

Amides as Nucleophiles: Reaction of Alkyl Halides with Amides or with Amides and Water. A New Look at an Old Reaction

Neal O. Brace

Wheaton College, Wheaton, Illinois 60187

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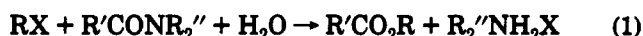
Heating of formamide with an alkyl halide (with or without water) affords a mild, nonhydrolytic, high-yield synthesis of alcohols and formate esters. Yet the way in which substitution on the alkyl halide actually occurs remains obscure. To explore this question, thermal reaction of 1-bromooctane (1a) with formamides (HC(O)NHR, R = H, Me; 2a, 2b) was studied quantitatively. Major products are 1-octanol (3) and *n*-octyl formate (5); minor products are 1-octene (4), di-*n*-octyl ether (6), and *N*-octylformamide (7, from 2a, only). Solid coproduct is HC(=NR)NHR + Br⁻ (e.g., 8a, R = H, methanimidamide hydrobromide). Analogously, 1a and *N*-methylformamide (2b) give alkylated products 3, 5, and 6 along with 8b (R = Me). 1-Iodooctane (1b) reacts similarly. Probe samples show that 1-octanol (3) is first formed, followed by 5 and 6. Occurrence of 8a-c is key to a mechanistic interpretation of the reaction. An imidate ("salt I"), e.g., [HC(=NHMe)O(CH₂)₇CH₃·HBr] from 1a and 2b, is first formed and reacts with amide 2b to give [HC(=NMe)N(Me)CHO·HBr] and 3. Now alcohol 3 is converted to ester 5 and 8b by reaction with this same formylamidine. Water, if present, adds to the imidate and gives a new tetrahedral intermediate that cleaves to ester 5 and amide salt, RNH₃X. Analogous reaction steps are proposed to generate side products 4, 6, and 7. Alkylation of formamide by C₆F₁₃CH₂CH₂I (1c) is considerably slower and less efficient than alkylation by 1-bromooctane. This result stands in sharp contrast to fast, efficient reaction of 1c with *N*-methylformamide or with DMF and water.

Introduction

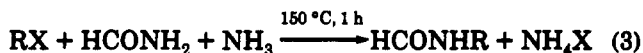
Alkylation of neutral amides by alkyl halides was reported over 60 years ago. Erickson¹ (1926), Joyce² (1946), and Bredereck and co-workers in 1954^{3a} successfully alkylated formamide or other amides by merely heating with primary alkyl halides to give a mixture of alcohol and ester. However, this procedure has not been widely practiced. Considering overall behavior of amides one review states, "Amides can normally be alkylated successfully with alkyl halides only as their imolate silver salts."⁴ The reason for this appears to be that, in this way, dealkylation by nucleophilic halide ion of the imidate salt intermediate, e.g., RC(=NH₂OR⁺ X⁻), may be avoided. Another review states more comprehensively, "Direct alkylation, using reagents such as alkyl halides or sulphates under neutral conditions, rarely leads to the required purely *N*-alkylated product. Instead, either pure *O*-alkylated product (an alkyl imidate) or a mixture of *O*- and *N*-alkylated products are obtained."^{5a} In summary, though nucleophilic behavior of anhydrous amides has been extensively studied and thoroughly reviewed,⁴⁻⁶ little

recent attention has been given to thermal alkylation by alkyl halides.

In 1969 Matthews and Cookson^{7a} significantly broadened and improved thermal alkylation of amides by using water as a coreactant. The alkyl halide (primary or secondary) and an amide (primary, secondary, or tertiary) are heated with water at 135 to 160 °C, and 1 mole of amide and 2 mol of water are consumed to give a high yield (98-100%) of alcohol and ester. Based on a careful material balance, the overall reaction was given (eqs 1 and 2):



In an analogous procedure,^{7a,b} NH₃ is substituted for H₂O. Heating of 1-bromooctane (1a, RX) with HCONH₂ (2a) and NH₃ gives *N*-octylformamide in high yield (92%, eq 3). If the reaction had occurred with NH₃ merely



substituting for water as a nucleophile, the products should have been the alcohol and the amidine salt, HC(=NH)NH₂·HBr (methanimidamide hydrobromide).^{4,6} Detailed mechanisms were not provided for either synthesis, however, to account for the reported results.

Recently, alkylation of amides has gained new significance as a superior synthetic method^{8,9} for certain fluorine-

(1) (a) Erickson, J. L. *E. Chem. Ber.* 1926, 59, 2665. (b) Rudolph, CH. *Ibid.* 1879, 12, 1297. Erickson found that the procedure reported^{1b} gave very poor yield of product.

(2) Joyce, R. M. U. S. Patent 2,375,301, 1945, to E. I. Du Pont de Nemours and Co; *Chem. Abstr.* 1945, 39, 3304(4).

(3) (a) Bredereck, H.; Gompper, R.; Theilig, G. *Chem. Ber.* 1954, 87, 537-546. (b) Gompper, R.; Christmann, O. *Ibid.* 1959, 92, 1935-1943. (c) Bredereck, H.; Gompper, R.; Rempfer, H.; Klemm, K.; Keck, H. *Ibid.* 1959, 92, 329-337. (d) Bredereck, H.; Effenberger, F.; Simchen, B. *Ibid.* 1963, 96, 1350-1354. (e) Bredereck, H.; Effenberger, F.; Henseleit, E. *Ibid.* 1965, 98, 2754-2761. (f) Bredereck, H.; Effenberger, F.; Beyerlin, H. F. *Ibid.* 1964, 97, 3076.

(4) Nielson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley and Sons: New York, 1975; Chapter 9, p 400.

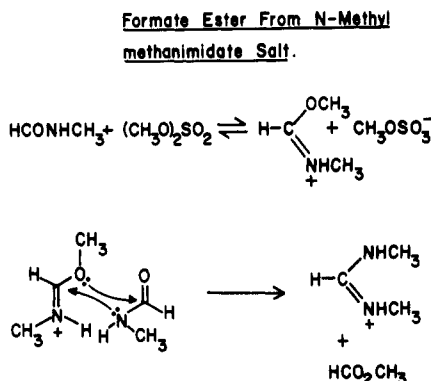
(5) (a) Challis, B. C.; Challis, J. A. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Sutherland, I. O., Eds.; Pergamon Press: New York, 1979; Vol. 2, Chapter 9.9, p 1011. (b) Challis, B. C.; Challis, J. A. In *The Chemistry of the Amide Group*; Zabicky, J., Ed.; Interscience: New York, 1970; Chapter 13.

(6) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Sutherland, I. O., Eds.; Pergamon Press: New York, 1979; Vol. 2, Chapter 8, pp 490, 492.

