334. *A Study of the Stephen Reaction.*

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A modified form of the Stephen reagent has been used in comparing the rates of reduction of a number of unsubstituted aliphatic and substituted aromatic nitriles. The reaction is of neither the first nor the second order. Precipitation of the aldiminium stannichloride appears to be the main factor which drives the reaction to completion. In unsubstituted aliphatic nitriles, structure has little effect on the rate of reaction, whereas in substituted benzonitriles electron-repelling groups increase the rate appreciably.

The scope of the reaction in the aliphatic series has been clarified by measuring the yields of aldehyde from the simpler nitriles. The yield increases with chain-length, but is lowered by chain-branching in the α-position.

Attention is drawn to the usefulness of the nitrile-exchange reaction [1] in the synthesis of *iso*butyro- and pivalo-nitrile.

THE Stephen reaction,[2] in which nitriles are reduced to aldimines (subsequently hydrolysed to aldehydes) by ethereal stannous chloride and hydrogen chloride, has recently been reviewed,[3, 4, 5] whence it is clear that the scope of the reaction in the aliphatic series is in doubt, and that there is little or no evidence concerning its mechanism. The present work consists of exploratory studies of the kinetics of the reaction, and of the determination of the yields of aldehydes from the lower aliphatic nitriles.

The reagent, as normally prepared,[2] is not suitable for kinetic studies, since it consists of two immiscible layers. A homogeneous reagent may be conveniently prepared by adding acetyl chloride to stannous chloride dihydrate in ether, the anhydrous salt being produced, together with some of the hydrogen chloride required for the reaction. Extra hydrogen chloride may be added by running in acetyl chloride and water in equimolar amounts. The acetic acid so produced renders the mixture homogeneous, and the reagent is stable for some weeks in a stoppered flask.

The course of the reaction has been followed by periodical determination of the stannous chloride concentration by standard, aqueous iodine. During the reaction the aldimine, which is the final product of the reduction, is precipitated as stannichloride. Fortunately, when the modified reagent was used, this precipitation was delayed, and measurements could be made under homogeneous conditions over the first 10—20% of the reaction.

The effects of varying the concentration of nitrile, of stannous chloride, and of hydrogen chloride are shown, for benzonitrile, in Tables 1—3. The rate varied with the concentration of each, and, as would be expected, the usual calculations showed that the reaction was kinetically neither of the first nor of the second order. An increase in the concentration of either the nitrile or hydrogen chloride increased the rate. The same was true for stannous chloride, except that there was an inversion of two of the concentration–time curves

TABLE 1. *Variation of rate with concentration of benzonitrile.*

Temp.: 23·6° ± 0·1°. Solvent: 30% v/v acetic acid in ether.

[$SnCl_2$] = 0·471M. [HCl] = 0·444M.

Time (hr.):	2	5	10	20	50
	$SnCl_2$ (10^{-3} mole) consumed				
Concn. of nitrile (M)					
0·551	0·91	1·95	2·82	3·25	3·35
0·184	0·16	0·36	0·65	1·12	1·84
0·055	0·08	0·16	0·26	0·38	0·49

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[1] B.P. 722,843.

[2] Stephen, *J.*, 1925, 1874.

[3] Wagner and Zook, "Synthetic Organic Chemistry," J. Wiley and Sons, New York, 1953, p. 292.

[4] Mosettig, "Organic Reactions," J. Wiley and Sons, New York, 1954, Vol. VIII, p. 246.

[5] Bayer, "Methoden der organischen Chemie (Houben–Weyl)," G. Thieme, Stuttgart, 4th Edn., Vol. VII, Pt. 1.

TABLE 2. *Variation of rate with concentration of stannous chloride.*

Temp. and solvent as in Table 1. [Ph·CN] = 0·551M. [HCl] = 0·767M.

Time (hr.):	1	2·5	5	10	25
	$SnCl_2$ (10^{-3} mole) consumed				
Concn. of $SnCl_2$ (M)					
0·384	1·38	2·54	3·27	4·02	4·93
0·145	2·02	2·54	2·97	3·38	3·87
0·055	0·98	1·28	1·38	1·48	1·62

TABLE 3. *Variation of rate with concentration of hydrogen chloride.*

Temp. and solvent as Table 1. [Ph·CN] = 0·551M. [$SnCl_2$] = 0·325M.

