TABLE I

ALKYL DERIVATIVES OF THIOPHENES

Starting materials		Mole ratio	Reaction products	Yield, %	B. p., °C.	Mm.	Sulfur, % Calcd.	Found	$n^{20}D$	d^{20}_4
Thiophene	Propylene	1:1	Isopropylthiophene	19[a]	153–154	760	25.0	24.70	1.5039	0.9634
Thiophene	Propylene tetramer[b]	1:0.8	Dodecylthiophene	77[a]	75–143	2	12.8	12.76		
Thiophene	Hexene-1[c]	1:1.5	Hexylthiophene	23	97–98	20	19.03	19.50	1.4969	
			Dihexylthiophene	6	98–100	2	12.69	13.00	1.4909	
Thiophene	Diisobutylene	1:2	Tri-*t*-butylthiophene[d]	11	94–95	2	12.69	12.40	1.4885	.8565
			Tetra-*t*-butylthiophene[e]	62	125	2	10.38	10.60	M. p. 28.4°	
2-Methylthiophene	2-Ethyl-1-butene	1:1.2	Hexyl-2-methylthiophene	6	98–101	11	17,58	17.30	1.5025	.9419
			Dihexyl-2-methylthiophene	16	150–152	10	12.02	11.64	1.4995	.9214
3-Methylthiophene	Diisobutylene	1:1.7	3-Methyloctylthiophene	23	69–70	1	15.23	15.06	1.4969	.9219
			3-Methyldioctylthiophene	43	133–134	1	9.98	9.89	M. p. 29.3°[f]	
2-Chlorothiophene	Diisobutylene	1:1.7	2-Chlorodibutylthiophene	14	75–76	2	13.88	13.31	Cl calcd.: 15.38 Found: 14.30	
			2-Chlorotributylthiophene	15	136–138	1	11.17	10.6	Cl calcd.: 12.38 Found: 10.6	
2-Thiophene-carboxylic acid	Isopropyl ether	1:4	Isopropyl-2-thiophencarboxylic acid	30			18.82	18.43	M. p. 81°	

[a] Yield based on olefin. All other yields are based on the thiophenes. [b] A commercial product, b. p. 175–246°. [c] When equimolecular amounts of benzene and thiophene were alkylated with hexene-1 (0.75 mole per mole thiophene) the reaction product distilled from 98.5–100° (20 mm.); S, 2.81%. [d] This product could be sulfonated. [e] This product could not be sulfonated. [f] A mixed melting point with the tetra-*t*-butylthiophene showed a strong depression.

elementary analysis. The principal object of this paper was to show that hydrogen fluoride, in spite of previous reports, could be used very advantageously for the alkylation of thiophene.

The following thiophenes were alkylated: thiophene, 2-methylthiophene, 3-methylthiophene, 2-chlorothiophene, 2-bromothiophene and 2-thiophenecarboxylic acid, using as the alkylating agents propylene, isopropyl ether, propylene tetramer, hexene-1, 2-ethyl-1-butene and diisobutylene.

Experimental

The experimental procedure was in general that described in a previous paper.[1] The essential part of a successful alkylation was the simultaneous addition of the thiophene and olefin to the hydrogen fluoride. Only in cases where the substituted thiophenes were stable in hydrogen fluoride could ethers or alcohols be used.

The experimental results are summarized in Table I.

Summary

Hydrogen fluoride has been shown to be an effective condensing agent for the preparation of nuclear alkylated thiophenes.

WILMINGTON, DELAWARE RECEIVED APRIL 21, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS AND FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WISCONSIN]

The Fluorination of Sulfuryl Chloride

BY MARK M. WOYSKI

Volatile inorganic fluorides are frequently prepared by reaction of the corresponding chlorides with such agents as antimony trifluoride, zinc, lead, or sodium fluorides. In all but a few cases complete fluorination is achieved at moderate temperatures and pressures. An exceptional case is that of sulfuryl chloride,[1] which reacts with antimony trifluoride rapidly only at elevated temperatures and pressures and gives the chlorofluoride, SO_2ClF, as the only product. A second exception is carbon tetrachloride which is readily fluorinated only to the difluoro stage, CCl_2F_2.

Equilibrium in halogen exchange reactions has not been discussed in the literature. Available thermochemical data are summarized in Table I as differences of free energies of formation of chlorides and fluorides so that the algebraic difference of any two "couplets" gives the free energy of an exchange reaction. The table is therefore a list of fluorinating agents in order of decreasing thermochemical activity. Since some of these values may be in error by several thousand calories this table is presented only as a guide to investigators. Data for most of the volatile chlorides and fluorides are not available.

