The Alkylation of Ambident Anions. IV. The Alkali Metal and Silver Salts of Formanilides[1,2]

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Systematic studies of the alkylation of a number of ambident or ambifunctional anions have been reported. For the vast majority of the anions examined reaction involved competition between carbon and a heteroatom and few competition between two heteroatoms. A study of the factors influencing the site of alkylation of the ambident anion of mono-*N*-substituted amides, where competition is between oxygen and nitrogen, has been undertaken. With the alkali metal and tetraalkylammonium salts of formanilide anions, the alkylation product is invariably the corresponding *N*-alkylformanilide. No detectable *O*-alkylation is observed as the solvent is varied from nonpolar through polar aprotic solvents, the alkylating agent through the various benzyl halides and *para*-substituted benzyl halides and the *para*-substituent on the formanilide from strongly electron donating (—OCH_3) through strongly electron withdrawing (—NO_2) groups. In contrast, with the silver formanilide salts, *O*-alkylation predominates but here the *O*:*N* alkylation ratio varies with the parameters examined. A rationale based on thermodynamic *vs.* kinetic control and reaction of dissociated *vs.* undissociated anion is presented to predict the site of reaction in these and other ambident systems.

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On rapporte les études faites sur l'alkylation de certains anions ambidentates ou ambifonctionnels. Pour la plupart des anions étudiés, la réaction fait intervenir une concurrence entre le carbone et un hétéroatome et peu de concurrence entre deux hétéroatomes. On étudie les facteurs qui influencent le site d'alkylation de l'anion ambidentate des amides *N*-monosubstitués où la concurrence se fait entre l'oxygène et l'azote. Avec les sels de métaux alcalins oû les sels de tétraalkylammonium des anions formanilides, le produit de l'alkylation est invariablement le *N*-alkylformanilide correspondant. On n'observe pas de *O*-alkylation alors qu'on fait varier le solvant de nonpolaire à polaire aprotique, et qu'une variété d'halogénures de benzyle et d'halogénures de benzyle *para*-substitués servent à l'alkylation et que pour les substituants en *para* du formanilide on utilise une variété de groupes allant de groupes fortement donneurs d'électrons (—OCH_3) à des groupes fortement accepteurs d'électrons (—NO_2). Par contre, avec les sels d'argent du formanilide, la *O*-alkylation prédomine, mais ici le rapport d'alkylation *O*:*N* varie avec les paramètres examinés. On présente une explication logique pour prévoir le site de la réaction pour les systèmes ambidentates et aussi pour d'autres systèmes. Cette explication est basée sur une comparaison entre la thermodynamique et le contrôle cinétique d'une part et entre une réaction à anions dissociés et une réaction à anions non-dissociés d'autre part. [Traduit par le journal]

The term "ambident anion" was introduced by Kornblum *et al.* in 1955 (1) for anion systems containing two centers susceptible to electrophilic attack but in which only one of the centers takes part in the transition state of the electrophilic attack. Ambident or ambifunctional anions were, of course, known much earlier. For example the alkylation of polyhydroxylic benzene salts was first examined in the 1880's with carbon and oxygen alkylation being observed (2) and as early as the 1860's it was recognized that the reaction of silver cyanide with alkyl halides gave an isomer of the product obtained with potassium or sodium cyanide (3). Such ambifunctional nucleophilic species are far more commonly encountered than most practicing chemists realize. Gompper has, for example, listed some three dozen classes of compounds and anions exhibiting such behavior (4*a*). It is only in the past two decades however, that systematic studies of the factors involved in the competition between the nucleo-

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[1] While not sequentially numbered, refs. 20, 21, and 6*a* are considered to be parts I, II, and III of this series.

[2] Taken in part from the M.Sc. Thesis of S.-H. Tan (1971), available on interlibrary loan from Memorial University of Newfoundland Library, St. John's.

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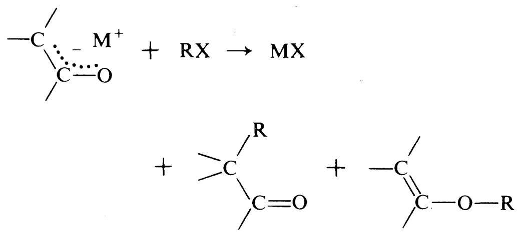
TABLE 1. A summary of the effect of some variables on the site of alkylation of phenol and pyrrole anions

	Effect of change on ambifunctional anion alkylation			
Variable and change made	Phenol anions	Reference	Pyrrole anions	Reference
Temperature; increasing	Increased *ortho*-carbon alkylation	22	Small increase in 2-alkylation	11
Counter ion; $R_4N^+ \rightarrow K^+ \rightarrow Na^+ \rightarrow Li^+(MgX^+)$	Increased *ortho*-carbon alkylation, slower reaction	22, 24	Greatly increased 2-alkylation	11, 23
Solvent; increasing polarity, aprotic	Increased oxygen alkylation	22, 24, 25	Increased *N*-alkylation	11
Solvent; aprotic to polar protic	Much *para*-carbon alkylation	26, 27	—	
Alkyl halide; saturated to allylic halide	Much increased *ortho*-carbon alkylation	22	—	
Substituents on anion electron donors	*meta*, increased *ortho*-carbon, *para*, increased oxygen alkylation	22, 20	—	
Physical state; homogeneous to heterogeneous reaction media	Increased *ortho*-carbon alkylation	22, 28, 6*a*	Increased 2-alkylation	11