Time (hr.):	1	2·5	5	10	20
	$SnCl_2$ (10^{-3} mole) consumed				
Concn. of HCl (M)					
3·47	0·91	1·65	2·45	3·54	5·50
2·14	0·27	0·58	0·98	1·50	2·16
0·98	0·08	0·19	0·34	0·51	0·62

in the early stages of the reaction. These results are in conformity with a mechanism proposed for the reaction by Meerwein,[6] the first step in which may be interpreted as the formation of the nitrilium salt from the nitrile and chlorostannous acid:

$$R{\cdot}CN + H_2SnCl_4 \longrightarrow [R{\cdot}C{\equiv}NH]^+HSnCl_4^-$$

Since the concentration of chlorostannous acid must depend on the concentration of both stannous chloride and hydrogen chloride, the rate of reaction should vary with the concentration of all three reactants, as is found.

Attention was next turned to the effect of the structure of the nitrile on the reaction rate. The reaction being of indeterminate order, no quantitative comparison of rate-constants was possible. It was also impossible to take the initial slope of a concentration–time curve as a measure of rate since the necessary pipetting of the 1 ml. aliquot parts of ethereal solution involved an error estimated to be about 1·5—2%, which was significant in the very early stages of the reaction. However, reasonably smooth concentration–time curves were obtained, covering an adequate portion of the reaction, and the rates for various nitriles could be compared qualitatively.

For aliphatic nitriles the reagent used contained four mols. of hydrogen chloride per mol. of stannous chloride, the reaction being inconveniently slow at smaller concentrations. The results (Table 4) show that the structure has only a minor effect on the *rate* of reaction of aliphatic nitriles (the effect on the yield is later shown to be more marked). With acetonitrile, precipitation of the aldimine stannichloride occurred after 25 hr., and markedly accelerated the reaction. Such precipitation is thus a major factor in driving the reaction to completion, *i.e.*, in producing high yields (this was confirmed in the experiments with aromatic nitriles). It would also serve to remove the aldimine salt from the reaction zone, thus hindering the formation of the by-product isolated by Knight and Zook [7] in work with lauronitrile, *viz.*, the *NN'*-alkylidenebisacylamide $CHR(NH{\cdot}COR)_2$.

TABLE 4. *Variation of rate with structure: aliphatic nitriles.*

Temp. and solvent as Table 1. [R·CN] = 0·540M. [$SnCl_2$] = 0·372M. [HCl] = 1·49M.

	Time (hr.):	2	5	10	25	50
$SnCl_2$ (10^{-3} mole) consumed	MeCN	0·65	0·97	1·32	2·00 *	4·26
	EtCN	0·36	0·84	1·28	1·78	2·25
	Pr^{n}CN	0·48	0·90	1·18	1·49	1·74
	Pr^{i}CN	0·32	0·65	1·07	1·56	1·84
	Bu^{t}CN	0·69	1·45	2·18	2·74	2·90

* Precipitation of the aldimine stannichloride set in after about 25 hr.

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[6] Meerwein, personal communication to Bayer in ref. 5.

[7] Knight and Zook, *J. Amer. Chem. Soc.*, 1952, **74**, 4561.

The rates of reduction of benzonitrile, *o*- and *p*-tolunitrile, *o*- and *p*-chlorobenzonitrile, and α-naphthonitrile were next compared, reagent containing only two mols. of hydrogen chloride per mol. of stannous chloride being used since at higher concentrations early precipitation of the aldimine salt occurred, restricting the measurements to only a small proportion of the total reaction. The results are shown in Table 5. *o*- or *p*-Methyl or -chloro-groups in benzonitrile markedly increase the reaction rate. The acceleration caused by the precipitation of the aldimine salt was again pronounced in the experiment with *p*-chlorobenzonitrile (with benzonitrile, *p*-tolunitrile, and *o*-chlorobenzonitrile, precipitation accompanied by acceleration occurred at a later stage, not shown in the Table).

TABLE 5. *Variation of rate with structure : aromatic nitriles.*

Temp. : 23·6° ± 0·1°. Solvent : 41% (v/v) acetic acid in ether.

[R·CN] = 0·540M. [SnCl$_2$] = 0·300M. [HCl] = 0·600M.

