

Nuclear Magnetic Resonance Investigations of Iminium Ion Intermediates, Part 7.† Structure and Mechanism of Formation of the Intermediates in the Reactions between Amides and CSCl_2 or PSCl_3 or between Thioamides and COCl_2 , POCl_3 , or PSCl_3

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Previous studies of the reactions between amides and Lewis acids (COCl_2 , SOCl_2 , POCl_3) have been extended to reactions involving amides with PSCl_3 or CSCl_2 and thioamides with POCl_3 or PSCl_3 . The products and intermediates were identified using ^1H , ^{13}C , and ^{31}P n.m.r. spectroscopy. Kinetic and variable temperature n.m.r. experiments have permitted the elucidation of the reaction mechanisms. The experiments also demonstrated exchange processes between the amides or thioamides and the iminium salts. Although the products are of various types a general feature is equilibria between the amide + PSCl_3 and the thioamide + POCl_3 . The reactivities are highly dependent on the structure of the starting amide or thioamide, the polarity of the solvent, and the nature of the Lewis acid.

We have previously studied the nature of the intermediates and exchange processes involved in reactions between oxyhalides (POCl_3 , COCl_2 , SOCl_2) and various amides.¹⁻³ These reactions are of synthetic significance and many formylations or carbonylations have been carried out using them.⁴⁻⁶ By contrast the analogous reactions between thioamides and oxyhalides or between thiohalides (PSCl_3 , CSCl_2) and amides are not well known although dimethylthioformamide has been claimed to be a better reagent than dimethylformamide in the Vilmeier reaction.⁷

With a view to confirming the mechanisms proposed in our previous papers and extending our knowledge of the conditions under which the reactions take place, we have studied a number of reactions involving thio-compounds. At first sight these reactions appear to be much more complicated than the formation of the usual Vilsmeier complex from dimethylformamide and POCl_3 or COCl_2 , since numerous intermediate species can be observed and several exchange processes intervene. However we shall see that the data prove the existence of the general mechanism amide + $\text{PSCl}_3 \rightleftharpoons$ thioamide + POCl_3 and provide information on the relative stabilities of the intermediate complexes.

The amides and thioamides considered in this study are *NN*-dimethyl-formamide (DMF), -thioformamide (DMTF), -acetamide (DMA), and -thioacetamide (DMTA), and 2-methylpropionamide (DMP) and 2-methylthiopropionamide (DMTP). The Lewis acids are POCl_3 , COCl_2 , PSCl_3 , and CSCl_2 .

EXPERIMENTAL

Materials.—The reagents were carefully dried and vacuum distilled twice. DMTA and DMTP were prepared from P_4S_{10} and amides (DMA, DMP) in C_6H_6 . DMTA was recrystallized from hexane.

† Part 6, Cl. Rabiller, J. P. Renou, and G. J. Martin, *J.C.S. Perkin II*, 1977, 536.

¹ G. J. Martin and M. L. Martin, *Bull. Soc. chim. France*, 1963, 1637.

² G. J. Martin and S. Poignant, *J.C.S. Perkin II*, 1974, 642.

³ M. L. Martin, G. Ricolleau, S. Poignant, and G. J. Martin, *J.C.S. Perkin II*, 1976, 182.

All reactions were performed in the manner previously described using an air-tight apparatus flushed with dry argon.¹

Spectra.— ^1H N.m.r. spectra were recorded on Varian A 60 A or XL 100 12 spectrometers operating in the continuous wave mode. The ^{13}C spectra (25.18 MHz) were recorded in the Fourier transform mode with the XL 100.12—620f (16 K) system. The spectra were usually run both with and without noise decoupling. The latter conditions allowed the $^1J(^{13}\text{C}-\text{H})$ values to be measured but in most cases these parameters were obtained with better accuracy from the satellite ^1H spectra. Variable temperature measurements were carried out with a Varian V4341 accessory; the temperature was calibrated by means of a chromel-constantan thermocouple. ^{31}P Measurements were obtained using a JEOL C 60 HL spectrometer.

