April, 1978] BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (4), 1197—1199 (1978) 1197

The Effect of Macrocyclic Polyethers on the Alkylation of Sodium 2-Naphtholate

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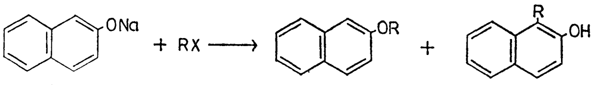
(Received October 18, 1977)

The alkylation of sodium 2-naphtholate, in the presence of benzo-18-crown-6 or 4,7,13,16,21,24-hexaoxa-bicyclo[8.8.8]hexacosane is found to give high ratios of *O*/*O*+*C* alkylation when conducted in THF, in benzene, and in water. The striking increase in the product ratio is attributed to a specific complexation of the macrocyclic polyethers, which facilitate the dissociation of the ion-pair aggregate of the sodio-derivative which exists in benzene or THF. The polyethers may act as phase-transfer catalysts when the reaction is run in water. In support of this conclusion, the reaction in DMF or acetonitrile, in which the dissociation of sodium 2-naphtholate takes place, fails to show any effect of the macrocyclic polyethers on the product ratio.

It is well known[1)] that the 2-naphthoxide ion is an ambident anion capable of forming a covalent bond at either the oxygen or carbon atom on alkylation. Kornblum *et al.*[2)] found that, whereas sodium 2-naphtholate (I) could be alkylated with benzyl bromide, propyl bromide, and methyl iodide, the solvent plays a decisive role in determining the reaction course of the ambident anion. For example, when sodium 2-naphtholate is treated with benzyl bromide in a dimethyl sulfoxide solution, benzyl 2-naphthyl ether (II) is produced in a 95% yield, whereas in water the main product is 1-benzyl-2-naphthol (III) (84% yield).



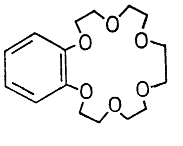
I II III

In recent years it has been generally accepted that quaternary ammonium halides and crown ethers can be used as phase-transfer catalysts[3)] in two-phase ionic reactions. In addition, crown ethers possess a unique ability to fill the coordination sites of cations[4)] and to convert contact ion-pairs into separated ions.[5)] The combination of these two effects may affect the alkylation of sodium 2-naphtholate in a serious manner. Therefore, we have investigated the effect of benzo-18-crown-6 (IV) and 4,7,13,16,21,24-hexaoxabicyclo-[8.8.8]hexacosane (V)[6)] on the reaction of alkyl and benzyl halides with sodium 2-naphtholate in various solvents.

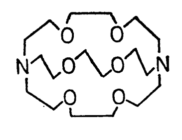
Results and Discussion

The following reactions of sodium 2-naphtholate with benzyl and alkyl halides were run in several solvents with or without added macrocyclic polyethers (IV and V). The reactions were carried out by stirring sodium 2-naphtholate in a given solvent with benzyl bromide in the presence or absence of a small quantity of a macrocyclic polyether (IV or V). After the usual work-up, the products were analyzed by GLC.

We first investigated the homogeneous benzylation of sodium 2-naphtholate in aprotic solvents with relatively high or low dielectric constants. The yields of the *O*- and *C*-alkylation products are listed in Table 1 (Runs 10—15). As the data show, the reaction of benzyl bromide with sodium 2-naphtholate in DMF and acetonitrile yields the *O*-alkylation product, whereas in the THF solvents, which have relatively a low dielectric constant, the *C*-alkylation occurs to a substantial extent. The addition of IV or V to the reaction mixture did not affect the product ratio in acetonitrile and DMF, but caused a remarkable increase in the ratios of *O*-alkylation to *C*-alkylation for the reaction in THF. In THF, sodium 2-naphtholate exists as ion pairs and higher aggregates.[2)] Therefore, in the reaction of sodium 2-naphtholate with benzyl bromide (Run 4), the *O*/*O*+*C* alkylation product ratio is rather low;[2)] however, in the presence of IV or V (Runs 5 and 6) a reaction under similar conditions gave a high yield of the ether (II), together with a small % of the *C*-alkylation product. In this reaction, clearly, the ion-pair separating ability of the macrocyclic polyether accounts for this dramatic effect; it is known[5,7)] that an equimolar amount of a crown ether suffices to convert ion-pairs into separated ions. In contrast, in a solvent with a high dielectric constant, such as acetonitrile or DMF, it is conceivable that the alkylation reaction involves free 2-naphthoxide ions (or loose ion pairs). Therefore, the polyethers fail to affect the products of alkylation.