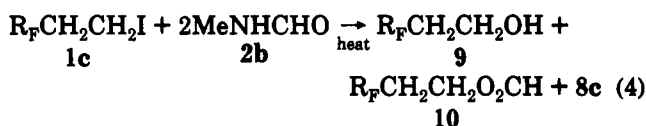
(7) (a) Matthews, J. S.; Cookson, J. P. *J. Org. Chem.* 1969, 34, 3204-3205. (b) Cookson, J. P.; Matthews, J. S. U.S. Patent 3,534,099, to Gulf Research and Development Co., Oct 13, 1970; *Chem. Abstr.* 1971, 74, 12637d.

(8) Brace, N. O. *J. Fluorine Chem.* 1986, 31, 151-174.

Scheme I. Methyl Formate from Heating of *N*-Methylformamide (2b) with *O*-Methyl-*N*-Methylmethanimidate Salt



substituted alcohols ($\text{R}_F\text{CH}_2\text{CH}_2\text{OH}$, $\text{R}_F = \text{C}_n\text{F}_{2n+1}$, $n = 6-10$), and has been patented⁹ and exploited commercially.¹⁰ Textbook synthetic methods are ineffective with this class of alcohols or are not suitable for large-scale application. Heating of 1-iodo-2-(perfluoroalkyl)ethanes with *N*-methylformamide (2b) provides the desired $\text{R}_F\text{CH}_2\text{CH}_2\text{OH}$ ($\text{R}_F = \text{perfluoroalkyl}$) in very high yield and conversion, typically 95%.^{8,9,11} Isolated products from 2-(*F*-hexyl)-1-iodoethane (1c; $\text{R}_F = \text{C}_6\text{F}_{13}$) and 2b include alcohol 3, formate ester 10, and $[\text{MeNHCH}=\text{NHMe}]^+ \text{I}^-$ (8c) (eq 4).⁸



The imidate salt of 1c was implicated as an intermediate, based on quantitative isolation of amidine salt 8c, rates of formation of 9 and 10, rate of disappearance of 1c, and other evidence.⁸ The alkyl imidate from 1c was not isolated; however, the imidate from 1c and 2-pyrrolidinone has recently been prepared and pinpointed conclusively as the key intermediate in an analogous synthesis of $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OH}$ (9).^{12,13}

In early work, Brederick and co-workers^{3b,c} prepared imidate salts from formamides 2a or 2b and dimethyl sulfate. Heating the imidate salt gave methyl formate and the methanimidamide salt, e.g., $[(\text{HC}=\text{NH})\text{NH}_2]^+ \text{MeSO}_4^-$ from 2a. See Scheme I. These reactions were extended^{3b,c} to higher homologues of amides and with many types of alkyl halides. Several amidine derivatives were also prepared.³ However, alkylation reactions of R_F-

(9) (a) Hayashi, T.; Matsuo, M. U. S. Patent 4,001,309, to Asahi Glass Co., Ltd., Jan 4, 1977. (b) *Ibid.* German Offen. 2,318,941, Oct 25, 1973; *Chem. Abstr.* 1974, 80, 14564a.

(10) Ukihashi, H. *Centenary of the Discovery of Fluorine, International Symposium Abstracts*, Aug 25-29, 1986, Paris, France; p 42. Using these methods, Asahi Glass Co. (Japan) produces "several thousand tons per year of commercial product comprised of perfluoroalkyl containing compounds."

(11) (a) Matsuo, M.; Hayashi, T. *Asahi Garasu Kenkyu Hokoku* 1976, 1(26), 55-61; *Chem. Abstr.* 1977, 86, 170772w. (b) 1c (10 mmol), 2a (150 mmol) at 140 °C for 4 h was reported^{11c} to give 4% conversion of 1c, at a selectivity of 80% for $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{OH}$ (9) and $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{O}_2\text{CH}$ (10), and 20% of $\text{C}_6\text{F}_{13}\text{CH}=\text{CH}_2$ (11). (c) Matsuo, M.; Hayashi, T.; Ukihashi, H. Abstract O-12 and Preprint, 8th International Symposium on Fluorine Chemistry; Kyoto, Japan, Aug 22, 1975.

(12) Brace, N. O. Paper presented at 9th Winter Fluorine Conference (ACS), St. Petersburg, FL, Jan 30, 1989: *Reaction of Ambidentate Lactams with 2-(Perfluoroalkyl)-1-iodoethanes; Synthesis of 2-(Perfluoroalkyl)ethanols.*

(13) Brace, N. O. To be published.

Table I. 1-Bromooctane (1a) with Formamide (2a); 1a:2a = 5.0 mol, at 150 °C

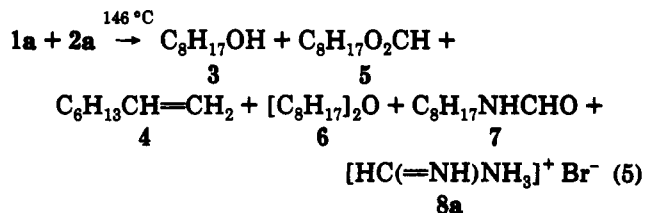
run	time (h)	a	substances, mol % yield by GC ^b					
			1a	3	4	5	6	7
c	10					92		
1 ^d	10	B	18.1	1.2	0.6	75.8	3.3	1.1
2 ^e	4	A	48.9	16.1		31.7	3.4	
3 ^f	10	A	25.6	8.5	0.4	57.6	3.9	0.9
4 ^g	15	A	12.6	6.9	0.4	75.6	4.4	0.9
5 ^h	24	A	2.3	4.9	0.5	86.6	3.8	1.8

^a Method A: Sealed glass ampule, small magnet bar. Method B: stirred, 10-mL flask, larger magnet bar. ^b GC analysis on DB-5, 1b-c column. Yield was calculated from mol of 1a charged to the reaction. In accord with stoichiometry mol of 6 was multiplied by 2. ^c From ref 3a. ^d 1a (1.9768 g, 10.237 mmol) and 2a (2.3565 g, 52.3202 mmol). ^e 1a (0.9731 g, 5.0396 mmol) and 2a (1.1064 g, 24.56 mmol). ^f 1a (1.9290 g, 9.9896 mmol) and 2a (2.3478 g, 52.13 mmol). ^g 1a (0.9770 g, 5.059 mmol) and 2a (1.1585 g, 25.72 mmol). ^h 1a (0.9619 g, 4.9806 mmol) and 2a (1.1199 g, 24.864 mmol).