A number of the reactions considered have half-reaction times greater than a few minutes. Thus kinetic measurements could be achieved by recording the n.m.r. signal areas, S , associated with the appearing and disappearing species as a function of time. In the absence of exchange phenomena the plots $S = f(t)$ directly yield the laws of variation of concentration $c = f(t)$. However, when the species considered are involved in exchange processes, the intensity plots $S = f(t)$ must be combined with plots of the averaged chemical shifts variations, $\delta = f(t)$, in order to obtain the kinetic curve $c = f(t)$ corresponding to a single compound.

RESULTS AND DISCUSSION

Reactions between Thioamides and PSCl_3 (Cases 1—3, Table 1).—Thioamides and PSCl_3 do not react easily. In case 1 (DMTF), for example, all that can be observed at room temperature is a coalescence of the *N*-methyl signals in the ^1H n.m.r. spectrum without any noticeable variation of the chemical shifts. The cations $(\text{CH}_3)_2\text{N}=\text{C}(\text{R})\text{Cl}^+$ have been identified in the course of the slow reaction between DMTA and PSCl_3 (Case 2) and when DMTP was heated at 340 K with PSCl_3 (Case 3). A

⁴ Z. Arnold and A. Holy, *Coll. Czech. Chem. Comm.*, 1965, **30**, 47.

⁵ G. F. Smith, *J. Chem. Soc.*, 1954, 3842.

⁶ H. Bredereck, R. Gompper, and K. Klein, *Chem. Ber.*, 1959, **92**, 1456.

⁷ J. G. Dingwall, D. H. Reid, and K. Wade, *J. Chem. Soc. (C)*, 1959, 913.

phosphorus signal at *ca.* +80 p.p.m. relative to the H_3PO_4 signal was also assigned to the $SPSCl_2^-$ anion [Scheme 1(A)].

The salt (1) is able to associate strongly with thioamides to give the crystalline species $(CH_3)_2N\cdots$

by n.m.r. kinetic studies. Furthermore hydrolysis of the crystalline layer gave approximately equal amounts of DMF and DMTF.

These results are rationalized by Scheme 2(A). Owing to the nucleophilic properties of the $OPSCl_2^-$ anion

TABLE 1

1H and ^{13}C chemical shifts of thioamides and iminium salts obtained from the reaction between thioamides and $PSCl_3$ [chemical shifts of the reference compound $(CH_3)_2N-CH=N(CH_3)_2^+$, Cl^- obtained by an independent method⁸ are: 1H δ 3.4 (1,1') and 8.8 (2); ^{13}C δ 40 and 45 (1,1') and 156.8 (2)]

Case	Reaction of thioamides with $PSCl_3$ Product	1H		^{13}C	
		1,1'	2-4	1,1'	2-4
1	DMTF	3.35	9.2	38.8, 45.1	186.6
	$(CH_3)_2N\cdots CH\cdots N(CH_3)_2^+$, $SPSCl_2^-$ 1,1' 2 1,1'	3.35	7.9	39.2, 45.8	155.6
2	DMTA	3.5	2.8	42.7, 44.0	198.5, 32.5
	$(CH_3)_2N=C(CH_3)Cl^+$, $SPSCl_2^-$ 1,1' 2 3	3.8	3.0		
3	DMTP	3.5	3.36, 1.18	42.1, 43.0	208.4, 36.1, 22.6
	$(CH_3)_2N=C(Pr^i)Cl^+$, $SPSCl_2^-$ 1,1' 2 3,4	4.0, 4.08	3.72, 1.43		