IV



V

Phase-transfer Reactions. The results are summarized in Table 1 (Runs 1—3 and 7—9). While it was difficult for the reaction of benzyl bromide with sodium 2-naphtholate to proceed in benzene (Runs 7—9), it proceeded smoothly in the presence of V to afford alkylation products totalling a 77% yield, showing that V was effective in solubilizing sodium 2-naphtholate in benzene. In the absence of the macrocyclic polyether, because of the low solubility of sodium 2-naphtholate in benzene and the low dielectric constant of benzene, a heterogeneous (solid-liquid) reaction occurred to give 1-benzyl-2-naphthol in a low yield as the main product. This result was consistent with the observation by Kornblum[8)] that the heterogeneous alkylation of sodium phenolate proceeded through the

Table 1. Reaction of alkyl halides with sodium 2-naphtholate[a]

Run No.	Alkyl halide	Solvent	Catalyst	Reaction time (h)	Products (%)		$\frac{O}{O+C}$ ratios
					O-Alkylated	C-Alkylated[b]	
1	$PhCH_2Br$	H_2O		24	12	73	0.14
2	$PhCH_2Br$	H_2O	IV	24	60	18	0.77
3	$PhCH_2Br$	H_2O	V	24	77	8	0.91
4	$PhCH_2Br$	THF		24	51	30	0.63
5	$PhCH_2Br$	THF	IV	24	65	2	0.97
6	$PhCH_2Br$	THF	V	24	73	1	0.99
7	$PhCH_2Br$	C_6H_6		24	1	9	0.10
8	$PhCH_2Br$	C_6H_6	IV	24	58	12	0.83
9	$PhCH_2Br$	C_6H_6	V	24	76	1	0.99
10	$PhCH_2Br$	DMF		2	87	0	1.00
11	$PhCH_2Br$	DMF	IV	2	89	0	1.00
12	$PhCH_2Br$	DMF	V	2	90	0	1.00
13	$PhCH_2Br$	CH_3CN		42	63	4	0.94
14	$PhCH_2Br$	CH_3CN	IV	42	60	4	0.94
15	$PhCH_2Br$	CH_3CN	V	42	58	3	0.95
16	CH_3I	H_2O		48	27	15	0.64
17	CH_3I	H_2O	IV	48	65	10	0.87
18	CH_3I	H_2O	V	48	97	3	0.97
19	CH_3I	THF		3	79	8	0.91
20	CH_3I	THF	IV	3	94	4	0.96
21	CH_3I	THF	V	3	51	4	0.93
22	CH_3I	C_6H_6		120	0	0	
23	CH_3I	C_6H_6	IV	120	14	10	0.58
24	CH_3I	C_6H_6	V	120	7	6	0.54
25	CH_3I	CH_3CN		3	86	9	0.91
26	CH_3I	CH_3CN	IV	3	87	8	0.92
27	CH_3I	CH_3CN	V	3	71	6	0.92
28	CH_3I	DMF		3	90	0	1.00
29	CH_3I	DMF	IV	3	89	0	1.00
30	CH_3I	DMF	V	3	91	0	1.00

a) All the reactions were conducted at 25 °C. b) This yield includes any alkylated products arising from the further alkylation of 1-benzyl-2-naphthol or 1-methyl-2-naphthol.

C-alkylation process. In contrast, in the presence of IV or V, the reactivity of the oxygen site became enhanced relative to that of the carbon site of the ambident anion: these results may be interpreted by thinking that sodium 2-naphtholate is solubilized in a benzene solution to produce highly reactive naked anions to cause a reaction with benzyl bromide in the homogeneous phase. Obviously the crown ether functioned as a solid-liquid phase-transfer agent. The most pronounced effect on the ratio of O-alkylation to C-alkylation was found in water. The reaction of an aqueous solution of sodium 2-naphtholate with benzyl bromide in the absence of IV or V gave a 12% yield of the O-alkylation product (II) and a 73% yield of the C-alkylation product. The explanation for this result is that strong proton donors such as water in the absence of IV or V solvated the anionic oxygen atom and thereby suppressed the O-alkylation. In sharp contrast, in the presence of IV or V in water, the $O/O+C$ ratios of the alkylation products markedly increased. When IV or V was added to the reaction mixture, the ambident anion produced in water could be transported into the organic layer (benzyl bromide) as a loosely separated ion pair, with a cryptated cation as an escort; the O-alkylation now occurred. The results are completely consistent with a phase-transfer mechanism.[9] Similar results were found in the reactions of sodium 2-naphtholate with methyl iodide in aprotic solvents and water.