$\text{CH}_2\text{CH}_2\text{I}$ (1c) could not be entirely reconciled⁸ with earlier reports for simple analogous alkyl halides. The purpose of this paper is to describe quantitatively and mechanistically thermal alkylations of formamides by *nonfluorinated* alkyl halides. Subsequent papers in this series will give preparation of *F*-alkyl-substituted imidates and their reactions with nucleophilic amides and lactams to give the expected products. It is also demonstrated therein that *F*-alkyl imidates are indeed formed and can be isolated from reaction mixtures of 1c and lactams in certain alkylation reactions.^{12,13}

Results

1-Bromooctane (1a) with Formamide (2a): Isolation of Methanimidamide Hydrobromide (8a). According to Brederick and co-workers,^{3a} heating a mixture of 1-bromooctane (1a) and formamide (2a) at 150 °C for 10 h gives *n*-octyl formate (5) and NH_4Br in 92% yield. When reexamined, reaction of 1a and 2a gave an *inhomogeneous, colored mixture* at 150 °C, from which a few bubbles of gas evolved.^{3a} Workup and capillary GC, with appropriate response factors, gave the results shown in Table I (runs 1 and 2). 1-Octanol (3), 1.16%, *n*-octyl formate (5), 75.8%, and side products 1-octene (4), 0.57%, di-*n*-octyl ether (6), 3.25%, and *N*-octylformamide (7), 1.12%, were quantitatively measured. The solid coproduct was not NH_4Br , but 8a (IR NH, 3400-3200, $\text{CH}=\text{N}$ 1710 cm^{-1} ; NMR $\text{CH}=\text{N}$, 8.0 ppm) (eq 5).^{3b,14}



Reaction rate of the *inhomogeneous mixture* could be highly susceptible to stirring rate and related factors, and this was observed (Table I, runs 2-5). Conversion rate of 1-bromooctane 1a was slower in a narrow, sealed tube than in a stirred flask with greater interfacial contact (compare run 1 with run 3, 10 h each). After 4 h of reaction time (runs 2-5), alcohol 3 fell progressively as formate ester 5 increased in concentration. Eventually, combined 3 and

Table II. 1-Bromooctane (1a) with Formamide (2a) at 135 °C, with or without Water. A Comparison with Matthews and Cookson^a

run	time (h)	b	mol ratio (1a:2a:H ₂ O)	substances, mol % yield by GC ^c						
				1a	3	4	5	6	7	
a	3.0		1:20:2	0.0	26	0.0	66	nr ^d	d	
1 ^e	3.0	B	1:20:2	4.1	21.6	0.2	71.8	0.5	1.6	
2 ^f	3.0	A	1:20:2	48.2	15.3	0.1	34.6	0.4	1.3	
3 ^g	7.0	B	1:20:2	00.0	17.5	h	80.2	0.6	1.8	
4 ⁱ	7.0	B	1:20:0	0.2	18.4	h	79.0	1.8	0.6	

^a Reference 7a. ^b Method A: Sealed glass ampule, 3- × 7-mm magnet bar. Method B: stirred 10-mL flask, 10- × 15-mm magnet bar. ^c GC analysis on DB-5, 15-m column. Yield was calculated from mol of 1a charged to the reaction. In accord with stoichiometry mol of 6 was multiplied by 2. ^d nr indicates that the data were not reported (ref 7a). *N*-Octylformamide (7) was present in unspecified amount (ref 15). ^e 1a (0.9933 g, 5.143 mmol), 2a (4.6088 g, 102.33 mmol), and water (0.1918 g, 10.65 mmol). ^f 1a (0.9910 g, 5.131 mmol), 2a (4.5403 g, 99.98 mmol), and water (0.1907 g, 10.58 mmol). ^g 1a (1.0123 g, 5.2416 mmol), 2a (4.7084 g, 104.54 mmol), and water 0.1862 g, (9.780 mmol). ^h The amount of 4 was below the response limit of the GC column. ⁱ 1a (1.0269 g; 5.317 mmol), 2a (4.9026 g; 108.9 mmol) and *no water*. Initially homogeneous, two layers formed after 1 h, but with no observed gas evolution.

ester 5 reached 91.5 mol % at 97.3% conversion of 1a to products. Evidently the reaction process is more complex than originally thought.^{3a} Significance of the identified side products for an understanding of the reaction process is discussed below. These new results substantially agree with those reported⁸ for thermal reaction of 2-(*F*-hexyl)-1-iodoethane (1c) with *N*-methylformamide (2b).

1-Bromooctane (1a) with Formamide (2a) and Water. What effect does water have on this alkylation reaction? The procedure of Matthews and Cookson^{7a} was reproduced as given in Table II. Yield of alcohol 3 (22%) and ester 5 (72%, run 1) was comparable to that reported. Stirring rate of the *heterogeneous* mixtures had a large effect on reaction rate: conversion of 1a dropped from 96% (run 1, 3 h) to 52% (run 2, 3 h) with less vigorous stirring of the immiscible layers. Reaction for 7 h (run 3) gave 100% conversion of 1a and a yield of 97.7% of combined alcohol 3 and ester 5. More importantly, *overall* reaction rates were increased several-fold by the 4-fold increase in formamide concentration, with or without water present: Table I, run 1, compared with Table II, runs 3 and 4. This occurred despite the decrease in reaction temperature from 150 to 135 °C. Finally, ether 6 decreased 3- to 6-fold, when water was present; Table I, runs 4 and 5, about 4% of 6, Table II, run 3, 0.6%; run 4 (without water, 1:20 mol of 1a:2a), 1.8% of 6.

Without water present, a *clear, homogeneous mixture* was formed (Table II, run 4), and only after 1 h of reaction time did separate layers appear. Yield of products 3 and 5 (97.4%) after 7 h of reaction was essentially the same as in run 3 with water present. *N*-Octylformamide (7) was reduced to 0.35 the amount, but ether 6 was 3.3 times as great, as found in run 3. Thus, if sufficient stirring agitation can be provided, an aqueous mixture gives a slightly higher yield of 3, 5, and 7 and less of 6. In addition, water takes the place of 1 mol of 2a in the overall process.

Reactions of 1-Bromooctane (1a) with *N*-Methylformamide (2b). As a followup to work with formamide and to published work,⁸ reactions in *N*-methylformamide (2b) were explored. In comparison with formamide, it was found previously^{8,9,11} that 2b reacted with C₆-

Table III. 1-Bromooctane (1a) with *N*-Methylformamide (2b) at 135 °C; 1a:2b = 1:20 mols

sample	time (h)	substances, mol % yield by GC ^c				
		1a	3	4 ^b	5	6 ^c
1	1.00	7.7	51.5		39.4	1.4
2	2.00	1.4	53.1		43.8	1.8
3	3.00	0.6	50.2		47.3	1.8
4	6.00	0.4	45.7		51.3	1.7
5	8.00	0.0	41.8		56.5	1.7

^a 1a (0.9808 g, 5.0784 mmol) and 2b (6.111 g, 103.46 mmol), by method B. GC analysis on DB-5, 15 m. Yield was calcd from mol of 1a charged to the reaction. ^b 1-Octene was present in amounts too small to measure. ^c In accord with stoichiometry mol of 6 was multiplied by 2.

