Quasi-template Effect: a Tool for Controlling Stereochemistry in Acyclic Systems. Attempted Stereoselective Synthesis of α,α′-Dimethoxystilbene

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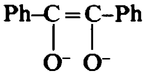
Alkylation with methyl tosylate of stilbenediol dianion, prepared in the reaction of benzoin with a series of alkali-metal hydroxides in THF, gave (*E*)- and (*Z*)-α,α′-dimethoxystilbenes as the major products in most cases, the *E*:*Z* ratio of which varies from 0.4 to 5.0 depending upon the alkali-metal cation employed; the results are rationalized in the quasi-template effect in an acyclic system and the hard–soft ion principle.

Stilbenediol dianion,  $Ph{-}C(O^-){=}C(O^-){-}Ph$, has aroused much interest in view of its doubly ambident nature giving *C*-, *O*-, *C*,*O*-, and/or *O*,*O*-alkylated products upon reaction with alkylating agents,[1] and also as a successful building block for the unsaturated crown ethers carrying the stilbene chromophore.[2] Heine[1b] and Merz and Tomahogh[1d] have shown that, in the alkylation of benzoin with a variety of alkylating agents using alkali-metal, mostly sodium, hydroxide in dimethyl sulphoxide[1b] or under phase-transfer conditions,[1d] the product ratio between *C*- and O-alkylation depends drastically upon the nature of the alkylating agent employed. The results in both cases have been accounted for in terms of Pearson's HSAB principle.[3] As is the case with enolate ions,[4] hard alkylating agents give predominantly *O*-alkylation, while soft ones tend to afford more *C*-alkylation. Although the conditions for predominant bis-*O*-alkylation producing α,α′-dialkoxystilbene have been established as above, the stereochemistry of the dialkoxystilbene produced appears to be nonselective, *i.e.* *E*:*Z* ratio 1.0—1.7,[1d] and the factors controlling the *E*:*Z* ratio of the dialkoxystilbene remained unresolved. Previous investigations[2b,c] on the synthesis of stilbenocrown ethers indicate that the use of appropriate cations facilitates ring-closure giving rise to size-fitted crown ethers with a stilbene chromophore of *Z*-configuration. This result prompted us to investigate the chemistry of stilbenediol dianion further and to examine the potential ability of the template effect in an acyclic system. In this work, the alkylation reactions were conducted mainly in homogeneous solution using a series of alkali-metal hydroxides as a base–counter cation in order to utilize the quasi-template effect for controlling the stereochemistry of the bis-*O*-alkylated product, dialkoxystilbene.

Results and Discussion

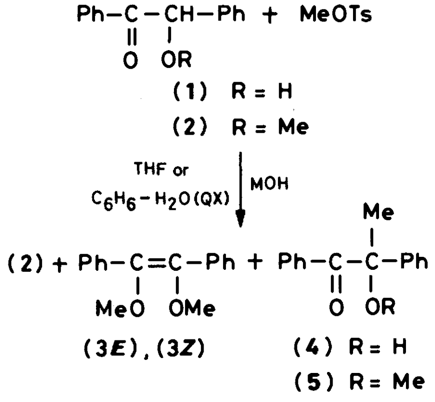
Alkylation in Homogeneous Solution.—The reaction of benzoin (**1**) with methyl tosylate in the presence of lithium, sodium, potassium, rubidium, or cesium hydroxides in tetrahydrofuran (THF) gave a mixture of benzoin methyl ether (**2**), (*E*)- and (*Z*)-α,α′-dimethoxystilbene (**3**), α-methylbenzoin (**4**), and α-methylbenzoin methyl ether (**5**), as *O*-, *O*,*O*-, *C*-, and *C*,*O*-alkylated products, respectively. The product yields are shown in the Table.

