Control of the Site of Alkylation of Ambident Anions

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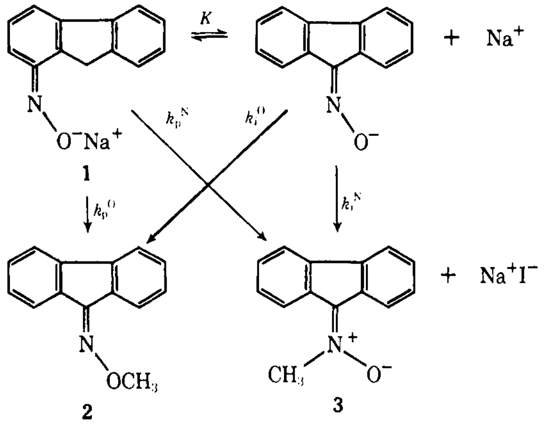
The reaction of sodium 9-fluorenone oximate with methyl iodide in 33.5% acetonitrile and 66.5% *tert*-butyl alcohol solvent at 25.0° gives a concentration dependent second-order rate constant and ratio of oxygen to nitrogen alkylation. The addition of stoichiometric amounts of dibenzo-18-crown-6 polyether eliminates the concentration dependence of the kinetic parameters over the region investigated, presumably by increasing the effective degree of dissociation of the sodium oximate. Sodium tetraphenylboride serves to depress the dissociation of the oximate salt and permits evaluation of the kinetic parameters for associated oximate. Methyl iodide is found to be more reactive toward the free ion than methyl *p*-toluenesulfonate, $k_i(\mathrm{MeOTs})/k_i(\mathrm{MeI}) = 0.68$, while the two reagents have nearly the same reactivity toward the associated sodium oximate, $k_p(\mathrm{MeOts})/k_p(\mathrm{MeI}) = 1.2$.

An understanding[1,2] of the interplay of the effect of cation,[3,4] solvent,[3-6] and alkylating agents[3-6] in the reactions of ambident anions is facilitated by studies which allow the dissection[1,4,7] of the overall reaction rate and product ratios into terms due to associated and dissociated ions. Failure to make this separation results in attempts to provide theoretical treatments[8,9] of rate levels and product selectivities of a series of reactions, each member of which may be proceeding through a different blend of reactants.

In a previous paper,[1] the alkylation[10] of sodium 9-fluorenone oximate (**1**) with methyl iodide in 33.5% acetonitrile-66.5% *tert*-butyl alcohol solvent at 25.0° (eq 1) was reported. This system displays a second-order rate constant which decreases by a factor of 8 as the concentration of sodium 9-fluorenone oximate is increased from 1×10^{-3} *M* to 88×10^{-3} *M*, suggesting that the dissociated ion is more reactive than the associated species. Furthermore, oxygen alkylation to form the *O*-methyl ether **2** was found to decrease from 65 to 46% over this concentration range.

Quantitative dissection of these data into contributions from free and associated ions requires extrapolation to very low and very high sodium oximate concentrations based on the shape of rate and product *vs.* concentration curves. In the present work, the use of dibenzo-18-crown-6 polyether[11] (**4**) to promote dissociation[12] and of sodium tetraphenylboride to suppress dissociation[13] is outlined.



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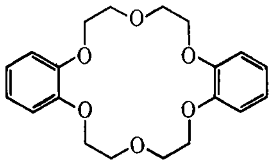

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Results and Discussion

The degree of dissociation of salts in a given solvent is influenced by, among other things, specific cation-anion interactions and the effective size of each ion.[14] Therefore, it is anticipated that the addition of dibenzo-18-crown-6 polyether (**4**) to a solution of sodium 9-fluorenone oximate in 33.5% *tert*-butyl alcohol-66.5% acetonitrile solvent would greatly increase the degree of dissociation[12] of the oximate salt.