F₁₃CH₂CH₂I (1c) more smoothly and with fewer side reactions.¹⁶ A reaction mixture, 1a:2b = 1:20 mol, remained clear when stirred at 135 °C, and conversion rate was close to that of reaction in formamide, with or without water (cf., Tables II and III). In this experiment (see Table III) samples were removed at intervals of time for analysis. Alcohol 3 rose to 53.1 mol % in 2 h and slowly decreased, while that of ester 5 slowly increased and *continued to increase after 1a had been used up*. The ratio of alcohol 3 to ester 5 (about 1.0) was much larger than in reactions of 1a with formamide (Table II, 0.22). The amount of alkene 4 was too small to determine by GC, and that of ether 6 was almost constant at 1.70 mol %. Any rate dependence of *products* on change in 1a concentration could not be determined from these data, as reaction was 92% complete before the first sample was taken. Alcohol and ester together reached 97.5% in 3 h and was 98.3% in 8 h. No 7, of course, was formed. These results parallel those found for reaction of C₆F₁₃CH₂CH₂I (1c) with 2b,⁸ which also showed that alcohol preceded ester in time sequence.

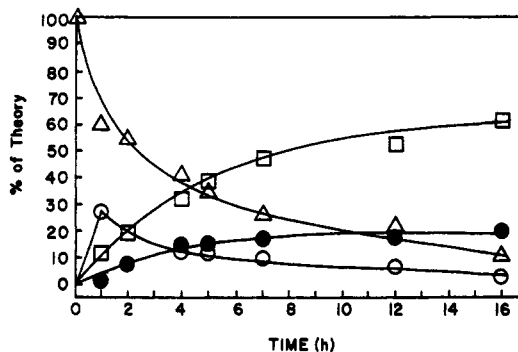


Figure 1. Reaction of 1-bromooctane (1a, 10.00 mmol) and 2b (50.00 mmol) at 146 °C. 1-Bromooctane, Δ ; *n*-octyl formate, \square ; 1-octanol, \circ ; di *n*-octyl ether, \bullet .

Reaction Rate of 1-Bromooctane and *N*-Methylformamide at a 1:5 mol Ratio. A stirred mixture of 1-bromooctane (1a) and *N*-methylformamide (2b) (1:5 mol) at 146 °C remained *homogeneous* over a 16-h time span (cf., Table I). Substances in mol % at time intervals are plotted in Figure 1 and given in Table IV.¹⁷ Conversion of 1a reached 76.5% in 10 h or 87.5% in 16 h, comparable to that with formamide 2a (Table I). Conversion to alcohol 3 peaked at 26.5 mol % in 1 h; at 2 h, the amounts of alcohol 3 and ester 5 coincided, and then diverged again.

(16) Substitution and elimination reactions of C₆F₁₃CH₂CH₂I (1c) with various nucleophiles were studied: Brace, N. O.; Marshall, L. W.; Pinson, C. J.; van Wingerden, G. *J. Org. Chem.* 1984, 49, 2361-2368.

(17) See supplementary material.

(15) In another experiment 7 was obtained in 1.5% yield, the difference in isolated products and the amount of 1-bromooctane (1a) consumed.⁷

Table VI. 1-Iodoctane (1b) and *N*-Methylformamide (2b), 1:15 mol at 146 °C^a

time (h)	substances, mol % yield by GC ^a				
	1b	3	4 ^b	5 ^c	6 ^c
1	21.9	42.6		26.5	9.3
2	5.8	54.2		31.0	9.1
3.5		51.1		38.0	11.0
4.5	1.0	50.0		39.0	11.9
5.5	0.00	40.6		48.8	10.2

^a GC was obtained by means of a 4-ft DC-200 column and a 6-ft QF-1 silicone oil column. Reaction mixture comprised 1b (2.4106 g, 10.039 mmol) and 2b (8.8461 g, 149.8 mmol). Method B: Amounts of substances plotted in Figure 2. ^b 1-Octene was not detected. ^c The amount of 5 and 6 was determined on the QF-1 column, as 1b and 5 could not be separated on the DC-200 column. In accord with stoichiometry mol of 6 was multiplied by 2.

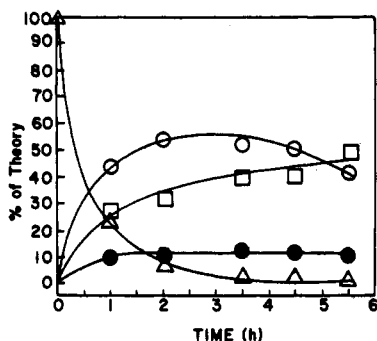


Figure 2. Reaction of 1-iodooctane (1b, 10.00 mmol) and 2b (150 mmol) at 146 °C. 1-Iodooctane, Δ ; *n*-octyl formate, \square ; 1-octanol, \circ ; di-*n*-octyl ether, \bullet .

From the yield profile of 3 and 5, it is clear that formation of 3 preceded that of 5. 1-Octene was a very minor product, but ether 6 increased dramatically from 4.45 mol % in one h to 21.4% in 24 h. This increased conversion to 6 compared with that attained in *formamide* 2a (Table I, only 3.84% in 24 h) may be related to thermal instability of 2a and is discussed below.

***N,N*-Dimethylmethanimidamide Hydrobromide (8b).**¹⁷ Workup of a reaction mixture from 1-bromooctane 1a with 2b (1:10 mol) at 146 °C (see Table V)¹⁷ gave isolated organic products in amounts that agreed well with GC analysis of a probe sample. Amide 2b was similarly recovered from the aqueous layer. This left a solid residue, a single substance (TLC), identified as 8b (100% yield) by elemental analysis and comparison of IR and NMR with the known HCl and HI salts of 8b.^{8,17,18}

Reaction Rate of Iodoctane (1b) with *N*-Methylformamide (2b): Isolation of *N,N*-Dimethylmethanimidamide-HI (8c). For a direct comparison with 2-(*F*-hexyl)-1-iodoethane (1c),⁸ a clear mixture of iodoctane (1b) and 2b (1:15 mol) was stirred at 146 °C, and samples were taken (Table VI). The time course of reaction (Figure 2) resembles closely that reported for 1c with 2b under these conditions.⁸ Characteristically, alcohol 3 increased faster than ester 5 in the first 2 h, and after 4.5 h, 3 decreased and ester 5 increased in concentration. Thus, as for reactions of 1a, ester 5 was derived from 3, and not the reverse. Ether 6 reached 11.9% in 3.5 h and remained nearly unchanged after iodoctane 1b was used up. This indicates that formation of 6 depends on