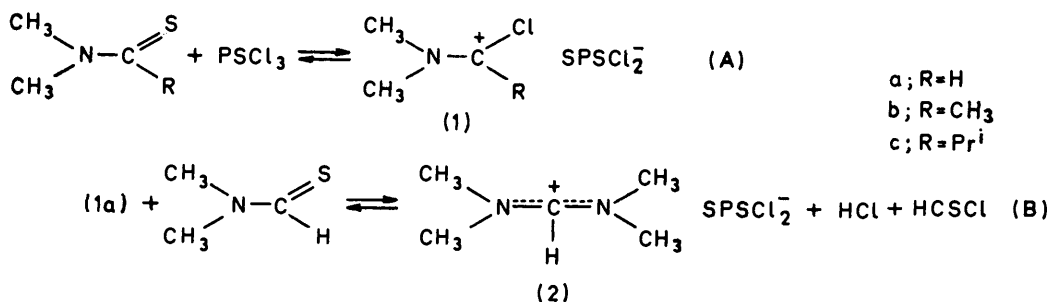
$C(R)\cdots S\cdots C(R)Cl\cdots N(CH_3)_2^+$, $SPSCl_2^-$. Upon heating a mixture of DMTF and $PSCl_3$ at 350 K for several hours, the iminium salt (2) [Scheme 1(B)] was characterized by comparison of its 1H and ^{13}C spectra with those of independently prepared salts⁸ of this cation with other anions (Cl^- , ClO_4^-), (Table 1).

Reactions between Amides and $PSCl_3$ (Cases 4-6, Table 2).—In a first step, the amides react with $PSCl_3$ to give the complex (3) [Scheme 2(A)]. The cation (3c) is the predominant species in the slow reaction of DMP and $PSCl_3$ and a ^{31}P resonance at +41 p.p.m. was assigned to the anion $OPSCl_2^-$ (Case 6). Complex (3)

complex (3a) is not stable but is converted into complex (4a) which rapidly decomposes further into DMTF and $POCl_3$. $POCl_3$ reacts with the remaining DMF to yield the Vilsmeier complex (5a) [Scheme 2(B)] which exchanges with DMTF.

When the reaction is run without a solvent complex (5a) crystallizes with DMTF to give the solid species $(CH_3)_2N-CH=S\cdots CH(Cl)\cdots N(CH_3)_2^+ OPOCl_2^-$.

In similar conditions the reaction of DMF is slower with $PSCl_3$ than with $POCl_3$. At 303 K in $CHCl_2CHCl_2$, DMF (2M) reacts almost immediately with $POCl_3$ (2M) but the reaction with $PSCl_3$ takes *ca.* 4 h.



SCHEME 1

however further reacts more or less easily according to the nature of the R and was not observed with DMF and DMA. When equimolar quantities of DMF and $PSCl_3$ are mixed without a solvent two layers are obtained and the lower liquid layer was identified as a mixture of DMTF and $PSCl_3$ (Table 2, Case 4). Only two proton signals were observed, either when the solid upper layer was dissolved in CH_2Cl_2 , or when the reaction was performed directly in a solvent. The δ and $^1J(^{13}C-H)$ values associated with these signals were interpreted as originating from a rapid exchange process between DMTF and the complex (5a). This interpretation was corroborated by the characterization of $OPOCl_2^-$ anions along with $POCl_3$ by ^{31}P spectroscopy (Table 3) and

⁸ J. P. Renou, Dissertation, Nantes, 1976.

We have proved that the mechanism elucidated in Scheme 2(A) may also occur when DMA reacts with $PSCl_3$ (Case 5) since small quantities of DMTA could be identified. However self-condensation³ of complex (3b) now competes with the transformation into (4b) and is noticeably more rapid [Scheme 2(C)]. The kinetic curves obtained from the combined study of the time dependence of both integral and weighted chemical shift show that the self-condensation product (6) (identified by its ^{13}C parameters, Table 2) appears simultaneously with complex (7), rapidly exchanging with DMA. At 250 K, this intermolecular exchange is still rapid according to 1H n.m.r. spectroscopy but it operates without loss of the diastereotopic character of the *N*-methyl groups. This behaviour suggests that the

C-O bond is retained and that an O-R bond is cleaved in the exchange mechanism. On this basis and on taking into account the $\delta(^1\text{H})$, $\delta(^{13}\text{C})$, and $J(^{13}\text{C}-\text{H})$ parameters (Table 2) complex (7) was recognized as

Reactions of Thioamides with POCl₃ (Cases 7—9).—The reactions of thioamides and POCl₃ follow the reverse of Scheme 2(A). On mixing equimolar quantities of DMTF (or DMTA) and POCl₃ in CH₂Cl₂ a progressive