Since the bisalkylation of (**1**) producing (**3**) and (**5**) is evidently a two-step process in which benzoin methyl ether (**2**),

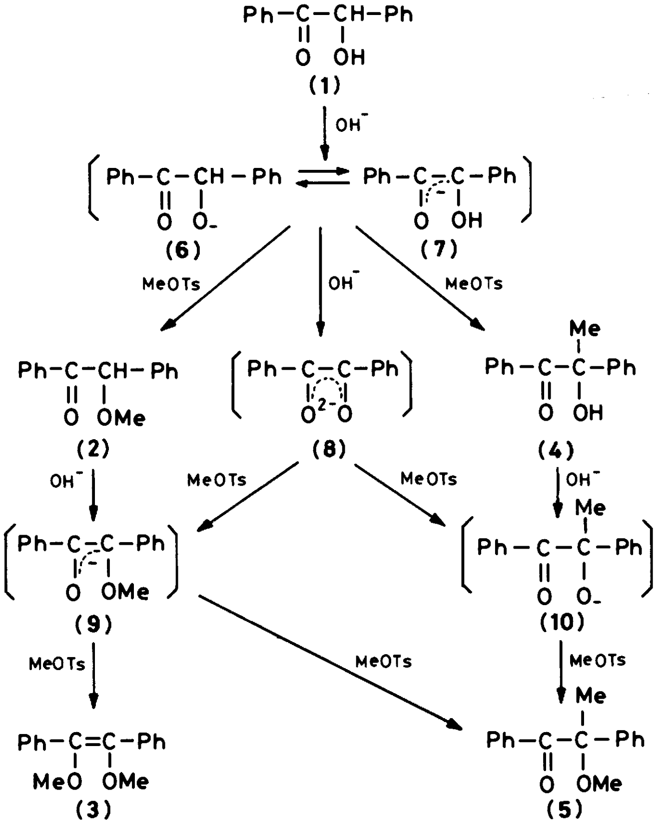
Table. Reactions of benzoin (**1**) or benzoin methyl ether (**2**) with methyl tosylate

Solvent (Temp.)	Substrate	MOH (Molar excess)	Reaction time (h)	Yield (%)[a]					(3*E*):(3*Z*)
				(**2**)	(3*E*)	(3*Z*)	(**4**)	(**5**)	
THF (67 °C)	(**1**)	LiOH (2.5)	15	66	0.9	1.6	*b*	*b*	0.6
			70	61	4.5	8.8	4	1	0.5
		NaOH (2.5)	15	*c*	17	43	6	8	0.4
		KOH (2.5)	15	*c*	50	10	4	8	5.0
		RbOH (2.5)	15	24	17	7	19	21	2.4
		CsOH (2.5)	15	11	25	13	10	16	1.9
	(**2**)	LiOH (2.5)	15	74[d]	1.1	2.1	*e*	*c*	0.5
			70	56[d]	5.4	11	*e*	*c*	0.5
		NaOH (2.5)	15	*c*	19	43	*e*	*c*	0.4
		KOH (2.5)	15	*c*	59	15	*e*	13	3.9
		RbOH (2.5)	15	*c*	41	16	*e*	20	2.6
		CsOH (2.5)	15	*c*	48	19	*e*	20	2.5
C_6H_6–H_2O[f] (76 °C)	(**1**)	NaOH (12.5)[g]	15	77	6.2	2.2	*b*	*b*	2.8
			30	41	12	5.0	3	3	2.4
			70	26	38	14	*c*	30	2.7
		NaOH (12.5)[h]	70	*c*	39	12	*c*	*c*	3.3
		KOH (12.5)[h]	70	*c*	48	20	*c*	24	2.4
	(**2**)	NaOH (6.3)[h]	70	*c*	46	19	*e*	4	2.4

[a] Yield based on (**1**) or (**2**) used, determined by l.c. and n.m.r. [b] Yield not determined. [c] Less than 1% yield. [d] Recovery. [e] Not applicable. [f] Tetrabutylammonium bromide used as a phase-transfer catalyst. [g] A 33% aqueous solution used. [h] A 50% aqueous solution used.