Table VII. 2-(*F*-Hexyl)-1-iodoethane (1c) with Formamides 2a or 2c and Water^a

1c + HCONR ₂ + H ₂ O - R _F CH ₂ CH ₂ OH + R _F CH ₂ CH ₂ O ₂ CH +	2a, 2c		9		10	
			R _F CH=CH ₂ + HC(=NR)NH ₂ R·HI		8a, 8c	
			11			
	2a, R = H; 2c, R = Me (R _F = C ₆ F ₁₃)					

run	time (h)	temp (°C)	amide	mol ratio 1c:2H ₂ O	volatile substances, mol % by GC			
					1c	9	10	11
1 ^b	4.5	140	2a	1:20:2.1	79.8	3.9	10.0	3.9
2 ^c	5.5	140	2a	1:22.6:1.6	93.9	2.2	3.8	.074
3 ^c	6.0	150	2a	1:22:1.5	86.2	5.2	7.2	1.4
experiments from the literature								
4 ^{d,e}	6	150	2a	1:22:1.5	0.7	60.4	27.3	nr ^d
5 ^f	6	142	2c	1:30:2.4	0.33	29.7	64.1	4.6
6 ^{e,f}	6	150	2c	1:22:1.2	5.9	4.5	86.1	3.5

^a Reactions in stirred or shaken glass ampule, method A. All reaction mixtures were inhomogeneous. GC analysis by DB-5, 30-m column. ^b No solvent was added; see Experimental Section. ^c 1,4-Dioxane (10.37 g, 118 mmol) was used, following ref 9a. ^d 1c (10 mmol), 2a (220 mmol), water (15 mmol), and 1,4-dioxane (10.2 g, 116 mmol) was shaken in a 100-mL glass ampule. Volatile products were weighed and analyzed by GC. 11 was not reported. ^e Reference 9a. ^f Reference 8. ^g 1c (10 mmol) and other substances as indicated.

concentration of 1b. 1-Octene was not detected. Reaction kinetics of 1b followed a pseudo-first-order rate law; at 146 °C, $k = 19 \times 10^{-5} \text{ s}^{-1}$. This compares with $k = 8.05 \times 10^{-5} \text{ s}^{-1}$ for 1c with 2b under these conditions of reaction.⁸ Workup of the reaction mixture gave 8c (HI salt) in 100% of theory. IR and NMR were consistent with published data.^{8,17,18}

2-(*F*-Hexyl)-1-iodoethane (1c) with Formamide and Water. Synthesis of 2-(*F*-Hexyl)ethanol. Hayashi and Matsuo reported^{9a} that heating a mixture of C₆F₁₃CH₂CH₂I (1c) and an amide, with a specific mol amount of water, gave 2-(*F*-hexyl)ethanol (9) and 2-(*F*-hexyl)ethyl formate (10) in high yield, very similar to reaction of 1-bromooctane (see above).^{7a} In contrast to reaction of 1c and *formamide* 2a in the absence of water,¹¹ which gives inefficient alkylation to 9 and 10, facile reaction of 1c with 2a and water in 1,4-dioxane solution was claimed.^{9a} Of particular significance and an unexpected result is the minimal amount of alkene C₆F₁₃CH=CH₂ (11) that is formed during reaction of 1c in DMF (2c) and water.^{8,9a} Typical substitution reactions of 1c often give substantial elimination to 11.^{11,16} In view of the present results with 1-bromooctane, 2a, and water (cf., Table II), this report^{9a} was briefly reexamined. New and old data are given in Table VII.

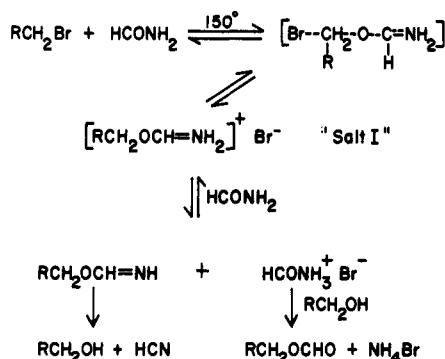
In runs 1-3, intended to bracket the reported results, conversion of 1c to the desired products 9 and 10 was poor. The greatest amount was obtained without 1,4-dioxane solvent, but elimination to alkene 11 was a serious side reaction. Run 3 should have given 99.3% conversion of 1c, but instead, only 14% of 1c had reacted in 6 h at 150 °C (compare also with Table II). Three experiments from the literature are also given in Table VII. The first (no. 4) is the reported reaction^{9a} of 1c with 2a and water. For comparison, analogous experiments in which DMF was used as reactant/solvent with 1c are listed as nos. 5 and 6. Here a *homogeneous mixture* is formed, and reaction of 1c is substantially complete to give 9 and 10 in a combined yield of 91-94% and a small amount of 11.

The surprising difference in reactions of 1c in forma-

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Scheme II. Reaction of Formamides with RCH₂X. Formamide (2a) and 1-Bromooctane (1a) According to Bredereck, Gompper, and Theilig

Formamide and 1-Bromooctane according to Bredereck, Gompper and Theilig.



amide-water mixtures when compared with those of 1a or 1b^{7a} cannot be attributed to the difference in *homogeneity* of reaction mixtures alone. Formamide 2a is a weaker base than 2c^{11a} and 2a may be less nucleophilic toward 1c than to the alkyl halides 1a and 1b. This presumed difference may be in part related to the highly associated nature of liquid formamide, which has a reported bp of about 215 °C or bp_{400 torr} 193.5 °C.¹⁹ By comparison DMF has bp 153 °C. Reaction mixtures of 1-bromooctane with 2a and water are also inhomogeneous, yet gave high conversion rates to alkylated products.

Discussion

Evidence for intermediacy of the imidate in thermal alkylations of amides was sought by Bredereck and co-workers,³ who proposed Scheme II for reaction of formamide 2a with 1-bromooctane. In this scheme *O*-alkylation by 2a gives an imidate salt ("salt I") that equilibrates with more 2a to form [HCONH₃⁺ Br⁻] and an imino ether RCH₂OCH=NH. The imino ether reverts to 1-octanol (3, RCH₂OH) and HCN (the reverse of the Pinner reaction); the formamidinium salt and 3 then give formate ester 5 and NH₄Br as coproducts. Imidate salts [HC(=NHR)OMe⁺ MeOSO₃⁻; R = H, or R = Me] were prepared and isolated at low temperature from 2a or 2b, respectively, and dimethyl sulfate. Heating the imidate salt from 2b with more 2b gives methyl formate in 60% yield (Scheme I). Here, the imino ether (because of methyl substitution on nitrogen) cannot be formed as in Scheme II; thus, a concerted displacement of methyl formate by 2b was proposed.^{3c}

Reaction sequences in Schemes I and II, however, do not account for the results of this study or of thermal reaction of C₆F₁₃CH₂CH₂I with 2a, 2b, or other amides.⁸ We wish here to propose schemes that can account adequately for all known observations in thermal alkylations of amides by alkyl halides. Scheme III adapts certain aspects of earlier proposals³ and is an extension of schemes devised for reactions of the fluorinated compounds.⁸⁻¹¹ Analogously, steps of Scheme III can be used to interpret the synthesis of *N*-octylformamide from 1-bromooctane, formamide, and ammonia.^{7a,b}

