anions to give proximal-**2** and one phenoxide anion to give distal-**2**. Provided that the nucleophilicity of these three phenoxide anions is similar, the distal-**2** vs. proximal-**2** ratio should be 1:2. In conclusion, the present paper clearly elucidated the controversial problem about the distal vs. proximal regioselectivity in di-*O*-alkylation of calix[4]arenes. We believe that this progress is important in further regioselective functionalization of calix[4]arenes. We believe that this progress is important in further regioselective functionalization of calix[4]arenes.

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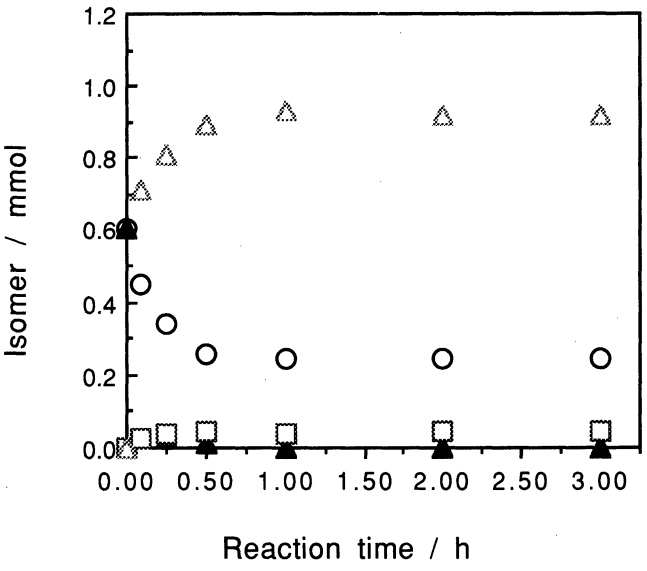

Fig. 1. Time course of *O*-benzylation of an equimolar amount of distal-**2** and proximal-**2**: ▲ distal-**2**, ○ proximal-**2**, □ tri-O-Bzl, △ tetra-O-Bzl.

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