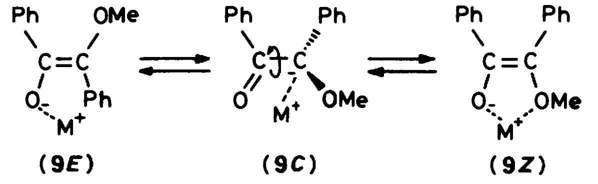
Scheme 1.



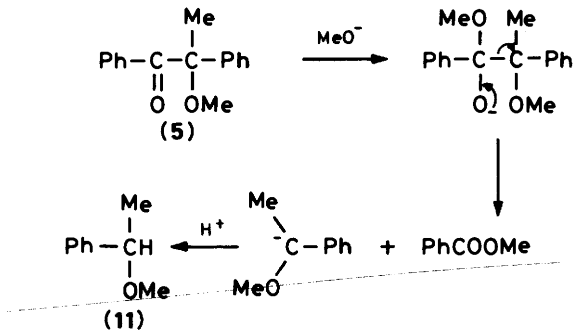
Scheme 2. Stereochemistry not specified

as well as α-methylbenzoin (**4**), intervenes, the mono-*O*-alkylated intermediate (**2**) was chosen as a starting material and was subjected to alkylation with an equimolar amount of methyl tosylate under identical reaction conditions. The reactions gave the final products (**3**) and (**5**) in yields analogous to those obtained in the corresponding runs starting with (**1**). The two-step alkylation mechanism is illustrated in Scheme 2.

As can be seen from the Table, the product yield and distribution are critical functions of the alkali-metal hydroxide, or more strictly the cation used. The reaction with lithium hydroxide afforded predominantly the mono-*O*-alkylated product (**2**) along with the mono-*C*-alkylated and bisalkylated products (**3**)—(**5**) in limited yields even for reaction periods as prolonged as 70 h. By contrast, sodium, potassium, rubidium, and cesium hydroxide gave bisalkylated products (**3**) and (**5**) as the major products in good combined yields, although the ratios between *C*- and *O*-alkylations depend considerably upon the counter cation. The cation-dependent *C*:*O*-alkylation ratios may be rationalized simply within the framework of the HSAB principle; a hard cation interacts with the hard side of the ambident anion and a soft one with the soft side, developing a negative charge at the hard oxygen for hard cations or at the soft carbon for soft cations. Thus the relative importance of the *C*-alkylated products (**4**) and (**5**) increases gradually with increasing softness of the alkali-metal cation.



Scheme 3. Quasi-template effect in (**9*Z***)



Scheme 4. Base-catalysed decomposition of (**5**)

More interesting is the fact that the *E*:*Z* ratio of the bis-*O*-alkylated product (**3**) changes dramatically with the alkali-metal cation employed. The *E*:*Z* ratios for hard cations like lithium and sodium are well below 1, while the use of the softer potassium, rubidium, and cesium ions leads to much higher *E*:*Z* ratios of 1.9—5.0; the *E*:*Z* selectivity is reversed between sodium and potassium. It should be noted that, in an attempted base-catalyse isomerization of (**3**) under the same reaction conditions, no interconversion between the (*E*)- and (*Z*)-isomers was observed and the *E*:*Z* ratio, for example for lithium hydroxide, did not change with the reaction time. These results clearly indicate that the *E*:*Z* ratios observed are particular to the cation and should be accounted for in terms of the nature of the cation. Since the *E*:*Z* ratios obtained in the alkylations of both (**1**) and (**2**) are comparable for every cation, the stereochemistry of (**3**) must be determined in the final step. In this context it is interesting to discuss the geometry of the enolate ion (**9**) in conjunction with the *E*:*Z* and *C*:*O* ratios obtained in the alkylation of (**2**).