According to Scheme III, O-attack by an amide on an alkyl halide reversibly forms an imidate (salt I) in the first

step of a four-step sequence. In step 2 the amide, this time acting as an N-nucleophile, adds to "salt I" to give a tetrahedral intermediate salt II. Unlike the *concerted displacement* that gives formate ester envisioned in Scheme I, alcohol cleavage of salt II occurs. The lone pair on the alkoxy leaving group and the two lone pairs on amino nitrogens are in a favorable stereoelectronic relationship for *alcohol cleavage*⁸ (step 3). Deslongchamps²⁰ showed that cleavage of such a tetrahedral intermediate occurs to give products under stereoelectronic control. In prior work by Schmir and co-workers,²¹ pH of the system was found to determine the type of products from a postulated tetrahedral intermediate. Reaction of an amide with imidate has not been studied kinetically, but displacement of alcohol from a lactim ether (a cyclic imidate) by an amide is known.^{22,23} Kinetics and products from reaction of 2-pyrrolidinone with the lactim ether derived (indirectly) from C₆F₁₃CH₂CH₂OH (9) and 2-pyrrolidinone^{12,13} are consistent with those found here in the amide-alkyl halide system.^{12,13} This present study and former work^{8,11} show that, indeed, alcohol 3 is first formed in these reactions of 2a or 2b (see Figures 1 and 2), *in the absence of water*.

Esterification of alcohol occurs in a separate stage of the process, as is clearly indicated by product-rate studies. It was demonstrated^{11c} that ester is *not* obtained by heating alcohol with the formamide. Unlike the process in which water is present,^{7,9} in which ester and the corresponding *amine salt* are obtained, the coproduct from reaction of alkyl halide and an amide is the acylamidinium salt. Thus, stoichiometry and reaction kinetics require that the acylamidinium salt reacts with alcohol to give formate ester and amidinium salt. An acylamidinium has a very labile acyl group analogous to HCO(NR₂) compounds, which give formylation of a variety of compounds including alcohols.²⁴ In effect, the *N*-formylamidinium behaves like an anhydride. The coproduct is the methanimidamide salt 8a, 8b, or 8c (Scheme IV).

The imidate salt (salt I) is susceptible to attack by nucleophiles such as amides 2a and 2b, but not by DMF (2c).^{3,8} However, imidates from reaction of alkyl halides with all three formamides react readily with water,⁷ ammonia⁷ or amines,⁶ and H₂S.⁶ In reactions with water present, salt I reacts to form a tetrahedral intermediate (Scheme V, step 1). This intermediate differs in having the ammonium ion as a good leaving group, and stereoelectronic factors favor cleavage of the formate ester, step 2. Hydrolysis of ester to alcohol (step 3) then occurs.

Side Reactions in Alkylation of Formamides by Alkyl Halides. Side reactions that occur when formamide and 1-bromooctane were heated to 150 °C gave 1-octene (4) and di-*n*-octyl ether (6) in small amounts (Tables I and II). Two sources for 4 may be considered: (1) E-2 elimination of 1a with a base such as NH₃ or, especially,

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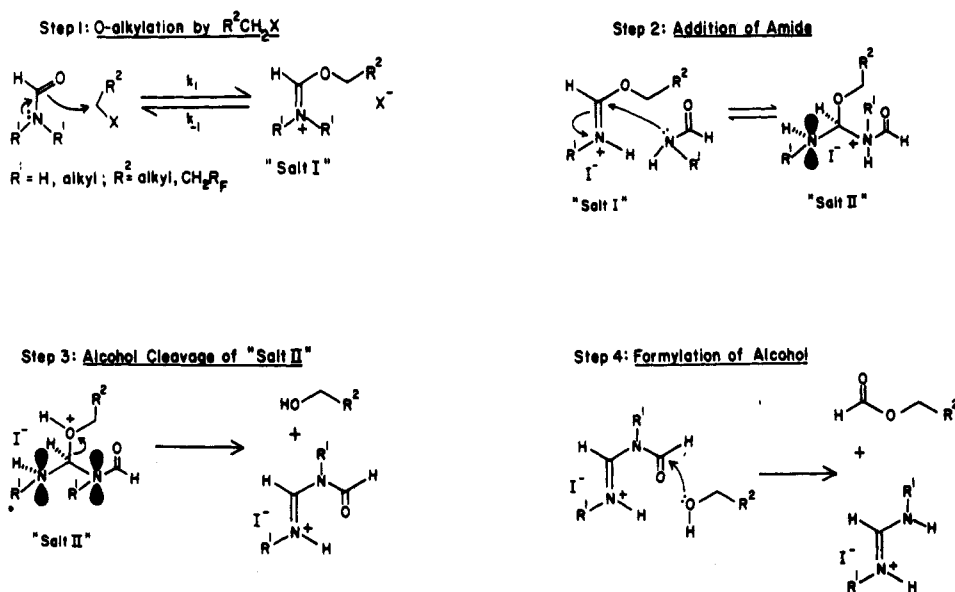
(21) (a) Schmir, G. L. *J. Am. Chem. Soc.* 1968, 90, 3478. (b) Chaturvedi, R. K.; Schmir, G. L. *J. Am. Chem. Soc.* 1968, 90, 4413-4420.

(22) Glickman, S. A.; Miller, E. S. U. S. Patent 3,040,004, to General Aniline and Film Corp., June 19, 1962.

(23) (a) Mazurkiewicz, R. *Acta Chem. Hung.* 1984, 116(1), 95-101; *Chem. Abstr.* 1984, 101, 191663e. (b) *Ibid.* 1986, 122(2), 163-7; *Chem. Abstr.* 1987, 107, 77162q.

(24) Davidsen, S. K.; May, P. D.; Summers, J. B. *J. Org. Chem.* 1991, 56, 5482-5485.

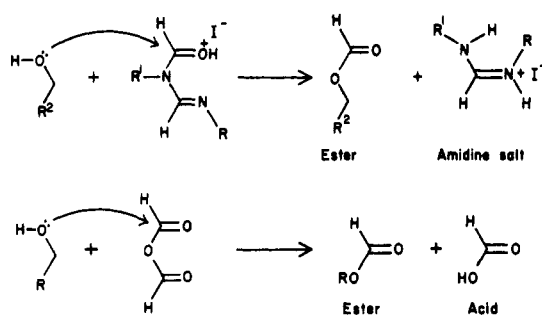
(19) *The Merck Index*, 10th ed.; Windholz, M., Ed.; Merck and Co.: Rahway, NJ, 1983; No. 1421, p 604.