Spectra.—A marked change in the color, indicative[12] of a change in the degree of dissociation, of a solution of the dissociation of sodium oximate **1** is observed upon addition of an equivalent amount of crown ether **4**. The visible absorption spectrum (Figure 1) indicates that the presence of crown ether results in a shift of a shoulder at 424 nm in sodium oximate **1** to a separate

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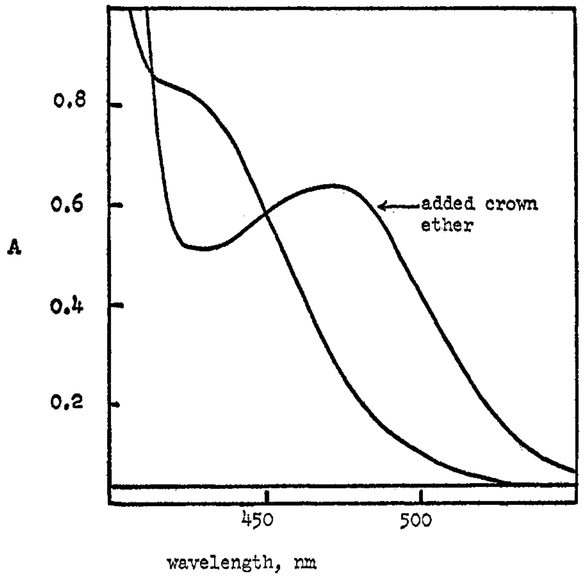

Figure 1.—Plot of absorbance *vs.* wavelength for 5 × 10^{-3} *M* sodium 9-fluorenone oximate in 66.5% acetonitrile-33.5% *tert*-butyl alcohol solvent with and without added dibenzo-18-crown-6 ether.

band with λ_{max} at 470 nm. Such shifts of absorption to longer wavelengths are characteristic of increased ion separation.[12]

Methyl Iodide.—Reaction kinetics provide further indications that the apparent degree of dissociation of sodium 9-fluorenone oximate in acetonitrile–*tert*-butyl alcohol solvent is markedly increased by the addition of stoichiometric amounts of crown ether III. As summarized in Table I, the observed second-order rate constant for alkylation with methyl iodide at 25.0° in the presence of the crown ether is constant, within experimental error, over a 14-fold variation in initial salt concentration. In the absence of the complexing ether, the observed second-order rate constant would have changed by a factor of *ca.* 2 over this concentration range. In addition, the rate level is substantially increased by added crown ether. For example, with 7 × 10^{-3} *M* sodium oximate solutions, complexing the sodium ion increases the observed rate constant by a factor of about 15.

The products of the reaction of methyl iodide with sodium 9-fluorenone oximate in the presence of the crown ether also reflect the properties of dissociated ions, with 64% alkylation on oxygen being observed, in agreement with previous estimates based on extrapolation to infinite dilution of 65% O- and 35% N-alkylation.

The addition of a salt such as sodium tetraphenylboride which has a large anion is the counterpart to increasing the effective size of the sodium ion to promote dissociation.[13] Sodium tetraphenylboride serves as a good source of free sodium ion to depress the dissociation of sodium 9-fluorenone oximate and permits exploration of the properties of the aggregated species. The data, summarized in Table I, indicate that with a *ca.* tenfold excess of $Na(C_6H_5)_4B$ the second-order rate constant for reaction with methyl iodide in this solvent system is depressed by a factor of 70 from that observed in the presence of the crown ether. In the presence of excess sodium ion the products now have the composition expected from the alkylation of the ion pair, with N-methylation (68%) dominating.