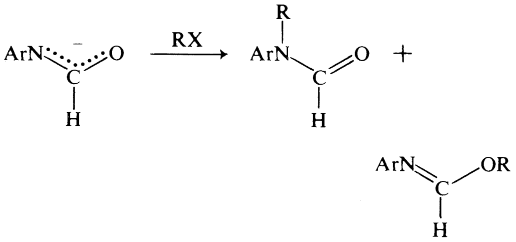
philic centers of ambident anions for reaction with electrophiles have been undertaken (4). These studies have greatly increased the appreciation of the importance of solvent character and composition, of ion pairs, of counter ion and related factors in such systems and in fact in any chemical reaction.

In Table 1 are summarized the effects of some of the variables examined upon the competition between the nucleophilic sites for reaction with alkyl halides in two of the most extensively studied systems, the ambifunctional anions of phenols and pyrroles. Obviously the variables listed are not all independent. Changing the solvent, for example, from a nonpolar one like toluene to a better cation solvating one like dimethylformamide (DMF) also changes the degree of heterogeneity of the reaction mixture and the degree of S_N1–S_N2 character of the transition state for alkylation. The heterogeneity of the reaction is also affected by the counter ion and by temperature. Attempts to explain the empirical observations on the basis of the S_N1 *vs.* S_N2 character of the alkylation (1) or the homogeneity *vs.* heterogeneity of the reaction media (5) have met with dubious success (4*c*, 6).

The most extensively studied ambifunctional anions are the enolate (4, 7) and the phenolate or phenoxide anions (4, 6*a*, 8) for which the competition for alkylation is between carbon and oxygen (reaction 1).

[1]


Other species studied to a greater or lesser extent include the cyanide (1, 18) and pyrryl anions (11), and the anions of the various esters, nitriles, etc. (4*a*) where the competition for alkylation is between carbon and heteroatom, usually oxygen, nitrogen, sulfur, or phosphorus. Relatively few systematic studies of anions in which there is competition between different heteroatoms have been reported. For example, the only ambifunctional anions in which alkylation competition between oxygen and nitrogen has been examined in any detail are the nitrite (1), 4-hydroxy-pyrimidine (9), pyridone (10), and oxime anions (4*c*). Consequently a systematic study of the factors influencing the oxygen–nitrogen alkylation competition on the salts of mono-*N*-substituted amides was undertaken.

[2]


Nitrogen alkylation of the ambifunctional anion (reaction 2) would lead to the amide, *N*-alkylformanilide, while oxygen alkylation would lead to that class of product variously called imidate (ester of an imidic acid), imidoester, iminoether, etc. In this article the imidate nomenclature will be used so that for R = benzyl and Ar = C_6H_5, the oxygen alkylation product is benzyl *N*-phenylformimidate.

The anion of formanilide was chosen for the initial studies because the various formanilides are easily prepared, *para*-substituents on the aromatic ring can be readily varied from strongly electron donating to strongly electron withdrawing substituents with little or no steric effect at the reaction center, the substituent effect would be far more pronounced at one of the ambident centers (nitrogen) than at the other and, finally, there are no acidic carbon hydrogens as there would be with, for example, acetanilides which could lead to complications. The study of *N*-aryl or alkyl benzamides was contemplated but initial examination showed the benzimidate products from alkylation of benzanilide anions were not sufficiently thermally stable for gas chromatographic analysis.

Results

The system examined is summarized in Table 2. Tabulations of results appear in the Experimental Section and some generalizations follow.

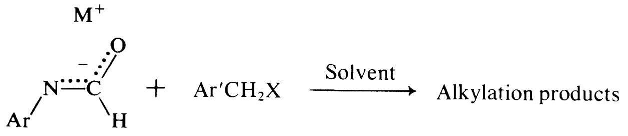
The Alkali Metal and Tetramethyl Ammonium Salts

Typical results appear in Table 3.

Reaction Product

The exclusive detectable alkylation product was the *N*-alkylated amide, that is the corre-

TABLE 2. Alkylation of salts of formamides: the cases examined*



Ar	M^+	Ar′	X	Solvent
C_6H_5—	$[(CH_3)_4N^+]$	C_6H_5—	Cl	Hexane, hex
(p-$CH_3C_6H_4$—)	K^+	p-$CH_3OC_6H_4$—	Br	(Benzene)
p-$CH_3OC_6H_4$—	(Na^+)	p-BrC_6H_4—	I	Toluene, tol
p-BrC_6H_4—	Li^+	(p-$NO_2C_6H_4$—)		Dimethoxyethane, DME Dimethylformamide, DMF
(p-$NO_2C_6H_4$—)	Ag^+			(Dimethyl sulfoxide, DMSO)†

*Not all combinations and permutations were run but except for those cases enclosed within parentheses where relatively few reactions were run, a large number for each variable were done.