Scheme III. Reaction of Formamides with RCH_2X^a 

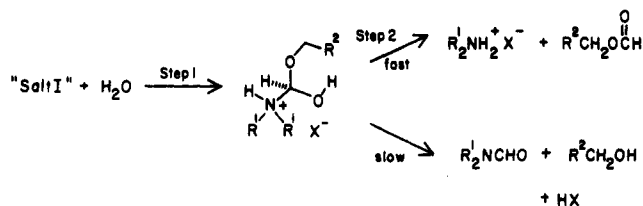
^a Four-step sequence: (1) O-alkylation by amide; (2) amide addition to imidate salt; (3) alcohol cleavage of tetrahedral intermediate; (4) esterification of alcohol by formylamide salt.

Scheme IV. Esterification of Alcohol by an Acylamide Salt. A New Acylating Agent?

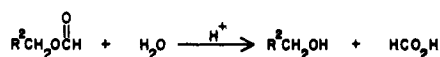
A New Acylating Agent?

Scheme V. Reaction of Formamides with RCH_2X and Water^a

Step 1: Water Displacement on "Salt I"



Step 3: Hydrolysis of Ester

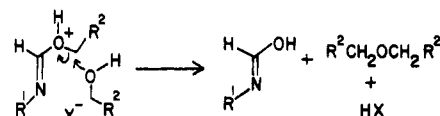


^a Three-step sequence: (1) water addition to imidate salt; (2) ester cleavage of tetrahedral intermediate; (3) hydrolysis of ester.

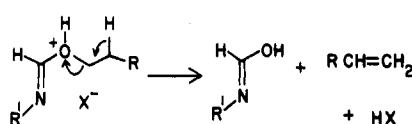
methanimidamide 8 or (2) acid-catalyzed elimination of 4 from imidate salt I. In this case the coproduct would be the amide 2a (Scheme VI). Direct dehydration of 1-octanol to 1-octene seems unlikely. Only with *N*-methylformamide (2b) did reaction mixtures become noticeably acidic. Since this was not observed in reactions of 1a with 2a, thermal decomposition of formamide 2a (see below) may have kept the mixture neutral in pH, by

Scheme VI. Side Reactions in Alkylation of Amides by Alkyl Halides

Ether Formation from "Salt I"



Alkene from "Salt I"

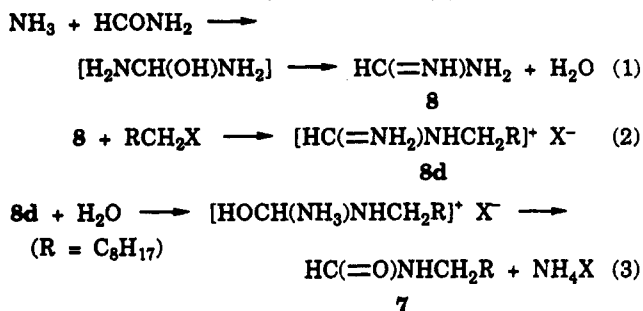


reacting with hydrobromide salts from alkylation of 2a. The polar reaction medium and elevated temperatures would provide favorable conditions for either E-2 or dehydration reaction.

By contrast, reaction of 1-bromooctane in *N*-methylformamide (2b) gave only traces of 4. Formation of 6 was a significant reaction and was related to concentration of 1a and 3, since greater conversion to 6 occurred in more concentrated reaction mixtures (compare Tables III and IV¹⁷). Kinetically, as seen in Figure 2, formation rate of 6 was greatest when reaction rate of 1b was fastest; 6 production ceased after 2 h, when 1b fell to near zero. In Table IV¹⁷ concentration of 6 continued to increase during the entire reaction period, while 1a and 3 were being used up at a steady rate. These observations seem to point to acid-catalyzed attack of 3 on imidate salt I of Scheme VI. This rationalization could account for the otherwise puzzling absence of alkene 4 in reaction mixtures of 1-bromooctane 1a with 2b. Had a Williamson-type ether process been operative, which seems unlikely in neutral or mildly acidic media, alkene 4 would have been expected as well.

Methanimidamide from Formamide as *N*-Nucleophile in Forming *N*-Octylformamide. *N*-Alkylation occurred when a mixture of ammonia (0.47 mol), formamide 2a (2.5 mol), and 1a (0.125 mol) was heated for 1.5

Scheme VII. N-Alkylation of Formamide with Alkyl Halide, by Way of Methanimidamide Salt. N-Octylformamide (7)



h at 150 °C.⁷ Under these conditions, with an excess of amine acting as base, the reaction products reported comprised *N*-octylformamide (7, 91%), *N,N*-dioctylformamide (2.7%), and 3 (6.3%).⁷ Nucleophilic attack by ammonia on 1a could possibly give octylamine and dioctylamine but not the amides. Scheme VII offers a rationalization for the reported reaction. Nucleophilic addition of NH₃ to 2a would give a tetrahedral intermediate and loss of water would form methanimidamide (8) (eq 1 in Scheme VII). 8 is a rather strong base (an amidine) and an ambident nucleophile ("degenerate ambident nucleophile") that would readily attack bromooctane 1a (eq 2 in Scheme VII). This gives *N*-octylmethanimide hydrobromide (8d) analogous to salt I of Scheme III. 8d would then react with water as in Scheme V, and eliminate NH₄Br from the tetrahedral intermediate (eq 3 in Scheme VII). The alkylated product is then *N*-octylformamide 7. Alternatively, rearrangement of the O-alkyl imidate to the N-alkyl imidate may have occurred. This reaction occurs in analogous cases⁵ and is catalyzed by RI (R = Me to *n*-Pr). Possibly, similar reaction steps could convert 7 by alkylation with 1a to an imidate which then rearranges to *N,N*-dioctylformamide. To substantiate this proposal, probe experiments will be required to show that *thermal rearrangement*^{4,5} can occur with 7. Alcohol 3 may have come from reactions of 1a and 2a as described in Scheme III, without the intervention of NH₃, or by reaction of NH₃ with imidate salt I. Since water that is formed is used up in the last step of Scheme VII, there is no reason to expect ester 5 among products of this reaction. Thus, Schemes III and VII could account for the products described.⁷

Methanimidamide (8a) of Scheme VII is one end product of Scheme III, and this substance, itself, could account for the presence of 7 in reaction mixtures of 1a and 2a, as given above. Ammonia may have been derived by thermal decomposition of 2a, a reaction with a reported equilibrium constant of 159 at 127 °C [(*p*CO₂NH₂/*p*HCONH₂)].^{3a,25}

Experimental Section

Materials and Methods. 1-Bromooctane (1a), 1-iodooctane (1b), 1-octanol (3), and 1-octene (4) were best available commercial materials, and their purity was ascertained by capillary GC. Octyl