Table I

Summary of Rate Constants and Products for the Reaction of Sodium Fluorenone Oximate with Methyl Iodide or Methyl Tosylate in 33.5% Acetonitrile–*tert*-Butyl Alcohol at 25°

10^3[oximate], *M*	10^3[CPE],[a] *M*	10^2[$NaBPh_4$], *M*	10^2k_2, l./mol sec	Oxygen-methylation, % yield
		Methyl Iodide		
50	51		97 ± 5[b]	64
46	48		88 ± 9	65
24.3	25.6		105 ± 4	61
14.9	15.5		110 ± 20	66
7.5	8.2		108 ± 5	65
3.6	4.1		99 ± 5	65
9.0		7.7	1.37 ± 0.02	46
9.3		10.1	1.44 ± 0.02	43
9.7		10.6	1.4 ± 0.1	
9.7		14.0		41
9.1		15.0	1.34	41
9.5		17.0		40
		Methyl Tosylate		
55.8	56.1		66 ± 1	97
53.0	52.5		54 ± 3[c]	
25.5	28.0		61 ± 1	98
21.4	22.5		69 ± 0.1	
17.4	19.0		67 ± 4	99
10.0	11.0		67 ± 4	99
9.8	10.5		69	
5.3	5.6		69	99
5.2	5.1		60 ± 1[c]	95
9.0		7.7	1.5 ± 0.1	48
9.3		10.1	1.59 ± 0.04	45
9.7		10.6	1.67 ± 0.01	
9.5		14.2	1.9 ± 0.1	
9.1		15.0		42
9.5		17.0		43

[a] Dibenzo-18-crown-6 polyether. [b] Error given is average deviation. [c] CPE not in excess.

Although supporting direct measurements of the state of aggregation of the crown ether complex of sodium 9-fluorenone oximate in this mixed *tert*-butyl alcohol–acetonitrile solvent are lacking, the spectral shifts, high rate levels, concentration independent second-order rate constants, and high fraction of oxygen alkylation suggest either that the salt is essentially completely dissociated under the conditions employed in these experiments or that, because of the properties of the complexed cation, associated species have kinetic reactivities closely approximating those of dissociated ions.

Methyl *p*-Toluenesulfonate.—The nature of the leaving group is known to affect the relative rate of alkylation at the two sites of an ambident anion.[3–6] The tendency of enolate ions to give largely oxygen alkylation with alkyl toluenesulfonates, carbon alkylation with alkyl toluenesulfonates, and carbon alkylation with alkyl iodides has been rationalized by a symbiotic effect[8] in which the hard oxygen center of the enolate ion reacts preferentially with alkylating agents with a leaving group such as toluenesulfonate which is classed as hard; and, in this terminology, the relatively soft carbon atom has enhanced reactivity toward those alkylating agents, such as methyl iodide, which have a soft leaving group.

Pearson and Songstad[8] have suggested that the ratio of rate constants for reaction with alkyl tosylates compared to alkyl iodides, k_{OTs}/k_I, is a rough guide to the hard–soft character of a reactant. Since the observed rate constant and composition of the product mixture resulting from the alkylation of oximates is a function of the state of association of the oximate salt, it is of interest to compare the reaction of methyl iodide with methyl *p*-toluenesulfonate.

As summarized in Table I, the reaction of methyl *p*-toluenesulfonate, like methyl iodide, gives a second-order rate constant which is essentially independent of oximate concentrations from 5×10^{-3} to 5×10^{-2} *M* when 1 equiv of dibenzo-18-crown-6 polyether is present. Only O-methylation was detected over the concentration region investigated when the sodium ion was complexed with crown ether. Excess sodium tetraphenylboride depresses k_{obsd} by a factor of *ca.* 40 and changes the product from 99% oxygen to 54% nitrogen methylation.

To the extent that the observed rate constant in the presence of crown ether may be identified as k_i, the rate constant for reaction of dissociated oximate ion, and to the extent that those rate constants measured in the presence of excess sodium tetraphenylboride correspond to k_p, the rate constant for reaction of sodium 9-fluorenone oximate ion pair, it is possible to compare the reactivities of methyl *p*-toluenesulfonate and methyl iodide toward the free and associated ion. Toward the free ion, methyl tosylate is not so reactive as methyl iodide, $k_i(\text{MeOTs})/k_i(\text{MeI}) = 0.68$, while the two reagents have nearly the same reactivity toward the associated sodium oximate, $k_p(\text{MeOTs})/k_p(\text{MeI}) = 1.2$. That is, the gap between k_i and k_p, as measured by these techniques, is smaller for methyl tosylate than for methyl iodide. Although many additional factors may be involved, this result may be rationalized by postulating an enhanced reactivity for the sodium oximate ion pair with methyl tosylate because of the formation of a relatively tight sodium *p*-toluenesulfonate ion pair.