†DMSO was partially reduced to the sulfide and the imidates were unstable in basic DMSO. It was used for few reactions.

sponding *N*-benzylformanilide product in all cases.

Reaction Rate

Since the majority of the reaction mixtures were visibly heterogeneous, meaningful kinetic studies were not possible. Any rate constants obtained could represent some combination of the alkylation rates for the dissociated, the associated or ion-paired, and the solid salt or possibly the rates for dissociation or solution of the salt. Some generalizations can be reported though.

(*i*) Solvent effects: the more ionizing, better solvating solvents give a faster, more nearly complete reaction. For example, with the potassium salt of *p*-bromoformanilide with benzyl bromide at 22° for 40 h the alkylation yields in hexane, toluene, DME, and DMF were 46, 63, 95, and 96% respectively.

(*ii*) Cation effects: in all cases the lithium salt reacted more slowly with progressively smaller rate increases through the series Li^+, Na^+, K^+, $(CH_3)_4N^+$. For example the lithium salts in the less solvating solvents, hexane, toluene, and often even DME, required heating to give appreciable conversion. In hexane even prolonged heating normally gave 5% or lower yields. By contrast the potassium and tetramethylammonium salts react readily at room temperature even in hexane.

(*iii*) Alkyl halide structural effects: benzyl iodide reacted readily at room temperature almost invariably while in the less ionizing solvents, especially hexane and toluene, with the lithium salts benzyl bromide alkylations required a reflux period. Benzyl chloride itself would not react with the lithium salts in any of the solvents. Substituents on the benzyl halides had the anticipated effects; *para*-electron withdrawing substituents retarded, donors accelerated the reactions.

(*iv*) Formanilide substituent effects: formanilide substituents with the lithium salts in particular have the opposite effect to that one might predict. Thus with benzyl iodide in DME, lithium *p*-methoxyformanilide was only 64% alkylated after 3 h at reflux while the *p*-hydrogen analog was 87% converted, and at room temperature the latter was essentially stable but the *p*-bromoanalog was nearly 90% alkylated in 4 days.

The Silver Salts

Reaction Product

In marked contrast to the alkali metal salts, where the product was exclusively that of *N*-alkylation, with the silver salts the major product was almost invariably that of oxygen benzylation, the corresponding imidate. Here however both *O*- and *N*-alkylation products resulted and the *O*/*N* product ratio varied with the parameters examined. Some typical results appear in Table 4.

Reproducibility in the *O*/*N* ratios was very difficult to achieve. While the amide is quite inert, the imidate is very susceptible to hydrolysis (14). Removal of the products, especially the imidate, from the solid, unreacted silver formanilide and the silver halide co-product was difficult and especially so in the less polar hydrocarbon solvents. Consequently, the specific *O*/*N* ratios should be considered minimum

TABLE 3. Some reactions of alkali metal and tetraethylammonium formanilides

M^+	Formanilide	Benzyl	Halide	Solvent	Conditions*	Yield†
Li^+	*p*-H	*p*-H	I	DME	24 h	negl.
				DME	1 h, reflux	87%
				DMF	24 h	81.2
		p-H	Br	hex	3.5 h, reflux	4.8
				tol	3.5 h, reflux	2.1
				DME	2 h, reflux	95
				DMF	20 h	77
		p-Br	Br	DME	7 d	88
				DMF	7 d	98
		p-NO_2	Br	DME	6 d	88
		p-CH_3O	Br	DMF	3 d	94
		p-H	Cl	DME	36 h, reflux	negl.
		p-CH_3O	Cl	DMF	3 d	97
K^+	*p*-H	*p*-H	I	DME	1 d	95
				DMF	1 d	93.5
		p-H	Br	hex	20 h	85.5
				tol	20 h	95
				DME	20 h	93.5
				DMF	20 h	96
		p-Br	Br	DME	7 d	98
				DMF	7 d	98
		p-NO_2	Br	DME	6 d	74
		p-CH_3O	Br	DME	3 d	99
				DMF	3 d	91.5
		p-H	Cl	DME	2 d	<2
				DMF	2 d	98
		p-CH_3O	Cl	DME	3 d	88
				DMF	3 d	90.5
Et_4N^+	*p*-H	*p*-H	Br	DMF	3 h, 20 °C	82%
Li^+	*p*-CH_3O	*p*-H	I	DME	3 h, reflux	64
				DMF	3 d	83
		p-H	Br	hex	24 h	negl.
				hex	16 h, reflux	5
				tol	24 h	negl.
				tol	16 h, reflux	6
				DME	45 min, reflux	73
				DMF	48 h	74
K^+	*p*-CH_3O	*p*-H	I	DME	3 d	88
				DMF	3 d	79
		p-H	Br	hex	20 h	77
				tol	20 h	78
				DME	20 h	67
				DMF	20 h	66
Li^+	*p*-CH_3O	*p*-H	I	DME	4 d	89
				DMF	4 d	98
Li^+	*p*-Br	*p*-H	Br	hex	19 h, reflux	4.3
				tol	19 h, reflux	82
				DME	6 h	negl.
				DME	20 min, reflux	92
				DMF	48 h	86
K^+	*p*-Br	*p*-H	I	DME	4 d	92
		p-H	Br	hex	40 h	46
				tol	40 h	63
				DME	40 h	95
				DMF	40 h	96
Li^+	*p*-NO_2	*p*-H	I	DME	4 d	36
K^+	*p*-NO_2	*p*-H	I	DME	4 d	93

*Reactions were run at room temperature, 22 ± 1 °C unless otherwise stated.
†Yields are based upon weight of formanilide salt. No detectable formanilide was found in any reactions.

