

Selectivity in the *N*- and/or *C*-Alkylation of Schiff Bases Catalyzed by Crown Ether

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Synopsis. The reaction of anions derived from Schiff bases (*N*-(α -methylbenzylidene)aniline and *N*-cyclohexylideneaniline) with ethyl iodide or diethyl sulfate in aprotic solvents, in the presence of 18-crown-6, is found to give a high ratio of *N*/(*N*+*C*) or *C*/(*N*+*C*) alkylation when conducted in benzene or in dioxane.

It is well known that the separation of ion-pairs and thus the anion activation can be obtained through the selective complexation of cations by organic ligands. This is dramatically shown by the enhancement in reaction rates by addition of crown ethers¹⁾ and cryptands to homogeneous or heterogeneous reaction media. In previous papers,^{2,3)} we have shown that alkylation of sodium 2-naphtholate and sodium phenolate, in the presence of macrocyclic polyethers, is found to give high ratios of *O*/(*O*+*C*) alkylation when conducted in aprotic solvents and in water. Heiszwolf *et al.*⁴⁾ found that ambident anions, derived from the reaction of a Schiff base with a strong base, could be alkylated with alkyl halide or dialkyl sulfate in aprotic solvents and that the nature of the solvent and of the alkylating agent played a decisive role in determining the reaction course of the ambident anion. Thus, in analogy with sodium phenolate or sodium 2-naphtholate,^{2,3)} it may be expected that in the presence of these macrocyclic polyethers the alkylation in solvents having low dielectric constants will result in predominant formation of the *N*- or *C*-alkylation product. Therefore, we have investigated the effect of 18-crown-6 on the yield and on the *N*/(*N*+*C*) ratios of alkylation products in the reaction of anions (**2**), derived from Schiff bases, with ethyl iodide and diethyl sulfate under mild reaction conditions.

The following alkylations of ambident anions (**2a** and **2b**) derived from Schiff bases (**1a** and **1b**) with ethyl iodide or diethyl sulfate were run in aprotic solvents with or without added 18-crown-6 at appropriate temperatures. Table 1 summarizes the results of

alkylation, where the effects of 18-crown-6 on the yields and on the *N*/(*N*+*C*) ratios of the products can be seen. As the data in Table 1 show, the addition of 18-crown-6 to the reaction mixtures affects the *N*/(*N*+*C*) ratios of the products to remarkable extents. In the absence of 18-crown-6, the reaction of Schiff base with ethyl iodide in benzene gave no alkylation products, whereas in the presence of 18-crown-6 the reaction occurs to give the *C*-alkyl derivative as the main product. These results may be interpreted on the basis that ionization of **1a** did not occur due to the low solubility of sodium hydride in benzene. Indeed, we could not observe any deep color change of the reaction mixture due to ambident anion formation when the reaction of **1a** with sodium hydride was carried out in benzene for several h at 80 °C. Furthermore, in the presence of 18-crown-6, the reactivity of the carbon site is enhanced relative to that of the nitrogen site of the ambident anion. These results can be explained as follows. Sodium hydride is solubilized in benzene to produce a "crowned" ion pair, in which Na⁺ is linked coordinately to both the crown ether and the more electronegative nitrogen atom of the ambident anion. But the possibility of *C*-alkylation due to formation of a free naked anion cannot be ruled out. The *C*-alkylation is thought to take place as the main process.

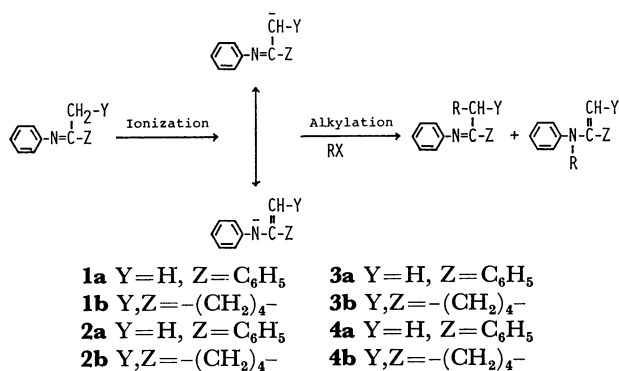
In the reaction of the ambident anion (**2**) with diethyl sulfate in dioxane, the *N*/(*N*+*C*) alkylation ratio is rather low; however, in the presence of 18-crown-6, the reaction under similar conditions gives a high yield of the *N*-alkylation, together with a low yield of the *C*-alkylation. These findings suggest that in the absence of 18-crown-6, the ambident anion (**2**), in analogy with sodium naphtholate²⁾ in dioxane and THF, exists as ion pairs and aggregates of a relatively high order; in the presence of 18-crown-6, however, the resulting ambident anion exists as an almost free anion due to solvation of the "crowned" sodium cation by dioxane because of the *N*-alkylation takes place. In support of this