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formate (5),²⁶ di-*n*-octyl ether (6),^{27,28} and *N*-octylformamide (7)^{29,30} were prepared as described.¹⁷ Formamide (2a, 99+ %) and *N*-methylformamide (2b, 99%) were obtained from Aldrich Chemical Co. The amount of water present was determined by Karl Fischer titration and for 2a by index of refraction from a calibration curve. 2-(*F*-Hexyl)-1-iodoethane (1c) was obtained from CIBA-GEIGY Corp.; properties and preparation of 1c have been reported.¹⁶ Note that that 1c is a highly toxic substance and breathing and contact must be avoided, by careful handling in a well ventilated space. TLC, combustion, and Karl Fischer analyses were performed by courtesy of the Analytical Division of CIBA-GEIGY Corp., Ardsley, NY. GC analyses^{8,16} made use of either the QF-1 fluorosilicone oil column or, for mixtures of 1b and 2b, a 4-ft × 1/4-in. DC-200 silicone oil (15% on Chromosorb P) column. Capillary GC analyses utilized Megabore DB-5 columns as described in the supplementary material.¹⁷ Retention time and response factor for each substance were determined by means of mixtures of the pure substances on each column. In this way, accurate (±0.2%) and reproducible quantities of all volatile compounds were ascertained. More than one column was needed to separate substances with overlapping retention times.

Representative Experiment: 1-Bromooctane (1a) with Formamide (2a) in a Sealed Glass Ampule. Method A. A Fisher tissue culture tube (No. 9825, 19 × 110 mm) was charged with a 3- × 7-mm magnet bar, 1a (1.9290 g, 9.9896 mmol), and 2a (2.3478 g, 52.13 mmol, >99.0%, spectrophotometric quality), while under nitrogen purge. The tube was sealed by a Teflon-lined cap, weighed, and immersed in a stirred oil bath kept at 148 °C for 10 h. Two immiscible layers were stirred vigorously by the magnet. Initially colorless, the upper layer became cloudy and the lower layer gradually turned light pink and tan in color. When cool, the tube was weighed (loss of 0.013 34 g) and opened. There was no buildup of pressure and no distinct odor of HCN. The mixture was shaken with water (10 mL) and the upper oil layer drawn off (1.5455 g; no. 1). The lower aqueous layer was mixed with brine (5 mL) and extracted with dichloromethane (three times, 1.0 mL) and with diethyl ether (3 and 2 mL; no. 2). The aqueous layer was extracted with diethyl ether (5 mL); GC was done on separate solutions and then on combined samples. The aqueous layer was neutral in pH. Oil and extract were combined, dried over MgSO₄, and passed over 6 cm of alumina (100 mesh) to remove yellow color. Toluene (0.1744g, reference) was added, and GC (DB-5) gave substances listed in Table I (run 3). Calculation gave a total of 9.958 mmol of substances (99.0% of charge). The aqueous layer was distilled (8-in. Vigreux column, column B) to remove water and then (without column) formamide, bp 90 °C/10 mm, 0.64 g; temperature of bath 125 °C. The residue of salts weighed 2.35 g (contained 2a). IR (Nujol mull): strong HC=NH band at 1710 cm⁻¹; other bands at 1120, 1080, and 720 cm⁻¹.

Representative Experiment: 1-Bromooctane (1a) and N-Methylformamide (2b) in a Stirred Flask at 135 °C, for Reaction Kinetics. Method B. 1a (0.9808 g, 5.0784 mmol) and 2b (6.111g, 103.46 mmol) were charged under nitrogen purge to a 10-mL flask, stirred vigorously by a 10- × 15-mm magnet bar under a reflux condenser connected to an oil-seal trap, and kept at 135 ± 0.1 °C by a temperature-controlled oil bath also stirred by magnet bar. After 1.00 h and intervals thereafter, listed in Table III, the clear, light yellow liquid mixture was cooled (under nitrogen) and sample (e.g., 0.1851 g) withdrawn by pipet into a vial. The pH of the liquid was tested by pH paper (initially 7, decreased to 6, and then to 4 during reaction after 2 h and then 3 h reaction time). Toluene (reference, e.g., 0.0393 g) was weighed into the vial. Two mL of dichloromethane and 1.5 mL of brine solution was added, and the mixture was extracted with diethyl ether (1 mL). The extract was dried (MgSO₄) and passed down a 6 × 0.5-cm column of Al₂O₃. The total weight of sample was then, e.g., 2.8724 g. During 8 h of reaction the mixture remained clear and light yellow in color.

2-(F-Hexyl)-1-iodoethane (1c) and Formamide (2a) with Water at 140 °C; See Table VII, Run No. 1. 1c (2.6378 g, 5.458 mmol), 2a (4.97 g, 110 mmol), and water (0.21 g, 11 mmol) were charged to a Fischer tissue culture tube (20 × 110 mm) and stirred by a 10- × 15-mm magnet bar. The tightly capped tube was heated at 140 °C in a stirred oil bath for 4.5 h, cooled, and weighed

(0.323 g loss in wt). The clear, colorless liquid mixture contained two layers that were vigorously mixed by stirring with no change in appearance. The mixture was poured into 50 mL of water, and a clear lower layer weighed 2.2252 g (no. 1). The aqueous layer was extracted with CCl_4 (1.00 mL) twice and weighed (2.8959 g, no. 2). Both samples were dried (MgSO_4). Samples 1 and 2 were diluted with acetone, and 1,2-dichlorobenzene (1,2-DCB) was weighed in: to no. 1 (0.14332 g), 0.0220 g of 1,2-DCB; to no. 2 (0.2258 g), 0.0455 g of 1,2-DCB. Making use of response factors,¹⁷ GC analysis (DB-5) gave weights and mol amounts of substances as follows (two analyses averaged): no. 1, 5.124 mmol (97.6% of theory); no. 2, 0.2833 mmol (5.190% of theory). The mol % yield of individual substances from samples 1 and 2 combined are listed in Table VII.

Acknowledgment. The author is grateful to CIBA-GEIGY Corp., Central Research, Ardsley, NY, for the gift of starting material 2-(*F*-hexyl)-1-iodoethane (1c) and to

The Analytical Services Division for assistance. The author wishes to thank Dr. Larry L. Funck and Dr. Timothy J. Wilkinson for valuable discussions and assistance in preparation of this manuscript.

Supplementary Material Available: Alkylation reactions of 1-bromooctane (1a) with *N*-methylformamide (2b), isolation and characterization of methanimidamide hydrobromide (8a), *N,N*-dimethylmethanimidamide hydrobromide (8b), and hydroiodide (8c), experimental procedures used for GC analysis, synthesis of reference substances *n*-octyl formate (5), di-*n*-octyl ether (6), and *N*-octylformamide (7), and Tables IV and V giving results of reactions of 1a or 1-iodooctane (1b) with 2b (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.