

## Solvent Properties of Dichloromethane. II. The Reactivity of Dichloromethane Toward Amines

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The reactions of dichloromethane with various amines have been studied under homogeneous conditions in dichloromethane as solvent at 25.0 °C. With initial concentrations of the amines in the 0.15–0.3 M range the tertiary amines yield 1 mol of ionic chloride per mol amine consumed while secondary and primary amines yield 1 mol of ionic chloride *per* 2 mol of amine. The mechanism of the reactions is discussed and it is concluded that the reactions exhibit the normal characteristics for  $S_N2$  reactions toward aliphatic carbon and thus resemble the usual Menschutkin reactions between amines and alkyl halides. The reactions with secondary amines proceed more rapidly than the reactions with tertiary amines but no evidence for any inter- or intramolecular N–H---Cl assistance could be observed.

The rates of the various reactions do not conform with the nucleophilicities of the amines as derived from rate studies of reactions between amines and the usual alkyl halides but seem to depend upon the steric requirements and particularly the basicities of the amines in a way which appears to be unique for dichloromethane. *N*-Methyl-substituted amines are far more reactive toward dichloromethane than the corresponding *N*-ethyl-substituted amines; the half-lives of the  $CH_2Cl_2$ -*N*-methylpiperidine and the  $CH_2Cl_2$ -*N*-ethylpiperidine reactions are ~160 and ~1070 h, respectively. The  $CH_2Cl_2$ - $NMe_3$  and the  $CH_2Cl_2$ - $NEt_3$  reactions proceed with greatly different rates; half-lives of ~18 and ~580 h. The  $CH_2Cl_2$ -quinuclidine reaction is particularly rapid with a half-life of less than 2 h. The rate constants of the  $CH_2Cl_2$ -piperidine and the  $CH_2Cl_2$ -morpholine reactions, half-lives of 15 and ~330 h, and the  $CH_2Cl_2$ -*N*-methylpiperidine and the  $CH_2Cl_2$ -*N*-methylmorpholine reactions, half-lives of ~160 and ~3000 h, suggest the Brønsted slope for  $CH_2Cl_2$ -amine reactions to be at least 0.55.

The exceptionally large Brønsted slope for reactions between dichloromethane and nucleophiles is suggested to be the principal cause for the very low reactivity of aromatic amines and the exceedingly low carbophilicity of trialkylphosphines,  $R_3P$ , toward dichloromethane. The  $CH_2Cl_2$ - $Bu_3P$  reaction, half-life of ~160 h, seems to proceed exclusively through nucleophilic attack at the chlorine atoms.

More than 40 years ago it was shown that trimethylamine,  $Me_3N$ , and dichloromethane in acetone at 55 °C react in a second order reaction forming the *N*-chloromethylammonium salt as depicted by eqn. (1).



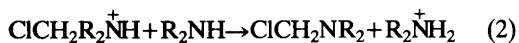
The reaction was found to proceed with a rate constant approximately 1/5 of that of the reaction between  $Me_3N$  and ethyl chloride under the same experimental conditions.<sup>1</sup>

Since then numerous reports have appeared in the literature confirming that some amines do indeed react with dichloromethane,<sup>2-3</sup> but no further kinetic studies have been performed. Although several authors have pointed out that particular care has to be exercised when dichloromethane is to be used as an extraction agent when compounds with amine functions are present,<sup>6-11</sup> this solvent is widely used without the necessary precautions. Presumably, the observation by Beard and Plesch<sup>12</sup> that no ions could be detected conductometrically in a solution of triethylamine in dichloromethane after several hours, have led to the belief that reactions between amines and dichloromethane proceed

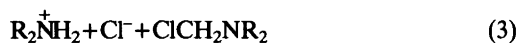
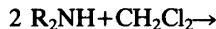
slowly at room temperature and can in most cases be neglected. Furthermore, tertiary amines are known to make fairly stable adducts with dichloromethane,<sup>13-14</sup> and the generally very nucleophilic trialkylphosphines, R<sub>3</sub>P,<sup>15</sup> exhibit only a very low reactivity.<sup>16</sup>

However, mixtures of dichloromethane and certain amines, particularly secondary aliphatic amines, become visibly heterogeneous already after a day or two and leave no doubt that some of these reactions proceed fairly rapidly at room temperature. In contrast, solutions of other amines in dichloromethane, and even generally quite nucleophilic ones<sup>12,17,18</sup> remain stable for long periods. To obtain some information about the reactivity of amines toward dichloromethane we have performed a kinetic study of some of these reactions in dichloromethane as solvent at 25.0 °C. As reagents were chosen some of the most frequently used acyclic and cyclic amines. With rate data for some representative amines available one may in principle predict with some confidence when, or alternatively, in which way, dichloromethane can be used as a solvent when amines are present in a reaction mixture.