TABLE 1. ALKYLATION OF SCHIFF BASES^{a)}

Substrate	Alkylating agent	Solvent	18-Crown-6	Ionization		Products, Yield/% ^{b)}					<i>N</i> / <i>N</i> + <i>C</i> ratio
				time h	temp °C	<i>C</i> -alkylation		<i>N</i> -alkylation	Total		
1a	EtI	C ₆ H ₆	presence	25	80	3a	58	4a	5	63	0.08
1a	EtI	C ₆ H ₆	absence	25	80	3a	0	4a	0	0	
1a	Et ₂ SO ₄	dioxane	presence	2	80	3a	5	4a	68	73	0.93
1a	Et ₂ SO ₄	dioxane	absence	4	80	3a	56	4a	6	62	0.10
1b	EtI	C ₆ H ₆	presence	16	80	3b	67	4b	11	78	0.14
1b	EtI	C ₆ H ₆	absence	16	80	3b	0	4b	0	0	
1b	Et ₂ SO ₄	dioxane	presence	2	100	3b	7	4b	84	91	0.92
1b	Et ₂ SO ₄	dioxane	absence	2	100	3b	52	4b	19	71	0.27

a) The alkylations of ambident anions with ethyl iodide or diethyl sulfate were carried out at 15 °C for 60 min. b) These results were obtained by GLC.

explanation, the reaction in Diglyme, in which the dissociation of sodio-derivative (**2**) takes place, fails to show any effect of the 18-crown-6 on the product ratio. It is quite remarkable that *C*-alkylation of Schiff bases proceeds smoothly to afford **3a** and **3b** in good yields. Furthermore, in the case of **1b**, the yield of *N*-alkylation products **4b** (84%) was higher than the yield reported from the described procedures,⁴ whereas for **1a** yields were relatively low compared with those obtained by reported methods. Our method, however, requires milder conditions of the reaction than alkylation by means of Et₃OBF₄ in Ethyl Cellosolve and ethyl iodide in xylene.⁴



Experimental

The products were analyzed on a Hitachi-023 gas chromatography equipped with a flame-ionization detector. We used a 2 m × 3 mm stainless steel column packed with 60–80 mesh Chromosorb-W NAW (washed with acid and treated with dimethyldichlorosilane) coated with 20% Apiezon-T (for the analysis of alkylation products of *N*-(α-methylbenzylidene)aniline at ca. 222 °C) or a 1 m × 3 mm stainless steel column packed with 60–80 mesh Chromosorb-W NAW (washed with acid and treated with dimethyldichlorosilane) coated with 20% Versamide (for the analysis of alkylation products of *N*-cyclohexylideneaniline at ca. 140 °C).

Materials. *N*-(α-methylbenzylidene)aniline,⁵ *N*-cyclohexylideneaniline,⁵ and authentic samples (*N*-(α-propylbenzylidene)aniline,⁵ *N*-ethyl-*N*-(α-methylbenzylidene)aniline,⁶ *N*-(2-ethylcyclohexylidene)aniline⁵ and *N*-(1-cyclohexenyl)-*N*-ethylaniline⁶) were prepared according to the procedures described in the literature. Sodium hydride and 18-crown-6 were of commercial origin and were used

without further purification. Ethyl iodide and diethyl sulfate were purified by distillation, as were the solvents.

General Procedure. Typical procedures for the reaction of ethyl iodide or diethyl sulfate with *N*-(α-methylbenzylidene)aniline and *N*-cyclohexylideneaniline follow.

Alkylation of *N*-(α-Methylbenzylidene)aniline with Ethyl Iodide in Benzene. Into a 50 ml round-bottomed flask equipped

with a magnetic stirring bar, 60% sodium hydride in oil (7.5 mmol), *N*-(α-methylbenzylidene)aniline (6.2 mmol), 18-crown-6 (7.6 mmol), and 13 ml of benzene were introduced. The reaction mixture was stirred at 80 °C. There was evolution of hydrogen, which ceased after 25 h. The resulting turbid brown solution was cooled to 15 °C and ethyl iodide (13 mmol) was added with cooling. The color changed to light yellow at the end of the addition. The reaction mixture was stirred for a further 1.0 h and then filtered to remove inorganic salts and the filtrate was analyzed by GLC. GLC analysis revealed the presence of three components, which were identified as **4a** (5%), unreacted Schiff base **1a** (37%), and **3a** (58%); the relative retention times of these three components were 1.00 : 1.08 : 1.30.

Alkylation of *N*-cyclohexylideneaniline with Ethyl Iodide in Benzene. A solution of **1b** (9.2 mmol) and 18-crown-6

(9.1 mmol) in 20 ml of benzene was stirred with 60% sodium hydride in oil (13 mmol) at 80 °C for 16 h. There was evolution of hydrogen, which ceased after 16 h. The resulting turbid yellow-brown solution was then cooled to 15 °C and treated with diethyl sulfate (9.3 mmol). The color changed to light yellow at the end of the addition of diethyl sulfate. After the reaction mixture was stirred for 10 h, the inorganic salts were filtered off and the filtrate was analyzed by GLC. The analysis by GLC revealed the presence of **4b** (11%), **1b** (18%), and **3b** (67%); the relative retention times of these compounds were 1.00 : 0.28 : 1.20.

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