	Time (hr.) :	1	2	5	10	25
SnCl$_2$ (10^{-3} mole) consumed	Ph·CN	0·29	0·36	0·60	0·87	1·66
	o-Cl·C$_6$H$_4$·CN	0·55	0·87	1·30	1·74	2·45
	p-Cl·C$_6$H$_4$·CN	1·13	1·74	2·26	2·44 *	4·66
	o-Me·C$_6$H$_4$·CN	1·20	1·48	1·71	1·81	2·10
	p-Me·C$_6$H$_4$·CN	0·62	0·88	1·26	1·52	1·77
	α-C$_{10}$H$_7$·CN	0	0	0	0	0·57

* Precipitation of the aldimine stannichloride set in after about 12 hr.

o-Tolunitrile and α-naphthonitrile both give low yields of aldehyde in the Stephen reaction,[4] although some reduction to the aldimine occurs, as shown by the above results. Rather surprisingly, *o*-tolunitrile was found to be reduced faster than was benzonitrile, in the early stages, after which period the reaction virtually stopped, probably because of the failure of the *o*-tolualdiminium stannichloride to be precipitated and so drive the reaction forward. During the earlier work, it had been noticed that the precipitation of the aldimine salt was favoured by low stannous chloride and high hydrogen chloride concentration, but under these conditions neither nitrile gave the desired precipitate, even after some weeks.

The scope of the reaction in the aliphatic series has been clarified by determining the yields of aldehyde from aceto-, propio-, *n*-butyro-, *n*-valero-, *iso*butyro-, and pivalo-nitrile. The modified reagent, as initially prepared, contained two mols. of hydrogen chloride per mol. of stannous chloride, and was saturated with hydrogen chloride before use. The exact concentration of hydrogen chloride was not determined.

Lieber [8] has claimed that, under certain conditions, the aldimine from lauronitrile was not precipitated as its stannichloride but remained in solution. In these experiments, therefore, both the precipitated salt and the mother-liquor were worked up for aldehyde, which was indeed produced from both sources on hydrolysis. The yield of aldehyde was determined quantitatively by the bisulphite method of Bell and Brown.[9] Control analyses of samples of the pure aldehydes enabled corrections to be made for losses during hydrolysis. The results are summarised in Table 6. The figures quoted in footnote (*b*) show that the modified reagent gives yields of aldehyde comparable with those obtained by the normal procedure. The reaction was much slower in the former case, and the modified reagent has little to recommend it in preparative work.

The lower aliphatic nitriles give only poor to moderate yields in the Stephen reaction, the yield from normal nitriles increasing with chain length. Chain-branching in the α-position lowers the yield (this may be confirmed from Table 6 in Mosettig's review [4]).

Knight and Zook [7] have cast some doubt on the constitution of the precipitate obtained by Lieber [8] from lauronitrile, implying that it might not have been the aldiminium stannichloride. Analyses of the precipitates isolated during this work showed that they were probably somewhat impure samples of the expected aldimine salt. They yielded about 90% of the theoretical amount of aldehyde on hydrolysis, and contained about 90% of the theoretical content of tin.

[8] Lieber, *ibid.*, 1949, **71**, 2862.

[9] Bell and Brown, *J.*, 1954, 774.

Attention is drawn here to the extremely useful " nitrile-exchange " reaction,[1] details of which have recently been published as a Patent. When a carboxylic acid is boiled with phenylacetonitrile, in the presence of a strong acid catalyst, *e.g.*, sulphuric acid or a sulphonic acid, an exchange occurs, and the nitrile corresponding to the acid may be removed by fractional distillation, provided that its boiling point is lower than that of any other component. The direct preparation of *iso*butyro- and pivalo-nitrile from the corresponding acids is now reported, the yields being 49 and 56% respectively.

TABLE 6. *Yields (%) of aldehydes from the lower aliphatic nitriles.*

	Yield of aldehyde from		Aldehyde semicarbazone[a]			Yield of aldehyde from		Aldehyde semicarbazone[a]	
Nitrile	pre-cipitate	mother-liquor	m. p.	lit.	Nitrile	pre-cipitate	mother-liquor	m. p.	lit.
MeCN ...	25[b]	5	—	—	Bu^nCN...	44[b]	17	103—104°	[c]
EtCN ...	15	8	88°	89°	Pr^iCN ...	13	12	125	126°
Pr^nCN ...	40	13	104	106	Bu^tCN...	10	12	189	190

[a] Semicarbazones were recrystallised from ethanol–water. [b] When Stephen's original procedure [2] was followed, aceto- and *n*-valero-nitrile gave, respectively, 32% and 42% yields of aldehyde from the aldiminium stannichloride only. [c] New compound. An authentic specimen of *n*-valeraldehyde semicarbazone had m. p. 104° (Found: N, 29·1. $C_6H_{13}ON_3$ requires N, 29·4%).