Since dichloromethane in this study was both one of the reactants as well as the solvent and the initial concentration of the amines was in the 0.15–0.3 M range, *i.e.* maximally 2 % of that of dichloromethane, pseudo-first order conditions were maintained in all kinetic runs. With initial concentrations of the amines in this range the majority of the reactions were found to remain homogeneous for several half-lives. In the case of the tertiary amines, R<sub>3</sub>N, the reactions proceed as shown in eqn. (1), and secondary reactions leading to methylenediammonium cations, R<sub>3</sub>NCH<sub>2</sub><sup>+</sup>NR<sub>3</sub>, or other species seem to be of no kinetic importance. With secondary and primary amines, however, the first formed *N*-chloromethyl-dialkylammonium and *N*-chloromethyl-alkylammonium cations, are rapidly deprotonated by the unreacted amines owing to the low hydrogen basicity of the *N*-chloromethylamines,<sup>19</sup> eqn. (2).



The net reaction in the case of these amines will therefore be as depicted by eqn. (3).



2 mol of amines will thus liberate only 1 mol of Cl<sup>-</sup> which indeed was verified experimentally. Further reactions leading to bis(dialkyl-amino)methanes,<sup>5</sup> (R<sub>2</sub>N)<sub>2</sub>CH<sub>2</sub>, and products from ClCH<sub>2</sub>NR<sub>2</sub> can apparently be neglected. The maximum concentration of ClCH<sub>2</sub>NR<sub>2</sub> will necessarily be only half of that of the initial concentration of the amines and thus less than 1 % of that of dichloromethane.

For comparison, the reaction between dichloromethane and Bu<sub>3</sub>P in dichloromethane as solvent was studied kinetically.

## EXPERIMENTAL

**Materials.** Dichloromethane was purified and stored as previously described.<sup>20</sup> The amines were of highest purity available, mostly Fluka *puriss p.a.*, or were synthesized according to standard procedures. The tertiary amines were treated with 4-methylbenzoyl chloride and were fractionated from potassium hydroxide and finally from calcium hydride in an argon atmosphere prior to use. Trimethylamine and dimethylamine, both Fluka *purum*, were used without further purification. Quinuclidine was made from the corresponding hydrochloride,<sup>21</sup> Fluka *purum*, and was twice sublimed. All manipulations with this compound were performed in an argon-filled dry box.

Piperidine-*d*<sub>1</sub> and pyrrolidine-*d*<sub>1</sub> were prepared from carefully purified samples of the corresponding tris(dialkylamino)-phosphines, Pip<sub>3</sub>P and Pyrr<sub>3</sub>P, respectively, and deuterium oxide, D<sub>2</sub>O, in the ratio 1:2.3.<sup>22</sup> The deuterated amines were finally fractionated from freshly ignited calcium oxide in an argon atmosphere. Tributylphosphine, Bu<sub>3</sub>P, was twice distilled in vacuum with an argon leak.

**Rate studies.** The initial concentration of the amines was in the 0.15–0.3 M range and the solutions were kept in a thermostat at 25.0 °C and carefully shielded from direct sunlight to avoid light-induced reactions.<sup>23</sup> Samples were withdrawn periodically and added to some water and pentane in a separatory funnel. The aqueous phase was washed once with pentane, its pH adjusted to 5.5 with dilute nitric acid and the concentration of chloride ions determined by the usual AgNO<sub>3</sub>-titration. Up to 10 aliquots were

withdrawn for each kinetic run. The reactions were usually followed for approximately two half-lives, some of the more rapid ones for up to four half-lives. Additionally, the reaction between piperidine and dichloromethane was followed for 10–15 half-lives to confirm the basic assumption of 1 mol Cl<sup>-</sup> being liberated *per* 2 mol of piperidine according to eqn. (3). The very slow reactions with half-lives of several months were only followed to an extent of ~25 %.