TABLE 2

¹H and ¹³C chemical shifts and ¹J(¹³C-H) coupling constants of thioamides and iminium salts obtained from the reactions between amides and PSCl₃ (or thioamides and POCl₃): Case 4 DMF + PSCl₃, Case 5 DMA + PSCl₃, Case 6 DMP + PSCl₃. N.m.r. spectra have been recorded for CDCl₃ solutions except as otherwise stated (for assignments of atoms in thioamides and salts see Table 1)

Case	Reaction of amides with PSCl ₃ Product	¹ H Chemical shift		Coupling constant [¹ J(¹³ C-H)/Hz]		¹³ C Chemical shift [δ (p.p.m. from Me ₄ Si)]		
		1,1'	2-4	C(1)- H(1)	C(2)- H(2)	1,1'	2,2'	3,4
4	DMTF, PSCl ₃ ^b	3.25	9.10	139	176	36.9—	187.7	
	DMTF, (CH ₃) ₂ N=CHCl ⁺ , OPOCl ₂ ^{-c} in CD ₃ NO ₂	3.8 3.5	10.40 9.50	146 140 ^a	212 190 ^a	44	182.4	
5	DMTA (CH ₃) ₂ N=C(CH ₃)Cl ⁺ , B ⁻	3.9 ^a	3.10 ^a			34.9 47.5—	194 177.0	28.8
	(CH ₃) ₂ N=C(CH ₃)OH ⁺ , B ⁻	3.34 ^a	2.60 ^a	144		48.0 39.2	174.7	18.3
	(CH ₃) ₂ N=C(Cl)---CH---C(CH ₃)---N(CH ₃) ₂ ⁺ , B ⁻ 1,1' 2 3 2' 4 1,1'	3.4 ^a	5.25— 2.55 ^a			43.6— 43.8	171.6— 156.5	91.9— 20.8
6	DMTP	3.42	1.18			41.2—	210	36.1—
	(CH ₃) ₂ N=C(Pr ⁱ)Cl ⁺ , B ⁻	3.95—	1.40			44.6 46.9—	22.8 184.4	36.7—
	(CH ₃) ₂ N=C(Pr ⁱ)---N(CH ₃) ₂ ⁺ , B ⁻ 1,1' 2 3, 4 1,1'	4.0 3.32	1.43			48.7 43.5	19.7 177.5	30.8— 18.0

^a Measured in CHCl₂CHCl₂ solution. ^b Reaction carried out without a solvent. Lower layer. ^c Reaction carried out without a solvent (360 K). Upper layer. The n.m.r. spectra of the reference, protonated DMA, are consistent with the data for (CH₃)₂N=C(CH₃)OH⁺, B⁻ in case 5 (DMA, HCl) ¹H δ 3.36 (1,1') and 2.60 (3), ¹³C 38.0 and 39.7 (1,1'), 175 (2), and 20.5 (3) (this work); DMA, HFSO₃ ¹H δ 3.45 (1,1') and 2.64 (3) (R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41**, 148); DMA, HBF₄ ¹³C, δ 38.4 and 40.4 (1,1') and 175.7 (2) (R. Merenyi in 'Structure Determination of Iminium Compounds by Physical Methods,' eds. J. S. Boum and H. G. Viehe, in the press).

protonated DMA originating from the rapid reaction of the HX acids liberated in the self-condensation, with the remaining DMA [Scheme 2(D)]. It should be noted that intermolecular exchange between DMTA and small

TABLE 3

³¹P Chemical shifts (p.p.m. from 85% H₃PO₄) of Lewis acids and of anions resulting from the reaction between amides or thioamides and PXCl₃. A positive chemical shift indicates a deshielding effect

Compound	Chemical shift ^a	
	Cases 1—3 (Table 1)	Cases 4—9 (Table 2)
PSCl ₃	31—32.5	30—34.5
POCl ₃		5—5.5
SPSCl ₂ ⁻	79.5—81	79.5—82.5
OPSCl ₂ ⁻		39.5—42.5
OPOCl ₂ ⁻		-3.5—9

^a Taken for CDCl₃ or CHCl₂·CHCl₂ solutions.

quantities of the complex of DMA, (3b), is also evident in the course of this reaction. The coalescence temperature independently determined for an equimolar solution in CH₂Cl₂ (10M) is ca. 310 K by ¹H n.m.r. spectroscopy.