TABLE 4. Some reactions of silver formanilides

Formanilide	Benzyl	Halide	Solvent	O/N product ratio	Yield* (%)
p-H	p-H	I	hex	0.1–0.2	60–80
			tol	0.6–0.7	80–83
			DME	14–21	>85
			DMF	1.3	70
p-H	p-H	Br	hex	8	58–74
			tol	8.5	80–92
			DME	17	80–98
			DMF	1.4	72.5
p-H	p-H	Cl	All solvents, negl. reaction in 20 days at 22°		
p-H	p-Br	Br	hex	4.8	69
			tol	7.0	79
			DME	13.2	83
			DMF	2.0	97
p-H	p-CH_3	Br	hex	10.7	79
			DME	12.6	79
			DMF	1.6	78
p-CH_3O	p-H	I	hex	0.4	71
			tol	0.6	93
			DME	4.2	95
			DMF	0.8	80
p-CH_3O	p-H	Br	hex	3.7	78
			tol	12.2	67
			DME	8.8	58
			DMF	1.0	61.5
p-Br	p-H	I	hex	0.04	93
			tol	0.3	93
			DME	9.4	85
			DMF	0.9	76
p-Br	p-H	Br	hex	1.3	82
			tol	6.0	77
			DME	10	88
			DMF	0.5	77

*Reactions were run 2 or 3 days at 22° with continuous shaking and yields are based upon the weight of starting silver salt and analysis of the product solution.

values, at best approximations, and interpreted with care. Some generalizations can, however, be made about the product distribution.

(*i*) Solvent effects: O/N ratio increases in going from hexane to aromatic hydrocarbons to DME where it normally maximizes and then decreases markedly in DMF.

(*ii*) Halide structural effects: in DMF, the O/N ratio is comparatively independent of the choice of benzyl halide and is about one. In the nonpolar hydrocarbon solvents benzyl iodide gives a markedly lower O/N ratio than benzyl bromide while in DME the ratios maximize and are about equal for the two halides. With benzyl bromide *para*-electron withdrawing substituents apparently decrease, donors increase the ratio in the less polar solvents.

(*iii*) Formanilide substituent effects: both electron donors and electron withdrawing *para* substituents lead to reduced O/N-benzylation ratios.

Reaction Rates

All reactions tabulated were run for 2 or 3 days at room temperature with continuous shaking and the variation in degree of completion in duplicate reactions using different salt preparations was often of the same order as that with different solvents, alkylating agents, and formanilides. No conclusions concerning rates can be reached.

Discussion

Since a difference in activation energy of only a few kcal/mol would result in a 100:1 product ratio, the activation energies must be nearly equal to get similar amounts of the two products in ambident anion alkylations. Imidates thermally rearrange to the corresponding *N*-substituted amide, a reaction known as the Chapman rearrangement (13). Under conditions where the amide is comparatively stable, imidates rapidly hydrolyze (14). Calorimetric studies have not been done but bond strength or bond dissociation energy values can be used to estimate the difference in stability between the imidate and amide. Unfortunately, values for bonds in appropriate systems are not readily available but by assuming that the only difference between the two products is that in the imidate, two C—O bonds and a C═N bond replace the appropriate C—N bonds and the C═O bond of the amide, the imidate can be estimated to be at least 3 kcal/mol higher in energy.

Imidates then are clearly thermodynamically less stable than the isomeric amide so that via the Hammond Postulate, the transition state for *N*-alkylation should lie lower than that for *O*-alkylation. The difference in activation energy for *N*- or *O*-alkylation would presumably be lower than the difference in product stability but should be an appreciable fraction of it.

Under what conditions would *O*-alkylation or *N*-alkylation of the formanilide anion be expected? Obviously when the alkylation proceeds by a mechanism which approximates thermodynamic control, the more stable *N*-alkylated formanilide will be the almost exclusive product. Only under reaction conditions where kinetic rather than thermodynamic product control occurs could *O*-alkylation be significant. In the alkylation of solvated or free anion the reaction would be expected to approach thermodynamic control since there should be no factors other than the energetic requirements favoring one product over the other. In the case of the alkylation of ion paired, aggregated, or crystalline salt, however, kinetic product determination is possible. If the counter ion is associated principally with one site of the ambifunctional species, that atom should be sterically and electronically less favorable for attack by the alkylating agent. The prediction then is that with the free or solvated formanilide anion, only *N*-alkylation would be observed while for associated material, when the counter ion is associated with nitrogen, oxygen alkylation should be favored. When the counter ion is associated with oxygen, nitrogen alkylation should again predominate. The predictions should apply whether the transition states are analogous to those proposed for phenolate alkylations (5) with linear, "classical" S_N2 displacement of the leaving group of the alkylating agent (here the negative charge would be developing on a leaving group far removed from the counteracting charge of the cation) or if bent, six center transition states occur.