The free energy values given in the table have been calculated from heat of formation data recorded in the tables of Bichowsky and Rossini[2] and from entropy data given by Kelley.[3] Several values have also been deduced from experimental results published by Jahn-Held and Jellinek.[4] Advantage has also been taken of the observation that for many chloride fluoride couplets the entropy difference is nearly the same.

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(1) Booth and Herrmann, THIS JOURNAL, **58**, 63 (1936).

(2) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936.

(3) Kelley, *U. S. Bur. Mines Bull.* **434** (1941).

(4) Jahn-Held and Jellinek, *Z. Elektrochem.*, **42**, 401 (1936).

TABLE I

FREE ENERGY OF CHLORINE–FLUORINE EXCHANGE AT APPROXIMATELY 25° (PER EQUIVALENT)

Couplet	$\Delta F^\circ_{MCl} - \Delta F^\circ_{MF}$
AgF(s)—AgCl(s)	17,800
CsF(s)—CsCl(s)	24,500
RbF(s)—RbCl(s)	27,300
KF(s)—KCl(s)	29,100
$^1/_4CF_4$(s)—$^1/_4CCl_4$(g)	33,400
$^1/_2CdF_2$(s)—$^1/_2CdCl_2$(s)	34,100
$^1/_2PbF_2$(s)—$^1/_2PbCl_2$(s)	34,700
NH_4F(s)—NH_4Cl(s)	34,700
$^1/_2ZnF_2$(s)—$^1/_2ZnCl_2$(s)	36,200
NaF(s)—NaCl(s)	36,400
$^1/_2CuF_2$(s)—$^1/_2CuCl_2$(s)	38,300
$^1/_2NiF_2$(s)—$^1/_2NiCl_2$(s)	40,300
$^1/_2BaF_2$(s)—$^1/_2BaCl_2$(s)	40,300
$^1/_3SbF_3$(s)—$^1/_3SbCl_3$(s)	40,500
HF(g, ideal)—HCl(g)	40,900
$^1/_2SrF_2$(s)—$^1/_2SrCl_2$(s)	44,300
LiF(s)—LiCl(s)	46,300
$^1/_2CaF_2$(s)—$^1/_2CaCl_2$(s)	48,300
$^1/_3AlF_3$(s)—$^1/_3AlCl_3$(s)	52,600
$^1/_4SiF_4$(g)—$^1/_4SiCl_4$(g)	53,900
$^1/_2MgF_2$(s)—$^1/_2MgCl_2$(s)	53,900
$^1/_3BF_3$(g)—$^1/_3BCl_3$(g)	55,300

The work of Booth and Herrmann on the sulfuryl chloride–antimony trifluoride system seems to indicate that equilibrium conditions are unfavorable for complete fluorination and that the use of a better fluorinating agent would bring about complete fluorination. This investigation has been started to study equilibrium in halogen exchange reactions. The present paper presents preliminary results on the reaction of sulfuryl chloride or its dissociation products, sulfur dioxide and chlorine, with alkali and alkaline earth metal fluorides.

Experimental

Reactions of Liquid Sulfuryl Chloride.—Fluorination of liquid sulfuryl chloride at its boiling point was attempted with magnesium, calcium, barium, lithium, sodium, potassium, and ammonium fluorides and potassium acid fluoride. Reaction was observed only with ammonium fluoride and potassium acid fluoride. Sulfuryl chlorofluoride, SO_2ClF, was formed in large amounts and was the only fluorination product. The reaction was always accompanied by the dissociation of some sulfuryl chloride into sulfur dioxide and chlorine.

A typical experiment on the reaction of sulfuryl chloride with ammonium fluoride was as follows. Eighty-one grams (2.19 moles) of ammonium fluoride, dried over calcium chloride and reduced to fine granular form, and 360 g. (2.67 moles) of sulfuryl chloride were heated to 80° in a 500-cc. flask under reflux. Gaseous products were condensed in a trap immersed in a dry-ice–acetone bath. After three hours no liquid was visible in the reaction flask. Distillation yielded 189 g. (1.58 moles) of sulfuryl chlorofluoride (b. p. 6.9–7.2°) corresponding to a 73% yield on the basis of ammonium fluoride. About 10 g. of chlorine and a similar amount of sulfur dioxide were also isolated.

Other experiments at temperatures varying from 60 to 80° gave comparable results with yields ranging up to 90%. Yields appeared to vary with different samples of ammonium fluoride. Use of a large excess of sulfuryl chloride resulted in extensive dissociation. Best results were obtained by using only a 20% excess of sulfuryl chloride. The glass reaction flask was attacked but the loss in weight per run amounted to only about 0.5 g.