We have mentioned previously that the formation of complex (3c) from DMP and PSCl₃ (Case 6) is very slow. On heating at 350 K the iminium salt (8) appears [Scheme 2(E)] and an increased concentration of DMTP and OPOCl₂⁻ anions is observed [Schemes 2(A) and (B)].

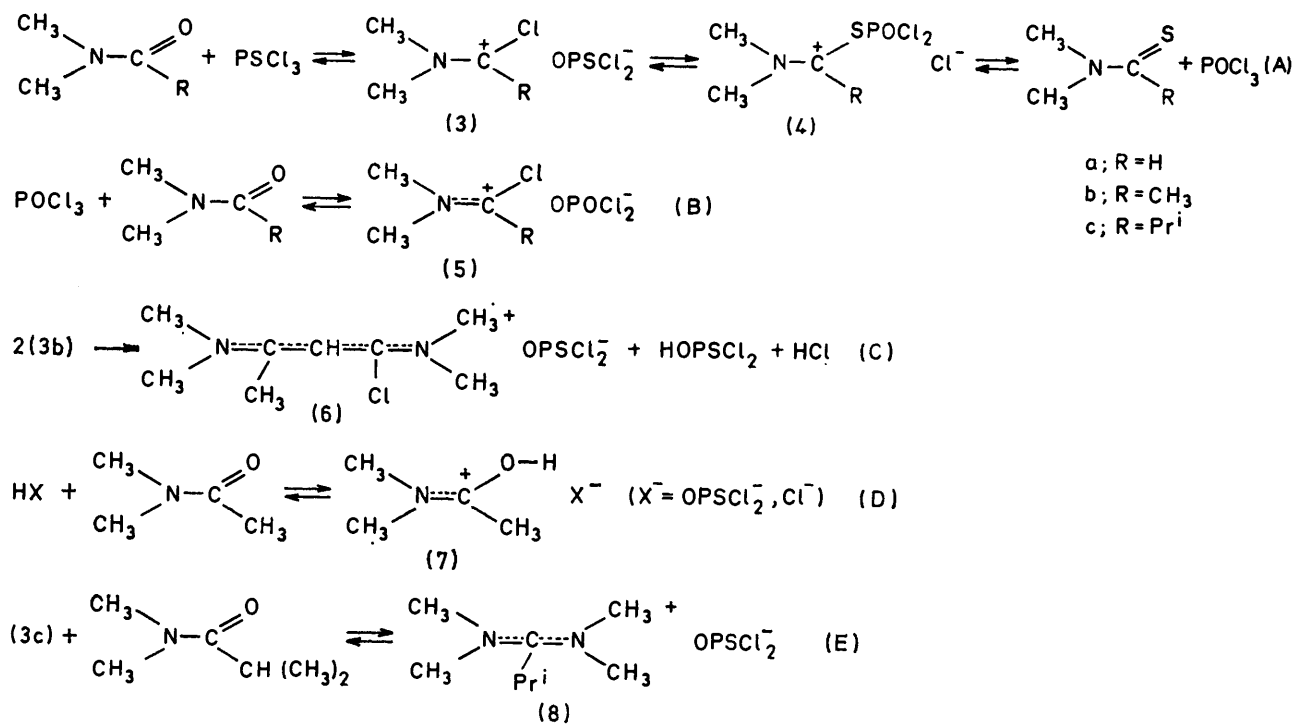
coalescence of the CH₃N resonances of the thioamide takes place accompanied with a shift towards higher frequencies. This shift is very small for DMTF but more important with DMTA. The time dependence of the coalescence excludes a first-order process and is typical of an exchange of DMTF (or DMTA) with an increasing amount of complex (3a) [or (3b)]. For a 10M solution of DMTA and POCl₃ in CH₂Cl₂ the NCH₃ and CCH₃ proton signals which widen out at 310 K split at 280 K into two sets of peaks of approximately equal intensity and may be assigned to complex (3b) and to DMTA. The NCH₃ signal of DMTA further splits at ca. 230 K; the lack of diastereotopic character of the N-methyl protons in complex (3b) is in fact fortuitous as can be independently verified by ¹³C spectroscopy.