In other systems, the rate of alkylation of dissociated material is invariably much higher than that of associated material (4*c*, 15). Thus in the more ionizing, better solvating solvents where appreciable concentrations of dissociated formanilide are present and equilibrium between associated and dissociated material should be maintained throughout the reaction, the thermodynamically favored *N*-alkylated product forms. Even if the reaction mixture is visibly heterogeneous, the reaction could occur almost exclusively on the dissociated anion especially with the tetraethylammonium and potassium salts (where the cation requires less solvation than for example the smaller lithium cation) in DMF and progressively less so in DME, the aromatic and saturated hydrocarbon solvents. At the other extreme, the concentration of the dissociated species would be extremely low for lithium formanilides in the nonionizing solvents like hexane so that the usually slower reaction of associated material, the heterogeneous reaction, would be the dominant one. Here kinetic control of the reaction still leads to the thermodynamically more stable product, that of *N*-alkylation.

The observation that especially with the lithium salts, electron withdrawing substituents in the *para*-position of the formanilide leads to a rate acceleration in DME, for example, rather than the retardation expected on electronic grounds is understandable in light of the above explanations. The electron withdrawing substituent further distributes the negative charge of the formanilide anion reducing the solvation necessary for dissociation, the concentration of the free anion is increased, and the faster reaction of the dissociated anion makes a larger contribution to the overall reaction rate.

In the cases reported here, both the homogeneous and the heterogeneous reactions of the alkali and tetramethylammonium cations lead to *N*-alkylation. These cations, if the proposed heterogeneous mechanisms are correct, must be associated with oxygen of the ambident formanilide anion. This is predicted by the theory of hard and soft acids and bases (16). While the lithium cation is "softer" than the potassium cation, all the alkali metal cations are considered to be "hard". Oxygen carrying a negative charge is "harder" than nitrogen. Since "hard" cations would associate with the "harder" oxygen center of the ambifunctional anion, *N*-alkylation occurs. With "soft" cations association would be at the "softer" nitrogen and oxygen alkylation should become important. The silver cation is "soft" and a standard route to the imidates is the alkylation of the silver salt of the corresponding mono- *N*-substituted amide (17).

Even with the silver counter ion, there would still be a competition between alkylation of dissociated and associated anion. Reaction of the dissociated species should be analogous to the alkylation of dissociated formanilide in the presence of any other cations and would be expected to lead to the thermodynamically more stable *N*-alkylated formanilide. Undissociated silver formanilide with the "soft" silver counter ion associated with the "softer" nitrogen would be expected to give principally *O*-alkylation through the kinetically controlled reaction. Thus in DMF where the degree of dissociation should be greatest among the solvents employed, the thermodynamically more favored amide product is more important than in DME where the degree of dissociation is lower.

It is perhaps initially surprising that the amount of *O*-alkylation falls off again in the least ionizing solvents employed, the hydrocarbons. There must be a change in mechanism. In these solvents with very low dielectric constant, even moderate separation of the ionic centers would be energetically undesirable so that a four-center reaction involving silver, halide, formanilide, nitrogen, and the halide carbon is a likely competitive transition state. Such a transition state would be more favorable for the iodide than bromide alkylating agent because the "soft" silver cation would form a more stable system with the "softer", larger iodide (16). With benzyl bromide, electron donors in the *para*-position would be expected to favor, withdrawers to disfavor this four center ion pair exchange mechanism.

Similar rationalizations and predictions of the sites of reaction for other ambifunctional anions with alkylating agents can be made. Given information as to which product's formation is thermodynamically favored, which center of the anion is "harder" or "softer", and assuming that reaction of dissociated material approaches thermodynamic product control while reaction of associated material is principally at the site not occupied by the counter ion, the empirical observations in the following illustrative examples are those that would be predicted.

The anion of pyridone is an ambident species somewhat analogous to the formanilide anion. Both oxygen and nitrogen alkylation can occur and while the products are more nearly equal in stability, *N*-alkylation is thermodynamically preferred at least for the less sterically demanding alkyl halides (10*b*). Again oxygen is the "harder" site. As expected on alkylation with benzyl bromide, the sodium salt in nonpolar or polar aprotic solvents gives predominantly *N*-benzylated product. The silver salt in nonpolar solvents (pentane or benzene) gives exclusively *O*-benzylation but in DMF the *O*/*N* ratio is nearly 1 (10).

Another anion in which there is competition between oxygen and nitrogen and in which the nitrogen is the "softer" center and leads to the more stable product, is the nitrite ion. Silver nitrite gives far more of the nitrite ester and less of the nitroalkane than does the sodium salt and solvent effects are logical (1). The cyanide ion has long been known to give alkyl cyanides or the considerably less stable isocyanides (17) depending upon the cation (1). Here nitrogen is the "hard" center and alkali metal cyanides give alkyl cyanides regardless of whether the solvent used is polar, nonpolar, protic, or aprotic (18). With "softer" cations like Ag^+, Cu^+, Hg^+, Zn^{2+} which associate at the "soft" carbon, alkylation occurs predominantly on the more available nitrogen, but in the more ionizing solvents more alkyl cyanide is found (18).