Reactions with potassium acid fluoride gave similar results. Glass was more severely attacked in this case.

Gas Phase Fluorination.—Fluorination at higher temperatures was investigated by passing sulfuryl chlorofluoride, sulfuryl chloride, or an equimolal mixture of sulfur dioxide and chlorine (obtained by thermal decomposition of sulfuryl chloride) over metal fluorides. The rate of flow of sulfuryl chlorofluoride was controlled by a capillary flowmeter in conjunction with the low temperature still which maintained a constant pressure. The rate of flow of sulfuryl chloride vapor was regulated by a flowmeter maintained at 100°. The finely granular metal fluorides (70 to 100 g.) were supported on broken glass in vertical glass tubes (40 mm. o. d.) forming a column 12 cm. high. The reaction tube was maintained at constant temperature in a fused salt bath. The composition of the products was determined by fractional distillation and partial analysis of the fractions. The low temperature still was patterned after that of Booth and Bozarth[5] but made use of a column packed with glass helices in place of the Dufton wire spiral. The packed column permitted higher rates of distillation and higher reflux ratios. Due to the wide separation in the boiling points of the constituents, fractions were very sharp and had substantially constant boiling points (0.2°).

Sulfuryl fluoride and chlorine form an azeotropic mixture. When these occurred together in a sample they were collected as one fraction which was then analyzed; or the chlorine was removed by reaction with antimony trichloride and the sulfuryl chloride redistilled.

Thermal Decomposition of Sulfuryl Chlorofluoride.—At temperatures up to 400° sulfuryl chlorofluoride appears to be completely stable in glass. No decomposition was observed in several hours. The chlorofluoride is, however, unstable with respect to decomposition into sulfur dioxide, chlorine and sulfuryl fluoride, $2SO_2ClF \rightarrow SO_2F_2 + Cl_2 + SO_2$, and the rate of decomposition is greatly accelerated by all the metal chlorides and fluorides used in this investigation. Metals such as nickel and stainless steel also catalyze the decomposition.

Fluorination of Sulfuryl Chlorofluoride.—When sulfuryl chlorofluoride was passed over metal fluorides both decomposition and fluorination took place. The results of experiments are summarized in Table II which gives the compositions of products and the fractions of sulfuryl chlorofluoride which underwent decomposition and fluorination. At the high rate of flow (40 g. per hour) at 400° lithium, magnesium, calcium and barium fluorides produced complete decomposition but no detectable fluorination; sodium fluoride produced chiefly decomposition but

TABLE II

GAS PHASE FLUORINATION REACTIONS

Rates of flow: SO_2ClF, 40 g./hour; SO_2Cl_2 12 g./hour; $SO_2 + Cl_2$ 12 g./hour.

Reactants	Temp., °C.	Composition of product, mole per cent. SO_2F_2	SO_2ClF	SO_2	Cl_2	Decompn., %	Fluor., %
KF, SO_2ClF	200	2.5	92.5	2.5	2.5	5	Trace*
KF, SO_2ClF	300	23	47	15	15	35	10
KF, SO_2ClF	400	100	0	0	0	...	100
KF, SO_2Cl_2	400	100	0	0	0	...	100
KF, SO_2Cl_2	400	100	0	0	0	...	100
NaF_2, SO_2ClF	400	36	0	32	32	93	7
NaF, SO_2Cl_2	400	5	0	47	47	...	10
LiF, SO_2Cl_2	400	0	0	50	50	...	0
BaF_2, SO_2ClF	400	33.3	0	33.3	33.3	100	0
BaF_2, SO_2Cl_2	400	Trace ±	0	50	50	...	Trace ±
CaF_2, SO_2ClF	400	33.3	0	33.3	33.3	100	0
MgF_2, SO_2ClF	400	33.3	0	33.3	33.3	100	0

± Indicated by presence of chloride in solid residue.

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(5) Booth and Bozarth, *Ind. and Eng. Chem.*, **29**, 470 (1937).

also 5 or 10% fluorination; potassium fluoride produced complete fluorination.

At 300° the rates of both reactions were so greatly reduced that much sulfuryl chlorofluoride came through undecomposed and little fluorination resulted.