When the reactions are carried out without a solvent yellow crystalline products are obtained which are attributable to an association between the thioamide and complex (3a) or (3b): (CH₃)₂NCH=S ··· CH(Cl)---N(CH₃)₂⁺ or (CH₃)₂NCH=S ··· CCH₃(Cl)---N(CH₃)₂⁺ OPSCl₂⁻. When dissolved these products decompose into the thioamide and (3) which further decomposes into the thioamide and POCl₃. Thus in the hydrolysis of the CH₂Cl₂ solutions mainly thioamide is recovered but if the hydrolysis is performed on the crystals similar proportions of DMF and DMTF are obtained.

In contrast to the reaction DMA + PSCl₃, the OPSCl₂⁻ anion is never observed in significant proportions with

DMTA + POCl₃ (Case 8). In the former case the self-condensation of (3b) is more rapid than the attack by the anionic sulphur and OPSCl₂⁻ is stabilized in the self-condensation product or in protonated DMA. In the present case, complex (3b) reacts with the anionic

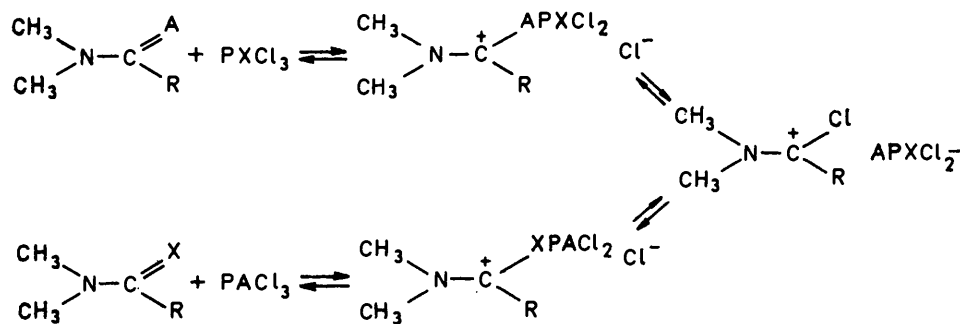
Reactions between Amides or Thioamides and COCl₂ or CCl₄ (Cases 10—12).—It is well known that phosgene reacts instantaneously with DMF to give the Vilsmeier complex (3a) with Cl as anion and with loss of CO₂. However, the reactions of CCl₄ with amides and thio-



SCHEME 2

oxygen to give DMA and PSCl₃ more rapidly than it self-condenses into (6). However it should be noted that the interaction between DMTA and (3b) probably limits self-condensation. This is verified by the fact that we observe, in mixtures of DMTA and OPOCl₂⁻

amides or of COCl₂ with thioamides have not been previously studied. Even at low temperatures COCl₂ and CCl₄ react very rapidly with DMF and DMTF and the complex (CH₃)₂N⁺CHClCl⁻ is obtained. With DMTF in an excess of Lewis acid only this complex



SCHEME 3

analogue of (3b) independently prepared, very small amounts of the OPOCl₂⁻ analogue of (6).

Even on heating at 350 K DMTP reacts slowly with POCl₃ (Case 9). In this case the DMP formed according to the reverse of Scheme 2(A) reacts more rapidly with POCl₃ [Scheme 2(B)] than with (3c) [Scheme 2(E)] and the complex (5c) is obtained along with (3c) and (1c) [Scheme 1(A)].

is found but with 2 moles of DMTF and one mole of acid a weakly soluble solid is produced. By analogy with the preceding results an interaction between the complex and the remaining DMTF may be postulated and a structure of type (CH₃)₂N-C(H)S ⋯ ⋯ CH(Cl) ⋯ ⋯ N(CH₃)₂Cl⁻ proposed.

