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STEREOCHEMICAL STUDIES ON AZIDATION OF β-BROMOHYDRINS UNDER PHASE TRANSFER CONDITION

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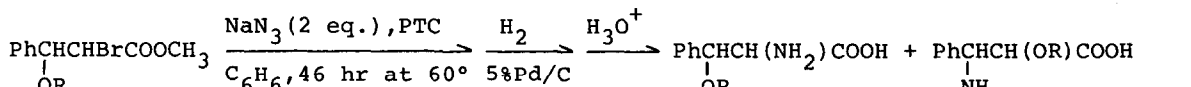
The application of two-phase catalytic systems in organic chemistry has been a subject of growing interest in recent years. In the previous paper[1], we have reported that crown ether can be used successfully as phase transfer catalyst in the azidation of organic halides. It has been especially noted that the azidation of bromohydrins proceeds with complete regiospecificity, resulting from the direct nucleophilic displacement of bromine on the α-carbon by azide anion; i.e. styrene bromohydrin and methyl β-hydroxy-α-bromopropionate gave exclusively the sole products, 1-amino-2-hydroxy-2-phenylethane and serine on subsequent reduction.

For a better understanding of these processes, we undertook the stereochemical study of the nucleophilic azide substitution in the solid-liquid system using crown ether and cryptand as catalyst. In this communication, we describe some findings which are fundamental to mechanistic consideration; on the function of phase transfer catalyst, and on the neighboring participation of hydroxyl or methoxyl groups. The stereochemical studies of nucleophilic displacement toward simple secondary alkyl derivatives by the aid of a PTC has revealed that the reaction proceeds with inversion of configuration at the central carbon atom[2]. In the present work, diastereomeric methyl β-hydroxy-β-phenyl-α-bromopropionates (I[3a] and II[3b]) and methyl β-methoxy-β-phenyl-α-bromopropionates (III[3c] and IV[3d]) were subjected to the reaction with sodium azide, catalyzed by 18-crown-6 or (221) cryptand in the solid-liquid system.



I: R=H *erythro* form
II: R=H *threo* form
III: R=CH_3 *erythro* form
IV: R=CH_3 *threo* form
V: R=H *erythro* form
VI: R=H *threo* form
VII: R=CH_3 *erythro* form
VIII: R=CH_3 *threo* form
IX: R=H *erythro* form
X: R=H *threo* form

The general procedure for nucleophilic substitution with sodium azide is exemplified by a typical run (run 1, Table I). Methyl *erythro*-β-hydroxy-β-phenyl-

α-bromopropionate (518.2 mg; 2 mmol) and sodium azide (260.1 mg; 4 mmol) were stirred in anhydrous benzene (5 ml) in the presence of 18-crown-6 (26.4 mg; 0.1 mmol) at 60°C for 46 hr, after which insoluble inorganic salt was filtered off. Benzene was evaporated *in vacuo* and the residue was hydrogenolyzed over 5%-Pd/C in the usual manner. The filtrate from the hydrogenolyzed mixture was concentrated and hydrolyzed with 3N-hydrochloric acid for 1 hr. The resulting products (V and VI) were purified on an Amberlite IR-120 column. Yield 180 mg(49.7%). Ratio of the isomeric products, *erythro*-[4] to *threo*-β-phenylserine[4] (V:VI), *erythro*-[5] to *threo*-β-phenylisoserine[6] (IX:X), and *erythro*-[7] to *threo*-*O*-methyl-β-phenylserine[8] (VII:VIII) was determined by the comparison of integral values on pmr spectrum.[9]

Table I The Reaction of Isomeric Methyl β-Hydroxy- and β-Methoxy-β-Phenyl-α-Bromopropionates (I-IV) with Sodium Azide.

Run	Substrate	PTC	(mol%)	V	:	VI	VII	:	VIII	IX	:	X	% Yield
1	I	18-crown-6	(5)	42		58							49.7
2	I	18-crown-6	(1)	13		87							14.1
3	I	(221)cryptand	(5)	45		55				60		40	50.3**
4	II	18-crown-6	(5)	100		0							59.4
5	II	18-crown-6	(1)	100		0							28.2
6	II	(221)cryptand	(5)	100		0							65.5
7	III	18-crown-6	(5)										0
8	III	(221)cryptand	(5)				5		95				7.0
9	IV*	18-crown-6	(5)										trace
10	IV*	(221)cryptand	(5)				95		5				10.9

* Methyl *threo*-β-methoxy-β-phenyl-α-bromopropionate was found to be contaminated with the *erythro*-isomer (11 %) on its pmr spectrum.