Experimental Section

Solvents

All solvents were reagent grade, thoroughly dried, and distilled in oven-dried glassware under a nitrogen atmosphere immediately before use. Hexane, benzene, toluene, and dimethoxyethane (DME) were dried by refluxing over sodium wire for some hours before distillation while dimethylformamide (DMF) was heated at 50° over calcium hydride for at least 24 h before vacuum distillation.

Formanilides

Formanilide obtained from Eastman Organic Chemicals was twice recrystallized from aqueous ethanol and dried as below. Substituted formanilides were prepared from the corresponding *para*-substituted anilines available from Eastman or Aldrich Chemical Co. The anilines were refluxed with a three- to five-fold excess of formic acid for 2–4 h, the excess formic acid and water were distilled, and the residue treated with a fresh portion of formic acid if necessary to increase conversion. The residue was cooled, allowed to crystallize, the solid broken into small pieces and then repeatedly washed with ice water until the washings were no longer acidic. Sharp melting, analytically pure colorless (except for the yellow *para*-nitro analog) crystals were obtained after several recrystallizations from aqueous ethanol and drying in a vacuum desiccator over phosphorus pentoxide.

Benzyl Halides

Benzyl chloride, bromide, and iodide were obtained from Aldrich and purified by vacuum fractionation. The purity of the *p*-methoxybenzyl chloride, *p*-methyl-, and *p*-nitrobenzyl bromide from Eastman and the *p*-bromobenzyl bromide from Aldrich was checked by gas chromatography and all were used without purification. *p*-Methoxybenzyl bromide was prepared according to Kornblum *et al.* (1) and used immediately.

Formanilide Salt Preparation and Alkylation

All glassware was oven dried, all manipulations were performed in a nitrogen filled drybox, and all reactions were conducted under a slight positive pressure for dry nitrogen.

Lithium Formanilides

Into a 500 ml flask containing 0.105 mol of formanilide, 200 ml of DME was distilled and after the formanilide was completely dissolved, 0.794 g (0.100 mol) of lithium hydride was added. The flask, equipped with a condenser topped by a dry nitrogen source and bubbler was slowly heated to reflux in an oil bath while being stirred magnetically. Hydrogen evolution commenced at about 50° and the white lithium formanilide salt gradually deposited at gentle reflux. Hydrogen evolution usually ceased after about 5 h but reflux was continued several additional hours. The flask was cooled, transferred to the drybox, and the white salt collected by suction filtration through a sintered glass funnel. After several washings with cold DME, the salt was sucked dry, transferred to a tarred 250 ml flask, heated at 50–60°, and pumped overnight to remove the last traces of solvent. Yields normally exceeded 90%.

Potassium and Sodium Formanilides

The procedure used was analogous to that for the lithium salt except that 0.100 mol of freshly cut and trimmed alkali metal was used and benzene replaced the DME. (Benzene was used as the solvent because, especially the potassium salts, were moderately soluble in DME.) With potassium, the reaction proceeded rapidly when the metal began to fuse. Sodium was coated with a layer of salt, reaction was slow and completion difficult to achieve. Yields exceeded 90% for the potassium salts.

Purity of the Alkali Metal Formanilides

Titrimetric determination of the neutralization equivalents by titrating an aqueous solution to the phenolphthalein end-point with standard hydrochloric acid showed the salts to almost invariably have an excess alkalinity of about 2%. In the case of the lithium salts this was mainly due to LiOH impurity in the hydride used. With potassium and especially the sodium salts which were little used for that reason, there were occasionally minute, salt encrusted globules of unreacted metal present. While some hydroxide would also invariably be present there was no apparent difference in the alkylation results when no or when considerable excess alkalinity was shown, only salt with 98% or greater titrimetric purity was used.

Tetraethylammonium Formanilides

The silver formanilides were prepared according to Comstock and Kleeberg (19) and about 0.025 mol was stirred in the dark for 3 days with a molar equivalent of tetraethylammonium chloride (Aldrich) in 60 ml of dry DME. The quantitatively precipitated silver chloride was removed by suction filtration in the drybox, the DME removed at 28–30° under vacuum, and the residual salt used without further purification.

Silver Formanilides

Silver formanilides and the substituted formanilides were prepared, collected, and purified by a process analogous to that of Comstock and Kleeberg (19) and dried over P_2O_5 in a vacuum desiccator for several days. The salts were protected from light throughout by subdued lighting and by wrapping flasks, etc. in aluminum foil. Yields of dry, finely ground powder were over 90%. Purity was checked by igniting a sample of 0.5–0.7 g of the silver salt in a porcelain crucible. The residual silver metal was taken up in 3 *N* nitric acid, any carbon and other residues removed by filtration, and the silver determined as silver chloride. Typical silver contents, determined and theoretical values respectively, are: silver formanilide 46.0%, 47.32%; silver *p*-methoxyformanilide 41.8%, 40.9%; silver *p*-bromoformanilide 35.1%, 34.6%. Because the silver formanilide salts smoked extensively on ashing, a very fine, powdery ash formed initially and even prolonged heating over a burner did not oxidize the last of the carbon, duplicate and triplicate runs normally agreed only to within about 2%.