The full description of enolate ion (**9**) is shown in Scheme 3. It is likely that, possessing a central C=C double bond, the *O*-anions (**9*E***) and (**9*Z***) are fixed geometrically and the two isomers interconvert mutually only *via* the *C*-anion (**9*C***) through rotation about the central C–C single bond. It seems plausible also that the isomeric ions (**9*E***), (**9*C***), and (**9*Z***) are the immediate precursors of the products (**3*E***), (**5**), and (**3*Z***), respectively, and therefore the product distribution reflects the enolate distribution. This does not mean, of course, that the percentage composition of (**9*E***), (**9*C***), and (**9*Z***) is directly equal to that of the products (**3*E***), (**5**), and (**3*Z***), respectively, since it is quite unlikely that the *O*-anion (**9*E***) or (**9*Z***) reacts with the alkylating agent at the same rate as the *C*-anion (**9*C***). In fact, in a separate alkylation reaction of (**2**) using sodium hydroxide in THF at 67 °C, the use of methyl iodide, instead of tosylate, as an alkylating agent gave (**3*E***), (**3*Z***), and 1-phenylethyl methyl ether (**11**) in 2.7, 12.7, and $>25\%$ yield, respectively. The last product is formed in the secondary base-catalysed decomposition of the *C*-alkylated product (**5**) (see Scheme 4).

The *C*:*O* and *E*:*Z* ratios for the iodide were >2.00 and 0.2, respectively, while the corresponding values for the tosylate were nearly zero and 0.4. This result, which is rationalized in terms of the HSAB principle, further indicates (1) that the equilibrium between (**9*E***), (**9*C***), and (**9*Z***) is established rapidly and the rate-determining step is the subsequent alkylation, and (2) that the relative rate of *C*- and *O*-alkylation processes depends on the alkylating reagent used, but the rates of alkylations for (**9*E***) and (**9*Z***) are comparable with each other. Consequently, the (**9*E***):(**9*Z***) ratio is inferred to be very close or equal to the (**3*E***):(**3*Z***) ratio, although the *C*:*O* preference in the enolate (**9**), estimated from the product distribution, may be exaggerated up- and down-wards for the iodide and tosylate, respectively. This aspect is important and the minimum requirement for the meaningful discussion of quasi-template effect in the enolate (**9**).

The relative importance of (**9*E***), (**9*C***), and (**9*Z***), as estimated from the product distribution between (**3*E***), (**5**), and (**3*Z***), is governed critically by the nature of the counter cation M^+. Hard lithium and sodium cations interact preferentially with the hard oxygen side of the ambident anion and stabilize (**9*Z***) rather than (**9*E***) through ligation by the adjacent methoxy oxygen, resulting in the exclusive formation of the *O*-alkylated product (**3**) with predominant *Z*-configuration. On the other hand, soft cations interact mainly with the soft carbon side, enhancing contribution of (**9*C***) at the expense of (**9*E***) and (**9*Z***), and, since the energy gain by the ligation by methoxy-oxygen in (**9*Z***) is minimal for soft cations, (**9*E***) is expected to be more stable than (**9*Z***) due to the steric effect and the dipole moment difference.

Alkylation in Heterogeneous Solution.—For comparison purposes, the alkylations of (**1**) and (**2**) under the phase-transfer conditions similar to those of Merz and Tomahogh[1d] were carried out with large excess of sodium or potassium hydroxides in benzene–water using tetrabutylammonium bromide as a phase-transfer catalyst. In sharp contrast to the alkylation in the homogeneous phase described above, the ratio (**3*E***):(**3*Z***) is practically invariant for the reactions with sodium and potassium hydroxides. This is simply because, under the phase-transfer conditions, the working counter cation in the benzene phase is not an alkali-metal cation but a common ammonium ion, regardless of the hydroxide used.

It is concluded that, when the reaction is carried out in a homogeneous solution, the quasi-template effect does work even in an acyclic system carrying as low as one additional donor atom. The effect can be utilized, to some extent, as a tool for controlling stereochemistry of the product, although its scope and limitations may be the subject of further investigations.