In the case of Me<sub>3</sub>N and *N*-methylmorpholine the solutions became heterogeneous after the reactions had proceeded only some 5 to 7 %. The rate constants for these reactions could thus be determined only with highly limited accuracy from each kinetic run. The CH<sub>2</sub>Cl<sub>2</sub>-Me<sub>3</sub>N reaction was therefore studied repeatedly with various initial concentrations of the amine allowing the rate constant for this reaction to be finally determined with a probable accuracy of 10 %. The CH<sub>2</sub>Cl<sub>2</sub>-morpholine reaction mixture also became heterogeneous but only after the reaction had proceeded some 60–70 % which did not seriously affect the accuracy by which the rate constant for this reaction was determined. Generally the rate constants for the more rapid reactions were determined with an accuracy well within 10 %. The rate constants for the reactions with half-lives of several months were only roughly determined.

The aqueous extracts from the CH<sub>2</sub>Cl<sub>2</sub>-Bu<sub>3</sub>P reaction mixture were distinctly acidic. This reaction could therefore be followed both by the liberated chloride ion as in the case of the amines and by the amount of hydrochloric acid by standard NaOH-titration. The amount of Cl<sup>-</sup> and HCl formed with time was found to be equal within experimental error.

**Calculations.** For the reactions of the tertiary amines and of Bu<sub>3</sub>P the usual pseudo-first order rate equation applies, eqn. (4).

$$\ln[a/(a-x)] = k_1 t \quad (4)$$

*a* is the initial concentration of the amine or the phosphine and *x* is the concentration of Cl<sup>-</sup> (and of HCl in the case of the CH<sub>2</sub>Cl<sub>2</sub>-Bu<sub>3</sub>P reaction) at time *t*. The second order rate constant, *k*<sub>2</sub>, is thus *k*<sub>1</sub> divided by 31.0, two times the concentration of CH<sub>2</sub>Cl<sub>2</sub>, 15.50 M at 25.0 °C, due to the statistical factor. The half-life, *τ*, of the reaction is given by *k*<sub>1</sub><sup>-1</sup> ln 2. For the reactions of the secondary amines and the one primary amine, BuNH<sub>2</sub>, the following rate equation is valid, eqn. (5).

$$\ln[a/(a-2x)] = 2k_1 t \quad (5)$$

The half-life of these reactions with respect to the concentration of the amines is given by  $(2k_1)^{-1} \times \ln 2$ .

## RESULTS

Table 1 summarizes the results from the present study. The estimated uncertainties in the rate constants are given in the first column. The half-lives of the reactions, the last column in Table 1, demonstrate clearly that the reactions between dichloromethane and some of the amines proceed quite rapidly at room temperature. The results confirm that the rate of the CH<sub>2</sub>Cl<sub>2</sub>-Me<sub>3</sub>N reaction is considerable;<sup>1</sup> within approximately 18 h is the concentration of the amine reduced to 50 %. The half-life of the CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>N reaction, however, is close to a month and explains why no ions could be detected in a solution of triethylamine in dichloromethane after only some hours.<sup>12</sup> *N*-Ethyl-substituted amines are generally significantly less reactive than the corresponding *N*-methyl-substituted ones, *cf.* half lives for *N*-ethylpiperidine and *N*-methylpiperidine being ~1070 and ~160 h, respectively. *N*-Ethylmorpholine is likewise significantly less reactive than *N*-methylmorpholine. Secondary amines appear to be far more reactive than tertiary ones, *cf.* piperidine and *N*-methylpiperidine. Trimethylamine, however, is approximately as reactive toward dichloromethane as is dimethylamine. The quinuclidine-CH<sub>2</sub>Cl<sub>2</sub> reaction proceeds particularly rapidly and the half-life of this reaction is less than two hours at room temperature.

Two aromatic amines, pyridine and *N,N*-dimethylaniline, were included in the present study. These two compounds were found to react exceedingly slowly with dichloromethane. As the half-lives of these reactions were several months at room temperature the rate constants were not accurately determined but only estimated. The one primary amine studied, BuNH<sub>2</sub>, was also found to exhibit only a highly limited reactivity toward dichloromethane. It is notable that the morpholines are all significantly less reactive than the corresponding piperidines.