General Alkylation Procedure

All manipulations were done in a nitrogen filled drybox and the silver salts were protected from light throughout. About 40–50 ml of the solvent chosen was distilled into a 100 ml flask containing 0.01–0.02 mol of finely ground formanilide salt. A 5% excess of the appropriate benzyl halide (neat if it was a liquid, in a small amount of the solvent if solid) was dropped in with stirring or swirling. The flask was stoppered and allowed to stand with either occasional stirring or shaking in the drybox or

TABLE 5. Melting points and elemental analyses of *O*- and *N*-alkylated products

		N-Alkylated product		*O*-Alkylated product		
R_1*	R_2*	M.p. (°C)	Found	M.p. (°C)	Found	Calculated
H	H	48 (lit. 48)		13–14	C: 79.59 H: 6.15 N: 6.56	C: 79.60 H: 6.20 N: 6.62
H	CH_3	45	C: 79.88 H: 6.68 N: 6.19	69	C: 80.11 H: 6.80 N: 6.25	C: 80.00 H: 6.66 N: 6.22
H	CH_3O	69	C: 74.43 H: 6.06 N: 6.00	†	†	C: 74.69 H: 6.22 N: 5.81
H	Br	77	C: 57.83 H: 4.15 N: 4.64 Br: 27.57	79–80	C: 57.89 H: 4.33 N: 4.87 Br: 27.34	C: 57.93 H: 4.13 N: 4.83 Br: 27.58
CH_3O	H	48.5–49	C: 74.59 H: 6.11 N: 5.86	80.5	C: 74.55 H: 6.39 N: 5.91	C: 74.69 H: 6.22 N: 5.81
Br	H	61.5	C: 57.72 H: 4.33 N: 4.63 Br: 27.35	71.5–72	C: 57.75 H: 4.20 N: 4.73 Br: 27.53	C: 57.93 H: 4.13 N: 4.83 Br: 27.58
NO_2	H	100				
H	NO_2	100.5–101				

*R_1 and R_2 are, respectively, the *para*-substituent on the formanilide and on the benzyl halide used to prepare the particular alkylated formanilide.

†Thermal rearrangement of the *O*- to *N*-alkylated product upon distillation prevented isolation of analytical samples.

with continuous shaking with a mechanical shaker for 4 h to 4 days at room temperature except for the lithium salts which were usually refluxed in hexane and DME to shorten the reaction time. No change in the alkylation product composition was observed with reaction time and *N*-alkylated or *O*-alkylated formanilide added to the reaction was recovered quantitatively in the products. The reaction mixture was suction filtered and the solid, a mixture of unreacted formanilide salt and of metal halide, was washed with several small fractions of fresh solvent. The filtrate volume was noted and it was subjected to quantitative gas chromatographic analysis. The column packing was 1.5% OV-17 on 60–80 mesh Chromosorb G in a 10-ft, 1/8 in. o.d. stainless steel column except for the analysis of products with *p*-bromo- or *p*-nitro- substituents where a 6 ft column was used. The thermal conductivity detector was calibrated for each formanilide and corresponding *N*- and *O*-alkylation product. With a 45 ml/min helium flow rate at 227° for the unsubstituted and 255° for the mono-substituted cases, the formanilides had a retention time of 0.5–1.2 min, the formimidates about 2.5 min, and the *N*-benzyl formanilide about 3.5 min. Unreacted benzyl halide eluted immediately after the solvent.

Detection limits for the unreacted and alkylated formanilides ranged from less than 0.3% yields for recovered unsubstituted formanilide and the corresponding formimidate to about 0.75% yields of the disubstituted *N*-benzylformanilides. No measurable formimidate was found in any of the alkylations of alkali metal or tetramethylammonium formanilide salts. Usually 95% or more of the starting formanilide was accounted for by products and/or recoverable from unreacted salt. Alkylation product yields and, for the silver salts, *O*/*N* product ratios are reported in the accompanying tables.

Preparation and Purification of the N-Alkylation Products

The *N*-alkylation products could be isolated in fair to good yields from the appropriate lithium or potassium formanilides after reaction with the benzyl halide usually in DME. A 1:1 molar ratio of reactant and halide in DME was refluxed for 3–4 h, the solvent was stripped off, and the residue taken up in ether and water. The ethereal extracts were dried over $MgSO_4$ and concentrated. After 2–3 recrystallizations from ether analytically pure *N*-benzyl formanilides were obtained in overall yields of about 50%. Melting points and analyses are reported in Table 5 while some spectral data appears in Table 6.