Fluorination of Sulfuryl Chloride.—In all experiments identical results were obtained in the reaction of sulfuryl chloride with metal fluorides and in the reaction of an equimolal mixture of sulfur dioxide and chlorine with metal fluorides. At 400° sulfuryl chloride decomposes rapidly into sulfur dioxide and chlorine. The reacting systems in the two cases were accordingly substantially the same consisting of sulfur dioxide, chlorine and a small equilibrium concentration of sulfuryl chloride. The over-all reaction may be written

$$SO_2 + Cl_2 + 2MF \longrightarrow SO_2F_2 + 2MCl$$

The fluorination reactions here observed were in accord with those involving sulfuryl chlorofluoride. With potassium fluoride complete fluorination resulted; sodium fluoride produced partial fluorination; other fluorides were without effect. Some of the results are given in Table II.

Discussion and Conclusions

The results of the fluorination experiments may be correlated with the data of Table I. Since in the reaction

$$SO_2 + Cl_2 + 2MF \longrightarrow SO_2F_2 + 2MCl$$

complete fluorination is obtained with potassium fluoride, it follows that all fluorinating agents which have a free energy difference of less than 29,000 cal. for their chloride fluoride couplet will produce similar results at equilibrium. Agents which have free energy differences for their couplets between the approximate limits of 34,000 and 40,000 cal. will produce observable equilibrium. Calcium fluoride and others which have values in excess of 48,000 cal. will be without appreciable effect. Some of the equilibrium systems are being investigated in order to obtain the free energies of formation of the metal fluorides.

Acknowledgment.—Part of the material in this paper is from a thesis prepared under the direction of Professor John Christian Bailar, Jr., and submitted by the author to the faculty of the University of Illinois in fulfillment of requirements for the degree of Doctor of Philosophy. The remainder of the experimental work was done subsequently at the University of Wisconsin.

Summary

1. Sulfuryl fluoride has been prepared by direct fluorination of sulfuryl chloride, or an equimolar mixture of sulfur dioxide and chlorine, with potassium or sodium fluorides at 400°.

2. Thermal decomposition of sulfuryl chlorofluoride into sulfur dioxide, chlorine and sulfuryl fluoride at 300 to 400° was observed.

3. The thermochemistry of halogen exchange reactions is briefly summarized.

MADISON, WISCONSIN RECEIVED AUGUST 8, 1949

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1305]

The Formation of Diketopiperazines from Dipeptide Amides[1a]

BY H. T. HUANG AND CARL NIEMANN[1b]

It has been observed that the acetates of glycyl-DL- and L-phenylalaninamide[2] and glycylglycinamide[2] are readily transformed into DL- and L-3(6)-benzyl-2,5-diketopiperazine and 2,5-diketopiperazine, respectively, when aqueous or methanolic solutions of the acetates are either warmed or allowed to stand at room temperature for several days. However, when the acetates of glycyl-DL-phenylalaninmethylamide, glycyl-DL-phenylalaninbenzylamide, diglycylglycine and triglycylglycine, or the hydrochloride of glycyl-DL-phenylalaninamide are similarly treated no diketopiperazine formation is observed.

From the data available for dipeptide esters and amides it appears that facile diketopiperazine formation is in part dependent upon the availability of a primary or secondary amino group and for dipeptide amides is restricted to primary amides. With either dipeptide esters or amides it is possible that the amino group may be activated, in the sense used by Gordon, Miller and Day,[3] by intramolecular hydrogen bonding.

Glycyl-L-phenylalaninamide has been recommended as a substrate for the quantitative estimation of chymotrypsin activity.[2] In view of the ease of formation of L-3(6)-benzyl-2,5-diketopiperazine from this dipeptide amide, even in weakly acidic solutions, it is clear that caution should be exercised in using this peptide as a substrate in enzymatic studies, particularly at low substrate concentrations and temperatures above 25°.

Experimental[4]

Carbobenzoxyglycyl-DL-phenylalaninamide (I).—Acylation of an ethyl acetate solution of DL-phenylalanine methyl ester prepared from 12 g. of the hydrochloride, with 12 g. of carbobenzoxyglycyl chloride[2,5] gave 12.9 g. of sirupy carbobenzoxyglycyl-DL-phenylalanine methyl ester (II). A portion of II was crystallized from methanol and then recrystallized from a mixture of benzene and ether to give II, clusters of soft fibrous needles, m. p. 80–81°.

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[1] (a) This work was supported in part by a grant from Eli Lilly and Co. (b) Responsible co-author.

[2] J. S. Fruton and M. Bergmann, *J. Biol. Chem.*, **145**, 253 (1942).

[3] M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948); **71**, 1245 (1949).

[4] All melting points are corrected.

[5] M. Bergmann and L. Zervas, *Ber.*, **65** II, 1192 (1932).