A few reactions were also studied in water-saturated dichloromethane, *cf.* entries 9, 14 and 23. Water-saturated dichloromethane at 25.0 °C is approximately 0.13 M in water<sup>24</sup> and the concentration of water was thus comparable with

Table 1. Pseudo first order rate constants,  $k_1$ , second order rate constants,  $k_2$ , and half-lives,  $\tau$ , for the reactions between some amines and tributylphosphine and dichloromethane in dichloromethane at 25.0 °C.

Entry No.	$k_1 \times 10^7$ s <sup>-1</sup>	$k_2 \times 10^{8a}$ M <sup>-1</sup> s <sup>-1</sup>	$\tau$ h
1. Quinuclidine	1070(50)	350	1.8
2. Trimethylamine	110	~35	~18
3. Pyrrolidine	102(4)	33	10
4. Pyrrolidine- <i>d</i> <sub>1</sub>	97(5)	32	10
5. Dimethylamine	66(3)	21	14.5
6. Piperidine <sup>b</sup>	64(2)	20	15
7. Piperidine (18.0 °C) <sup>b</sup>	34(1)	11	28
8. Piperidine (10.0 °C) <sup>b</sup>	16.5(5)	5.3	58
9. Piperidine (Sat. H <sub>2</sub> O)	54(4)	18	18
10. Piperidine- <i>d</i> <sub>1</sub>	64(4)	20	15
11. Piperidine-Et <sub>3</sub> N(1:1)	64(5)	20	15
12. Tributylphosphine	12.0(5)	3.8	160
13. <i>N</i> -Methylpiperidine	12.0(5)	3.8	160
14. <i>N</i> -Methylpiperidine (Sat. H <sub>2</sub> O)	7.2(3)	2.4	270
15. Diethylamine	8.6(4)	2.8	110
16. Triethylamine	3.3(5)	1.1	580
17. Morpholine	2.9(5)	0.9	330
18. <i>N</i> -Ethylpiperidine	1.8(3)	0.6	1070
19. Butylamine	1.1(6)	0.4	870
20. <i>N</i> -Methylmorpholine	~0.65	~0.2	~3000
21. Pyridine	~0.2	~0.05	~9600
22. <i>N</i> -Ethylmorpholine	<0.3	<0.1	>6400
23. <i>N</i> -Methylmorpholine (Sat. H <sub>2</sub> O)	<0.2	<0.05	>9600
24. <i>N,N</i> -Dimethylaniline	<0.4	<0.1	>4800

<sup>a</sup> Corrected for the statistical factor. <sup>b</sup>  $\Delta H^\ddagger = 62.7$  kJ mol<sup>-1</sup>,  $\Delta S^\ddagger = -130$  J mol<sup>-1</sup> (25.0 °C).

the initial concentration of the amines in the kinetic runs. The rate constants in water-saturated dichloromethane were found to be slightly but significantly lower than in the pure solvent. This observation is as anticipated in view of the facile solvation of amines in water and in other hydroxylic solvents.<sup>25,26</sup> Alkylation reactions of amines are well known to proceed considerably slower in protic solvents than in aprotic ones.<sup>26,27</sup> The data in Table 1 may suggest that the rates of tertiary amines are more affected by the presence of water than are secondary ones, but too few amines were studied to allow a general conclusion to be made. Presently the rate constants in pure dichloromethane as listed in Table 1 may serve as a measure for the rate constants in the moist solvent. These rate constants may prove to

be of considerable importance when extraction procedures are to be designed.

## DISCUSSION

*Mechanistic considerations.* The observed reactivities of the various amines toward dichloromethane seem to be highly unusual and do not conform with the nucleophilicities of amines toward other organic substrates.<sup>17,18</sup> Still, the reactions appear to exhibit the normal characteristics for S<sub>N</sub>2 reactions toward aliphatic carbon as for other Menschutkin reactions between amines and alkyl halides. The conclusion is based upon the following observations:

1. Several of the more rapid reactions were carefully examined for up to 4 half-lives and with

different initial concentrations of the amines in the 0.15–0.3 M range. The quality of the rate plots and the calculated rate constants were in no case found to be dependent upon the initial concentration of the amines. The usual rate equations, eqns. (4) and (5), were always found to be obeyed and no evidence for any higher-order terms in the amine concentrations could be detected. The high rates of the secondary amines as compared with the tertiary ones, *cf.* Table 1, can thus not be due to an intermolecular pull-mechanism of the type observed in numerous S<sub>N</sub>Ar reactions<sup>28</sup> by which the leaving group ability of the displaced chloride ion is enhanced through N–H···Cl<sup>–</sup> interaction.