Preparation and Purification of the O-Alkylation Products

The crude formimidates were obtained from the benzylation of the appropriate silver formanilide in DME. Separation from the *N*-alkylation product was achieved by collection from the gas chromatograph using an 8 ft, 1/4 in. o.d. stainless steel column packed with the same material as the analytical column run under similar conditions. Liquid materials were purified

TABLE 6. Spectral data of *N*-alkylated formanilides

R_1	R_2	Infrared C=O (cm^{-1})	Nuclear magnetic resonance (τ)*			Ultraviolet (mμ)†	Mass spectra (mass unit)	
			H—C=O	—CH_2—	CH_3—	λ_{max}(log ε)	Base peak	Parent peak (%)
H	H	1666	1.40	4.97		233(3.91)	91	211(47.75)
H	CH_3	1666	1.54	5.00	7.68	222(4.01)	105	225(22.80)
H	Br	1669	1.42	5.05		225(4.20)	169 171(96.49)	289(39.47) 291(38.60)
H	CH_3O	1669	1.44	5.03	6.26	227(3.98) 285(sh)		
Br	H	1666	1.42	5.00		243(4.23)	91	289(12.75) 291(12.75)
CH_3O	H	1675	1.75	5.06	6.31	230(4.02) 280(sh)	91	241(60.75)
NO_2	H	1670	1.07	4.85				
H	NO_2	1666	1.32	4.85				

*All show singlet absorption, the aromatic protons are multiplet and are not reported.
†Determined in methanol, measured from 220 mμ.

TABLE 7. Spectral data of *O*-alkylated formanilides

R_1	R_2	Infrared (cm^{-1})		Nuclear magnetic resonance (τ)*			u.v.(mμ)†	Mass spectra (mass unit)	
		C=N	C—O—C	H—C=N	—OCH_2—	CH_3—	λ_{max}(log ε)	Base peak	Parent peak (%)
H	H	1644	1160–1200	2.29	4.73		248(4.17)	91	211(16.57)
H	CH_3	1636	1150–1200	2.23	4.73	7.66	248(4.14)	105	225(13.10)
H	Br	1639	1150–1200	2.20	4.73		220(4.35) 250(sh)	169 171(98.50)	289(18.80) 291(18.80)
Br	H	1647	1150–1205	2.20	4.69		252(4.03)	91	289(5.55) 291(5.55)
CH_3O	H	1647	1170–1210	2.10	4.67	6.22	250(4.01) 290 295	91	241(71.92)

*Al' show singlet absorption, the aromatic protons are multiplet and are not reported.
†Determined in hexane, measured from 220 mμ.

by distillation at 65° or lower under the appropriate pressure (about 0.05 mm Hg), solids by repeated sublimation at similar pressures and temperatures 5° below their melting points. Samples were deemed pure when they were sharp melting if solids, gave only formimidate peaks on the gas chromatograph, and no carbonyl absorption was present even at high concentration in the infrared. Melting points and analytical results appear in Table 5 while in Table 7 some spectral data are presented.

Calibration of the Gas Chromatograph

Various concentrations in the appropriate range of the parent formanilide and the *N*- and *O*-alkylation products were prepared in the solvents employed for this study and constant volumes (5 μl) injected into the gas chromatograph. Calibration curves based upon the disc integrator area values were linear and were used to calculate the concentrations and yields of products for the individual alkylations.

Control Studies

Tests for the Rearrangement of Benzyl N-Phenylformimidate

To each of two flasks containing 5.70 g (0.025 mol) of silver formanilide, 50 ml of freshly distilled dry DMF was added. To one of the flasks 1.70 g of benzyl *N*-phenylformimidate was added and 4.20 g (0.025 mol) of benzyl bromide was added slowly to each flask. After 3 days at room temperature with continuous stirring the usual product work-up and analysis showed the control to contain 2.40 g of the formimidate and 0.66 g of *N*-benzyl formanilide while the reaction with 1.70 g of the formimidate added contained 4.10 g of formimidate and 0.65 g of the *N*-benzyl formanilide. The conversion was 58% in both cases. Similarly, all added formimidate appeared in the product of a 7-day reaction and in reactions in DME and hexane with benzyl bromide and iodide after 18 h of reflux with either silver or potassium salts. No rearrangement was taking place under the reaction conditions.

Test for Moisture Sensitivity

Since the formimidates are known to be much more sensitive to hydrolysis than are the *N*-alkylation products (14) controls with added water were performed. A series of four reactions were done in each of DMF and DME. In each solvent, 4.50 g (0.02 mol) of silver formanilide was dissolved in 50 ml of the solvent, 2.40 g (0.02 mol) of benzyl bromide was added. To the solvent in two reactions, no water was added, the other two had 0.45 g (0.025 mol) and 0.90 g (0.050 mol) of water added. For the four reactions in DMF the quantities of formimidate were in the ratio 1, 1, 0, 0; *N*-benzyl formanilide 1, 1.2, 2, 2, and formanilide (*i.e.*, formanilide in solution in DMF, not total unreacted material) 1, 1, 2, 2. Also more than five times as much benzyl alcohol was detected in the reactions with added water but at most trace amounts of aniline were present in the aqueous runs. The lack of *O*-alkylation product was clearly not due to hydrolysis of that product but due to little or no product being formed.

In contrast to the results in DMF, in DME the *O*/*N* alkylation ratio was not consistently affected but the alkylation yield was reduced with the bulk of the water accounted for in benzyl alcohol and free formanilide in the solution.

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