In the same way the complex (CH₃)₂N⁺(CH₃)Cl⁻

can be synthesized with DMA or DMTA and COCl_2 or CSCl_2 . However this complex self-condenses when the temperature is increased.

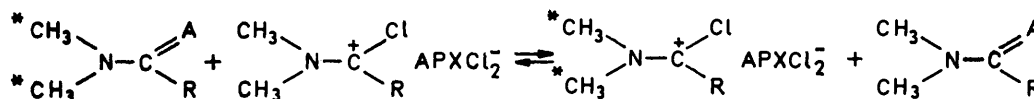
Conclusions.—Although the nature, the number, and the proportions of the species identified in the course of the various reactions seem rather diverse our results permit us to write the general mechanism in Scheme 3.

In previous papers we have definitively shown that the structure of the complex crystallized in the Vilsmeier reaction is $(\text{CH}_3)_2\text{N}^+\text{CHCl}$, OPOCl_2^- . The alternative formula $(\text{CH}_3)_2\text{N}^+\text{CHOPOCl}_2, \text{Cl}^-$ which intervenes accounts for < 1% reaction. The present study allows us to generalize this interpretation to the various re-

POCl_3 . This reaction still occurs when $\text{R} = \text{CH}_3$ but on a smaller scale as the complex prefers to self-condense. When $\text{R} = \text{Pr}^i$ complex (3c), being relatively inactive as regards the sulphur reaction, is observed separately. Both the decreasing positive charge and the increasing steric effects may be responsible for these phenomena.

From another point of view our results allow us to generalize the exchange process between amides and the corresponding complexes² (Scheme 4). The exchange rate increases from amide to thioamide and in the order $\text{R} = \text{Pr}^i < \text{CH}_3 < \text{H}$. These results have synthetic applications in complexation reactions.⁸

We have also generalized the occurrence of an exchange involving an attack of the cation by the anion of (3)



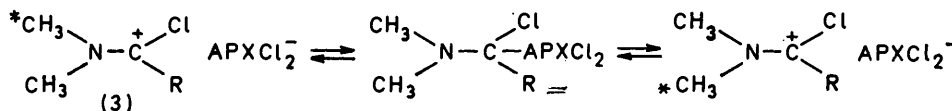
SCHEME 4

agents used. Structures of type (4) having phosphorus in the cation are never stable. They disappear either through the breaking of the A-P bond or through the exchange of APXCl_2^- with the chlorine anion.

The equilibria depend on the solvent; a more polar solvent, such as CH_3NO_2 compared with CDCl_3 or

(Scheme 5). Its rate decreases in the order $\text{R} = \text{H} > \text{CH}_3 > \text{Pr}^i$ and seems relatively independent of the counter anion.

When comparing the formation rates of the complex our kinetic studies establish the following order of decreasing rate constants: amide or thioamide +



SCHEME 5

$\text{CHCl}_2\text{CHCl}_2$ is associated with a shift towards the ionic species.

The reactions may be complicated in cases where $\text{R} = \text{CH}_3$ by possible self-condensation and if the basic reactions are slow complex (3) may react with the amide or thioamide on heating to yield the *NNN'*-tetramethylamidinium salt (8).

Drastic changes of reactivity are found according to the nature of the substituent R and of the atoms A and X . When considering the salt (3), the reaction of sulphur on the carbonium ion is rapid if $\text{R} = \text{H}$ and the equilibrium is displaced towards the thioamide and

$\text{COCl}_2 > \text{amide}$ or $\text{thioamide} + \text{CSCl}_2 > \text{amide} + \text{POCl}_3 > \text{amide} + \text{PSCl}_3 > \text{thioamide} + \text{POCl}_3 > \text{thioamide} + \text{PSCl}_3$. Furthermore, with a given thioacid the amide or thioamide reacts more rapidly in the order $\text{R} = \text{Pr}^i < \text{CH}_3 < \text{H}$.

Finally it should be emphasized that, when treated with CSCl_2 , amides and thioamides yield the same complex as obtained in the reaction between amides and COCl_2 . From a synthetic point of view CSCl_2 may be advantageous owing to its liquid state and lower toxicity.