2. The deuterated secondary amines react within experimental error with the same rates as do the non-deuterated ones, *cf.* entries 3 and 4 for pyrrolidine and entries 6 and 10 for piperidine. Apparently, an intramolecular leaving-group assistance through a four-center transition state can also be ruled out. The calculated activation parameters for the CH<sub>2</sub>Cl<sub>2</sub>–piperidine reaction, *cf.* footnote *b* in Table 1, are actually quite typical for simple substitution reactions toward aliphatic carbon compounds and do not indicate a particular structure of the transition state.

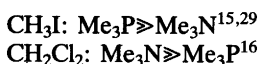
3. Triethylamine, known to make a fairly stable addition compound with dichloromethane,<sup>14</sup> does not seem to catalyze the reaction between piperidine and dichloromethane, *cf.* entries 6 and 11. This may suggest that dichloromethane itself, uncomplexed by the amines present, is the probable electrophilic agent in the reactions. The absence of any second-order terms in the concentration of the amines in the applied rate equations, eqns. (4) and (5), conforms with this conclusion.

While the CH<sub>2</sub>Cl<sub>2</sub>–amine reactions seem to proceed through nucleophilic attack at the methylene carbon atom, the reaction between dichloromethane and Bu<sub>3</sub>P is not a typical alkylation reaction. The first step of this reaction seems to be a nucleophilic attack at the chlorine atoms forming at first the *P*-chloro-phosphonium cation as depicted by eqn. (6).



When the reaction mixture from this reaction is treated with water, the *P*-chloro-phosphonium

cation is rapidly hydrolyzed in the usual way forming hydrochloric acid and the corresponding phosphine oxide. Since the concentration of Cl<sup>–</sup> in the aqueous phase was not at any time observed to exceed that of the concentration of HCl the reaction through nucleophilic attack at the methylene carbon atom forming the *P*-chloromethylphosphonium cation, ClCH<sub>2</sub>P<sup>+</sup>Bu<sub>3</sub>, must necessarily be exceedingly slow. The low carbophilicity of Bu<sub>3</sub>P toward dichloromethane may partly be due to steric effects but trimethylphosphine, Me<sub>3</sub>P, is also known to react very slowly with dichloromethane.<sup>16</sup> It is notable that the C-bonded phosphonium cation from these two reagents, ClCH<sub>2</sub>P<sup>+</sup>Me<sub>3</sub>, is only formed in aprotic solvents; in protic solvents hydrochloric acid and the phosphine oxide are the only products. Presumably, the first step in the reaction between Me<sub>3</sub>P and CH<sub>2</sub>Cl<sub>2</sub> is also the formation of the Cl-bonded phosphonium cation which in aprotic solvents is converted into the C-bonded cation, a reaction which cannot take place in protic solvents. Thus, with regard to the reactivity toward aliphatic carbon when methyl iodide and dichloromethane are the substrates we have two distinctly different reactivity orders:



*The steric effect upon rates of CH<sub>2</sub>Cl<sub>2</sub>-amine reactions.* The steric effect upon rates of substitution reactions toward dichloromethane has its origin in the one non-reacting chlorine atom which will prevent the ideal linear transition state to be attained.<sup>30,31</sup> The high rate of the CH<sub>2</sub>Cl<sub>2</sub>–quinuclidine reaction, the reactivity of secondary amines as compared with tertiary ones and finally the reactivity of *N*-methyl-substituted amines as compared with *N*-ethyl-substituted ones suggest that steric effects are of considerable importance upon rates of reactions between dichloromethane and amines.

In an attempt to obtain a measure for this effect we have made a comparison between the reactivity of some amines of greatly different steric requirements, quinuclidine, triethylamine and *N*-methylpiperidine, toward methyl iodide and dichloromethane, Table 2. The last column in Table 2, the column for the ratios between the rate constants, shows that this ratio for the very reactive quinuclidine is only 6 times that of the bulky triethylamine, Et<sub>3</sub>N; the ratio for *N*-

Table 2. A comparison between rate constants for reactions of some amines with methyl iodide in acetonitrile and with dichloromethane in dichloromethane at 25.0 °C.