Experimental

Materials.—Benzoin (**1**) and benzoin methyl ether (**2**) (both from Tokyo Kasei) were recrystallized from methanol and light petroleum, respectively. Methyl tosylate (Nakarai) was used without further purification. Methyl iodide (Nakarai) was distilled prior to use. Lithium hydroxide (Merck), sodium hydroxide (Nakarai), potassium hydroxide (Nakarai), rubidium hydroxide (Mitsuwa), and cesium hydroxide (Mitsuwa) were used as received. Tetrahydrofuran was dried over calcium chloride and distilled from sodium hydride. Benzene was used after distillation.

Analysis.—The product yields of (**2**) and (**3**) were determined by liquid chromatography. L.c. analysis was run on a YANACO L-4000W liquid chromatograph equipped with an M-313 UV monitor, operated at 300 nm, and a Waters data module M730 using a 25 cm column of ODS-T with water–methanol (1:9) eluant at a flow rate of 1.0 ml min^{-1}. Under the conditions, the products (**2**)—(**5**) were separated satisfactorily. The response of detector was calibrated at 300 nm for (**2**), (**3*E***), and (**3*Z***) by using the pure specimens obtained commercially or isolated from the reaction product by column chromatography over silica gel. Since pure (**4**) and (**5**) suitable for calibration could not be isolated, their yields were determined by n.m.r. spectroscopy on a JEOL JNM-PMX60 instrument; good peak separation of all methyl protons of the products (**2**)—(**5**) including (**3*E***) and (**3*Z***) enables quantitative analysis of the spectra of the reaction mixture.[1d]

Alkylation in Homogeneous Solution.—To a 200 ml round-bottomed flask fitted with a reflux condenser, thermometer, nitrogen-inlet tube, and magnetic stirrer introduced successively, with stirring, THF (75 ml), benzoin (**1**) or benzoin methyl ether (**2**) (0.01 mol), methyl tosylate (0.02 or 0.01 mol), and finely ground base (MOH; 0.025 mol). The mixture was heated to reflux with continued stirring and nitrogen bubbling. Reflux under nitrogen was continued for the period shown in the Table. In most cases starting with (**1**), the solution turned viscous and dull green immediately after heating and then pale yellow after 2—4 h reflux, indicating the intervention of stilbenediol dianion.[1d] The mixture was poured into water and extracted with benzene (3 ×). The combined extract was dried over magnesium sulphate, and the solvent was evaporated *in vacuo* to give a solid or viscous oil. The product was subjected to the analysis on l.c. and n.m.r. spectrometer to determine the yields of (**2**)—(**5**) (see Table).

Attempted Base-catalysed Isomerization of the Dimethoxystilbene (**3**).—A THF solution (75 ml) of a 5:1 mixture of (**3*E***) and (**3*Z***) (0.01 mol in total) and sodium hydroxide (0.025 mol) was refluxed for 15 h under nitrogen. The work-up procedure gave recovered (**3**) of exactly the same *E*:*Z* composition. Since the preferred *E*:*Z* ratio observed for the alkylation of (**1**) or (**2**) with sodium hydroxide is 0.4 as shown in the Table, this result indicates that no base-catalysed geometrical isomerization, or any secondary further reaction, of (**3**) takes place under the reaction conditions.

Alkylation under Phase-transfer Conditions.—To benzene (75 ml) in the similarly equipped flask were added successively, with stirring, the substrate (**1**) or (**2**) (0.01 mol), methyl tosylate (0.02 or 0.01 mol), tetrabutylammonium bromide (50 mg, 0.16 mmol), and the base (0.125 mol) dissolved in 5 or 10 ml water. The mixture was refluxed for 15—70 h with stirring under nitrogen. The work-up afforded the product, which was in turn analysed as above to give the yield listed in the Table.

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