EXPERIMENTAL

Sodium-dried ether, freshly-distilled acetyl chloride, and commercial stannous chloride dihydrate were used to prepare the reagent. Anhydrous stannous chloride was made by the method recommended by Stephen.[10]

Commercial samples of normal aliphatic nitriles and liquid aromatic nitriles were treated with concentrated hydrochloric acid until the smell of *iso*nitrile had gone, dried (K_2CO_3) and fractionated through a 6" Vigreux column. *iso*Butyro- and pivalo-nitrile were made by nitrile exchange between the corresponding acids and phenylacetonitrile. Solid aromatic nitriles were recrystallised from benzene–light petroleum (b. p. 40—60°), until of constant m. p. *o*-Chlorobenzonitrile had m. p. 45—46° (lit., 42°).

Preparation of the Modified Reagent.—A typical mixture was made as follows. Stannous chloride dihydrate (112·8 g., 0·5 mole) was suspended in ether (133 ml.), in a flask sealed by a U-tube containing a little mercury. Acetyl chloride (71 ml., 1·0 mole) was added at a such rate that no hydrogen chloride escaped past the mercury seal (slight cooling was necessary). The homogeneous liquid so produced contained 30% and 70% respectively of acetic acid and ether, by volume. It was diluted to 500 ml. by the addition of a mixture of acetic acid and ether in the same proportions (called below " mixed solvent ").

Effect of Nitrile Concentration on Rate.—Into each of three stoppered flasks containing the reagent (25 ml.) diluted with mixed solvent (to 50 ml.) were pipetted, respectively, 3 ml. (0·0292 mole), 1 ml. (0·00973 mole), and 0·3 ml.(0·00292 mole) of benzonitrile. The volume of each solution was raised to 53 ml. by the addition of mixed solvent. All solutions were brought to the thermostat temperature (23·6° ± 0·1° throughout all kinetic measurements) before mixing. Aliquot parts (1·00 ml.) were withdrawn at approximately zero, 1, 3, 8, 24, and 50 hr., and were run into N-hydrochloric acid (10 ml.). Stannous ion was then determined by titration (starch) against aqueous iodine (0·05M). The fall in stannous chloride concentration was calculated from the titration differences.

Effect of Stannous Chloride Concentration on Rate.—(*a*) Reagent solution containing 0·384 mole/l. of stannous chloride was made by diluting 25 ml. of a stock solution to 50 ml., with mixed solvent. Benzonitrile (3 ml., 0·0292 mole) was added. The hydrogen chloride concentration was 0·767 mol./l.

(*b*) Reagent solution containing 0·145 mole/l. of stannous chloride was made as follows. To the stock solution (10 ml.) were added acetyl chloride (2·13 ml., 0·03 mole) and water (0·54 ml., 0·03 mol.), which generated the hydrogen chloride sufficient to maintain the final concentration at 0·767 mole/l. Ether (4·0 ml.) was added to compensate for the acetic acid produced by the previous operation, and the whole was made up to 50 ml. with mixed solvent. Benzonitrile was added as before.

[10] Stephen, *J.*, 1930, 2786.

(*c*) Reagent containing 0·0554 mole/l. of stannous chloride was made as in the previous paragraph, from stock solution (5 ml.), acetyl chloride (2·84 ml., 0·04 mole), water (0·72 ml., 0·04 mole), ether (5·33 ml.), and mixed solvent up to 50 ml. Benzonitrile was added as before.

The concentration–time curve was constructed from measurements taken as in the preceding section.

Effect of Hydrogen Chloride Concentration on the Rate of Reaction.—To a known volume of the stock reagent, extra hydrogen chloride was added by running in equimolar amounts of acetyl chloride and water. The calculated amount of ether was added to restore the composition of the solvent to its standard value, and the mixture was diluted by mixed solvent to a fixed volume. The stock solution used contained 0·69 mole/l. of stannous chloride and 2·07 mole/l. of hydrogen chloride. Three experiments were carried out with the following quantities respectively: (*a*) Stock solution (25 ml.); mixed solvent up to 50 ml.; benzonitrile (3 ml.). (*b*) Stock solution (25 ml.), acetyl chloride (4·66 ml., 0·061 mole), water (1·19 ml., 0·061 mole), ether (8·8 ml.), and mixed solvent up to 50 ml. (*c*) Stock solution (25 ml.), acetyl chloride (9·32 ml., 0·132 mole), water (2·37 ml., 0·132 mole), ether (17·6 ml.), and mixed solvent up to 50 ml.

Effect of Nitrile Structure on the Rate of Reaction.—(*a*) *Aliphatic nitriles.* To a stock solution of reagent (25 ml., containing 0·788 mole/l. of stannous chloride and 3·152 mole/l. of hydrogen chloride) were added the nitrile (0·0286 mole) and mixed solvent (up to 53 ml.). The measurements of rate were made as before.