	$k_2(\text{CH}_3\text{I}/\text{CH}_3\text{CN})$ $\text{M}^{-1}\text{s}^{-1}$	$k_2(\text{CH}_2\text{Cl}_2/\text{CH}_2\text{Cl}_2)^a$ $\text{M}^{-1}\text{s}^{-1}$	$k_2(\text{CH}_2\text{Cl}_2)/k_2(\text{CH}_3\text{I})$
Quinuclidine	1.79 <sup>b</sup>	$3.5 \times 10^{-6}$	$1.96 \times 10^{-6}$
Et <sub>3</sub> N	$3.35 \times 10^{-2}$ <sup>c</sup>	$1.1 \times 10^{-8}$	$0.33 \times 10^{-6}$
<i>N</i> -Methylpiperidine	$6.27 \times 10^{-2}$ <sup>b</sup>	$3.8 \times 10^{-8}$	$0.60 \times 10^{-6}$

<sup>a</sup> This study. <sup>b</sup> From Ref. 27. <sup>c</sup> From Ref. 26.

methylpiperidine being intermediate as expected from steric considerations. Thus, while the steric interference by the non-reacting chlorine atom upon rates of reactions of dichloromethane with nucleophiles seems to be of some importance, this effect cannot alone be responsible for the order of reactivities as shown in Table 1. The ratio between the rate constants of the reactions of quinuclidine and triethylamine with methyl iodide and dichloromethane are 54 and 310, respectively. These ratios may be compared with the ratios of the rate constants of the same two amines reacting with methyl iodide, ethyl iodide and 2-propyl iodide in nitrobenzene at 25.0 °C, 57, 254 and 705, respectively.<sup>21</sup> From only a steric point of view one may thus conclude that an  $\alpha$ -chlorine atom affects reactivities of alkyl halides slightly more than does an  $\alpha$ -methyl group.

The electronic effect upon rates of  $\text{CH}_2\text{Cl}_2$ -amine reactions. Some of the rate differences as shown in Table 1 are apparently caused by electronic effects and by the basicities of the amines in a Brønsted fashion. The higher rate of the  $\text{CH}_2\text{Cl}_2$ -pyrrolidine reaction as compared with the  $\text{CH}_2\text{Cl}_2$ -piperidine reaction conforms with numerous other reactions involving these two amines,<sup>13,32</sup> and reflects not only the lower steric requirements of pyrrolidine but also the higher mesomeric potential and the higher basicity of this amine.<sup>33</sup> Furthermore, the low rate constants of the reactions between dichloromethane and the morpholines and particularly the aromatic amines can readily be rationalized when considering the low  $\text{p}K_a$ -values of these amines.

Unfortunately, no data on hydrogen basicities of amines in dichloromethane or in related solvents are presently available which makes it

difficult to obtain any reliable measure for the dependence of rate constants upon basicities, *i.e.* Brønsted slopes.  $\text{p}K_a$ -values in water may be highly erroneous to apply; as example may be given the difference in the  $\text{p}K_a$ -values of diethylamine and triethylamine; in water 0.33,<sup>34</sup> in ethanol 1.03,<sup>35</sup> in nitromethane  $-0.40$ <sup>36</sup> and in acetonitrile 0.29.<sup>34</sup> Furthermore, when attempting to arrive at a measure for the effect of the basicity upon the reactivity of amines toward dichloromethane one may only compare rate constants of amines with fairly equal steric requirements. The data in Table I only allow the rate constants of piperidine, entry 6, and of morpholine, entry 17, to be compared; the rate ratio being 21. A comparison between *N*-methylpiperidine, entry 13, and of *N*-methylmorpholine, entry 20, is less reliable owing to the limited accuracy by which the latter rate constant was determined. The ratio between the rate constants, however, is  $\sim 20$  which is in satisfactory agreement with the ratio of the rate constants of piperidine and morpholine.

The difference in the  $\text{p}K_a$ -values of piperidine and morpholine in dichloromethane, however, is difficult to assess. In water, ethanol and acetonitrile this difference is 2.51, 1.77 and 2.31, respectively.<sup>34,35</sup> If one applies the larger difference of 2.51 as observed in water (2.70 for the difference in the  $\text{p}K_a$ -values of *N*-methylpiperidine and of *N*-methylmorpholine) one obtains a Brønsted slope of no less than 0.55. A Brønsted slope for alkylation reactions of this magnitude is highly exceptional; slopes of  $\sim 0.2$  are generally observed for substitution reactions toward aliphatic carbon; for surveys of references, *cf.* Refs. 37–39.