Experimental

Analysis. The products were generally analyzed on a Hitachi 023 gas chromatograph equipped with a flame-ionization detector with a 1 m×3 mm column packed with 60—80 mesh Chromosorb W (washed with acid and treated with dimethyldichlorosilane) and coated with 20% Carbowax 20 M (for the analysis of benzylated products at *ca.* 240 °C) or with a 3 m×3 mm column packed with 80—100 mesh Chromosorb W (washed with acid and treated with dimethyldichlorosilane) and coated with 3% Silicone OV-17 (for the analysis of methylated products at *ca.* 210 °C).

Materials. Benzo-18-crown-6[4] and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane[6] were prepared according to the procedures described in the literature. Authentic samples (1-benzyl-2-naphthol,[10] benzyl 2-naphthyl ether,[2] 1,1-dibenzyl-2-naphthalenone,[11] 1-methyl-2-naphthol,[12] methyl 2-naphthyl ether,[2] and methyl 1-methyl-2-naphthyl ether[2]) were also prepared according to the procedures described in the literature. The sodium 2-naphtholate was prepared as has been described by Kornblum *et al.*,[2] while the alkyl halides (commercial samples) were used directly provided that the physical constants agreed with the reported values. The solvents used were purified by distillation.

General Procedure. The typical procedures for the reaction of alkyl halides with sodium 2-naphtholate are as follows.

Reaction of Benzyl Bromide with Sodium 2-Naphtholate. *In Water*: A magnetic stirring bar was placed in a 10-ml vial, after which sodium 2-naphtholate (1.06 mmol), benzo-18-crown-6 (0.3 mmol), and 4 ml of water were introduced. The mixture was stirred for 0.5 h at 25 °C. Benzyl bromide (1.2 mmol) was then added all at once, after which the mixture was stirred for a further 2.5 h. The resulting mixture was poured into 10 ml of water, acidified with 18% hydrochloric acid at 0 °C, and extracted with benzene four times. The extracts were combined and concentrated to a 5-ml volume. GLC analyses revealed the presence of four components, which were identified as 2-naphthol (17%), benzyl 2-naphthyl ether (60%), 1-benzyl-2-naphthol (9%), and 1,1-dibenzyl-2-naphthalenone (9%); the relative retention times of these components were 1.00: 2.11: 9.00: 16.6.

In Tetrahydrofuran: A mixture of sodium 2-naphtholate (0.92 mmol), benzo-18-crown-6 (0.2 mmol), and 4 ml of THF was stirred for 30 min at 25 °C. Benzyl bromide (1.0 mmol) was added all at once, after which the mixture was stirred for a further 65 h. The work-up and analysis were performed as has been described above. The analysis by GLC revealed the presence of 2-naphthol (25%), benzyl 2-naphthyl ether (65%), 1-benzyl-2-naphthol (1%), and 1,1-dibenzyl-2-naphthalenone (1%).

Reaction of Methyl Iodide with Sodium 2-Naphtholate. *In Tetrahydrofuran*: A mixture of sodium 2-naphtholate (6.01 mmol), benzo-18-crown-6 (0.32 mmol), and 10 ml of anhydrous THF was stirred for 30 min at 25 °C. Methyl iodide (7.2 mmol) was then added all at once, after which the mixture was stirred for a further 20 h. The resulting mixture was poured into 20 ml of water, acidified with 18% aq hydrochloric acid, and extracted with benzene. The benzene extract was washed with 10% aqueous sodium hydroxide and with water. Analysis by GLC identified the neutral fraction as consisting of methyl 2-naphthyl ether (94%) and methyl 1-methyl-2-naphthyl ether (4%); the relative retention times of these two components were 1.00: 2.26. The alkali and water extracts were combined and acidified with 18% aq hydrochloric acid at 0 °C, and then extracted with benzene. The subsequent analysis of the product by GLC indicated the presence of 2-naphthol (1%) and 1-methyl-2-naphthol (1%), whose retention times were 1.26 times that of 2-naphthol.

In Water: A mixture of sodium 2-naphtholate (6.01 mmol), benzo-18-crown-6 (0.32 mmol), and 10 ml of water was stirred for 30 min at 25 °C. Methyl iodide (7.2 mmol) was then added all at once, after which the mixture was stirred for a further 48 h. The work-up and analysis were performed as has been described above.

The authors wish to express their gratitude to Professor Michinori Ōki, the University of Tokyo, for his valuable discussion and suggestions.

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