(*b*) *Aromatic nitriles.* Measurements were made as for the aliphatic nitriles, a stock reagent solution containing stannous chloride (0·752 mole/l.) and hydrogen chloride (1·504 mole/l.) being used. At this lower hydrogen chloride concentration slight precipitation of white crystals occurred when the stock solution was diluted with the mixed solvent, and the final mixture was diluted to 63 ml. by the addition of acetic acid, which caused the crystals to redissolve.

Attempted Reaction of o-*Tolunitrile and α-Naphthonitrile under Forcing Conditions.*—To the stock reagent solution (5 ml., as used for aromatic nitriles, see previous paragraph) were added acetyl chloride (6·4 ml.), water (1·62 ml.), ether (15·9 ml.), and mixed solvent (up to 50 ml.). The nitrile (0·02 mole) was added, and the volume made up to 53 ml. with mixed solvent. The product contained 0·072, 1·834, and 0·377 mole/l. respectively of stannous chloride, hydrogen chloride, and nitrile. No precipitate was formed after two weeks at 20° and a further week at 0°.

Determination of the Yields of Aldehyde from Aliphatic Nitriles.—To a stirred suspension of stannous chloride dihydrate (16·8 g., 0·075 mole) in ether (50 ml.) was added an excess of acetyl chloride (13·0 ml., 0·195 mole). The mixture was saturated with dry hydrogen chloride, and to the homogeneous product the nitrile (0·05 mole) was added. After 7 days the precipitated aldiminium stannichloride was filtered off, washed with ether, and dried at 50°/20 mm. The combined filtrate and washings were retained for analysis.

The amount of aldehyde obtainable by hydrolysis of the precipitate was determined as follows. A weighed amount (*ca.* 0·7 g.) of the salt was boiled with N-hydrochloric acid (55 ml.), and about 20 ml. of the distillate were collected in an excess of aqueous sodium hydrogen sulphite (50 ml.; 0·5M), contained in three wash-bottles in series. The sulphite solution was made up to 100 ml. with water, and the excess sulphite in a 5 ml. sample destroyed by titration with 0·5M- and finally 0·03M-iodine. An excess of solid sodium hydrogen carbonate was added, and the liberated sulphite titrated against 0·03M-iodine. The percentage of aldehyde obtained from the salt was then calculated, and the value multiplied by the " recovery factor " of the aldehyde (see next paragraph).

The amount of aldehyde obtainable from the mother-liquor was determined by distilling off the solvent, drying the residue at 70°/20 mm., hydrolysing the product with N-hydrochloric acid (50 ml.), and determining the aldehyde produced as before.

Determination of Aldehyde " Recovery Factors."—A weighed quantity (*ca.* 0·005 mole) of freshly distilled aldehyde was added to a solution of stannic chloride (1 ml.) in N-hydrochloric acid (50 ml.). The mixture was distilled, and the aldehyde in the distillate estimated as above. The " recovery factor " was expressed as (wt. of aldehyde taken)/(wt. recovered). The factors were all about 1·1, except that of pivalaldehyde, which was 1·72.

Determination of the Tin Content of Aldiminium Stannichlorides.—The liquid remaining in the flask after hydrolysis of the salt and removal of aldehyde (see above) contained all the tin, as chloride. Water (to 100 ml.), and then concentrated hydrochloric acid (40 ml.) were added, and the liquid was boiled with a spiral of nickel foil for 1 hr., in a flask sealed by an outlet tube dipping into aqueous sodium hydrogen carbonate. A few marble chips were then added, to give an inert atmosphere of carbon dioxide, the nickel was removed and washed, and the stannous tin in the cooled solution titrated against aqueous iodine (0·03M) (starch). The tin content was in all cases about 90% of that calculated for $[R\cdot CH{:}NH_2^+]_2SnCl_6^{2-}$, except when R was Me, in which case values were consistently high.

Preparation of iso*Butyro- and Pivalo-nitrile.*—The appropriate carboxylic acid (1 mol.), phenylacetonitrile (3 mols.), and concentrated sulphuric acid (0·01 mol.) were boiled under reflux for 30 min. The nitrile was then slowly distilled off, through a 6-inch Vigreux column, and freed from traces of acid by a further fractional distillation from about one-tenth of its volume of *o*-toluidine. *iso*Butyronitrile (b. p. 103—104°) was obtained in 40% yield, and pivalonitrile (b. p. 104—105°) in 56% yield.

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