** % Yield of isomeric β-phenylisoserine (IX and X) was estimated about 25 % by integration of pmr spectrum.

The results were summarized in Table I. With the use of catalysts such as 18-crown-6 and (221) cryptand, the *threo* bromohydrin derivatives, methyl β-hydroxy-β-phenyl-α-bromopropionate (II) and methyl β-methoxy-β-phenyl-α-bromopropionate (IV), reacted with sodium azide to afford exclusively the normal displacement products with inversion of configuration, *erythro*-β-phenylserine (V) and *erythro*-*O*-methyl-β-phenylserine (VII) as was expected from the ordinary S_N2 mechanism (runs 4,5,6,and 10). However, the *erythro* substrates, I and III, exhibited unusual behavior under the same conditions (runs 1,2,3,and 8); i.e. bromohydrin I gave not only the normal displacement product of the inverted configuration, *threo* VI, but also the abnormal retention product, *erythro* V. In addition, it is worthy of note that the ratio of the retention product to the inversion product (V:VI) increased with the amount of catalyst used (runs 1 and 2). Furthermore, when (221) cryptand was employed as catalyst, an appreciable amount of the rearrangement products IX and X were detected in the azidation of *erythro* bromohydrin I, to-

gether with the direct displacement products V and VI (run 3). On the other hand, *erythro* bromohydrin III in the presence of (221) cryptand furnished the normal inversion product VIII along with a small amount of the retention product, VII (run 8). The present stereochemical outcome found for the reactions of diastereomeric bromohydrins can be considered as a result of the intervention of β-hydroxyl or methoxyl groups in the displacement process. Thus, the observed formation of the diastereomeric products V and VII from the *erythro* substrates suggests that the reaction involves the double Walden inversion by two successive S_N2 processes; the first by the neighboring β-oxy group participation and the second by the attack of external azide anion. The formation of the retention product in the reaction of the *erythro* substrate may reasonably be accounted for by the conformational preference of the *erythro* to the *threo* form for the stereochemical course of azidation, because the *erythro* form may easily adopt the conformation in which the oxy and the leaving groups orient anti-planar without any energetic stringency. Whereas, the severe steric interaction between phenyl and methoxycarbonyl groups prevents the *threo* counterpart from adopting the same conformation. This may satisfactorily explains the absence of both the retention and the rearrangement products in the reaction mixture of the *threo* isomer. Although it is well known that methoxyl group is a slightly more effective participator than hydroxyl group[10], the bulky methoxyl group seems to exert a steric hindrance rather than the neighboring effects in the present system, as was reflected in the observed lowering of chemical yield (runs 7-10).

Furthermore, it is of particular interest to note that the complexation of 18-crown-6 and (221) cryptand showed somewhat different catalytic action for the reactivity and regioselectivity in the present nucleophilic substitution, despite that these catalysts were employed in the same manner as PTC for two-phase system. In the substrate I, the complexation of 18-crown-6 with sodium azide yielded substantially no rearrangement products, while that of (221) cryptand gave the rearrangement products in moderate yields, which may be attributed to a neighboring oxgen interaction (runs 1 and 3). In the case of bromohydrins, III and IV, nucleophilic substitution occurred only in the presence of cryptand. As it has been accepted that an ion-pair is the dominating nucleophile in the halogen exchange reaction[11] or in the alkylation of methyl acetoacetate anion[12], one may well exclude the possibility that free azide anion functions as nucleophile in the present system. So that, the discrepancy noted above may be attributable to the steric size or different degree of ionization between the 18-crown-6-solubilized sodium azide ion-pair and (221) cryptand-solubilized one.

As an example of substrate lacking the neighboring group participation, methyl (*S*)-α-bromoisocaproate[13] derived from L-leucine was subjected to the same reaction under exactly the same conditions. Stereochemical outcome (Table II) obviously showed that under the conditions employed, the transformation to azidoester proceeded normally via an S_N2 mechanism.

Table II The Reaction of Methyl (*S*)-α-Bromoisocaproate with Sodium Azide in Benzene at 60° for 22 hr in the Presence of 18-Crown-6.

Run	Mol% of PTC	$[\alpha]_D^{25}$ [14]	% Optical Purity [15]	% Inversion	Config.	% Yield of Leu.
1	5	-9.95	65.9	93.3	*R*	37.8
2	1	-11.3	74.8	99.1	*R*	11.2

Studies on the formation of threonine and *allo*-threonine by the use of PTC in two-phase system are currently in progress in order to provide further evidence for the proposed mechanism.

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