Dissecting the values of k_i and k_p further into rate constants for reaction on oxygen and nitrogen by multiplying the observed rate constants by the corresponding fraction of reaction at each site indicates that for the free ion the major difference between the two alkylating agents lies in the reactivity at nitrogen. Both reagents react at oxygen at the same rate, within experimental error; *e.g.*, $k_i^{O}(\text{MeOTs})/k_i^{O}(\text{MeI}) = 1.0$. Methyl iodide, however, gives an additional 35% N-alkylation, while no reaction at nitrogen through the free ion is observed with methyl tosylate, $k_i^{N}(\text{MeOTs})/k_i^{N}(\text{MeI}) = 0$.

In marked contrast to the properties of the free ion, the associated sodium 9-fluorenone oximate reacts with methyl tosylate and methyl iodide at nearly the same rate and gives essentially the same ratio of oxygen to nitrogen alkylation. This behavior is reflected in the value of $k^{N}(\text{MeOTs})/k^{N}(\text{MeI})$ which is zero for the free ion and 1.2 for the associated species. Therefore, the classification of the hard–soft character of the two sites in this oximate, by the criterion of Pearson and Songstad,[8] depends on the state of aggregation of the ambident ion, possibly because of an interaction between the leaving group and the cation of the ion pair.

Experimental Section

Materials.—Dibenzo-18-crown 6 ether was prepared by method X of Pederson[11] in 24% yield, mp 162–163° (lit.[11] mp 164°) after recrystallization from tetrahydrofuran. 9-Fluoreneone oxime was prepared as previously described.[1] The solvent mixture used (33.5% CH_3CN–66.5% *tert*-butyl alcohol) has also been described.[1]

Solution Preparation.—Solutions of appropriate approximate concentrations were made by adding measured volumes of sodium *tert*-butoxide solution, acetonitrile, and mixed solvent to weighed amounts of oxime and crown ether or sodium tetraphenylboride in bottles equipped with silicon rubber serum caps. The precise oximate concentration was then determined by titrating an aliquot with standard HCl, with metacresol purple being used as an indicator. Prepared solutions were used immediately.

Kinetics.—Samples of the prepared solutions were placed in silicon rubber serum capped spectrometer cells or, in the case of slow-reacting solutions, into small bottles similarly capped. These samples were equilibrated in a thermostated bath at 25.0°. An appropriate amount of methyl iodide or methyl tosylate was added to an equilibrated sample with a microliter syringe and a cell filled with the mixture was placed in a spectrometer. The absorbance change was followed at an arbitrarily selected wavelength between 435 and 470 nm. A scale expander was used to increase the apparent change for dilute solutions. The temperature of the cell block was controlled to 25.00 ± 0.02° with a proportional temperature control.

The oximate remaining after at least ten reaction half-lives was titrated with standard HCl and the quantity of alkylating agent was determined by difference. For the dilute solutions, a 5-ml sample was titrated; 1 ml was titrated for the more concentrated solutions. An excess of methyl iodide was added to the reacting solution after the infinity value had been determined and a baseline correction had been found and applied to all absorbance readings.

Spectra.—The spectra of the ion pair and the free ion were recorded with a 1-cm cell in a Perkin-Elmer Model 202 spectrometer.

Product Determination.—Products were determined by the method described by Smith and Milligan.[1]

Registry No.—**4**, 14187-32-7; sodium 9-fluorenone oximate, 20474-42-4; methyl iodide, 74-88-4; methyl tosylate, 80-48-8.

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