A Brønsted slope of 0.5 to 0.6 is close to values found for reactions of carbonyl and phosphoryl

compounds.<sup>40</sup> Presumably, the carbon atom in dichloromethane, owing to the two electronegative chlorine atoms, is to be considered as a hard electrophilic center. It is to be admitted that the Brønsted slope as determined in the present study is quite weakly founded but it does provide a conceivable explanation for the high rate of the  $\text{CH}_2\text{Cl}_2\text{-N}_3^-$  reaction,<sup>20</sup> the exceedingly low reactivity of the weakly basic aromatic amines as pyridine and *N,N*-dimethylaniline and particularly the exceptionally low carbophilicity of trialkylphosphines toward dichloromethane. If this similarity between the carbon atom in dichloromethane and the carbon atom in carbonyl compounds is as distinct as the present data may suggest, amines which belong to the important class of nucleophiles termed  $\alpha$ -nucleophiles<sup>40</sup> may exhibit considerably higher reactivity toward dichloromethane than is to be expected from their basicities. The reactions between dichloromethane and various hydrazines and related compounds will therefore be the subject of a future study.

A particular problem arises with regard to the high reactivity of trimethylamine,  $\text{Me}_3\text{N}$ , as compared with dimethylamine, *cf.* entries 2 and 5 in Table 1. From a steric point of view the latter amine ought to be the more reactive one, particularly since it is also a considerably better base than is  $\text{Me}_3\text{N}$ ; the  $\text{p}K_a$ -values in water are 9.74 and 10.76, respectively. It has been argued, however, that trialkylamines are relatively more basic in solvents of low dielectric constants than are secondary ones.<sup>42</sup> This reasoning has been used to explain the fact that while morpholine is significantly more reactive than is triethylamine toward 4-nitrobenzyl bromide in the usual dipolar aprotic solvents, the two amines exhibit approximately the same reactivity toward this substrate in dichloromethane and in chloroform.<sup>43</sup> Trimethylamine is known to be a better nucleophile toward methyl iodide than is dimethylamine when the reactions are performed in benzene.<sup>44</sup> It is apparent that basicity studies in dichloromethane or in related solvents are highly desirable. Presently it seems that the rates of reactions between dichloromethane and methyl-substituted amines are mainly governed by electronic effects while rates of reactions with ethyl-substituted amines are governed by steric effects. The low rate of the  $\text{CH}_2\text{Cl}_2\text{-BuNH}_2$  reaction, entry 19, is presumably due to the generally low

nucleophilicity of primary amines and accords with the low reactivity of  $\text{BuNH}_2$  toward methyl iodide and ethyl iodide.<sup>44</sup>

## CONCLUSIONS

Some amines, particularly amines of low steric requirements like quinuclidines and some secondary amines, but also tertiary amines containing methyl groups, react fairly rapidly with dichloromethane at room temperature. Tertiary amines with larger alkyl groups and also weakly basic amines, particularly aromatic amines, react only exceedingly slowly with dichloromethane. The carbon atom in dichloromethane in its reactions with nucleophilic species seems to respond to the basicity of the nucleophiles fairly similarly to the carbon atom in carbonyl compounds.

Care should undoubtedly be exercised when dichloromethane is used as an extraction agent when amines are present. If the extraction is not performed sufficiently rapidly, the amines which exhibit some reactivity toward dichloromethane will be partly transformed into substituted ammonium chlorides and eventually into amines of higher molecular weight like  $\text{ClCH}_2\text{NR}_2, \text{R}_2\text{NCH}_2\text{NR}_2$  *etc.* The substituted ammonium chlorides may also be dealkylated by the chloride ions forming new amines and alkyl chlorides, particularly during mass spectral analysis.<sup>8</sup> The unreactive amines will remain unchanged by dichloromethane during the extraction process, but if *N*-chloromethylammonium salts from secondary and primary amines have been formed, the tertiary amines may be transformed into ammonium salts owing to their high proton basicity in this solvent.<sup>42</sup> The formation of artifacts from solutions of mixtures of amines in dichloromethane is thus to be anticipated<sup>9</sup> and the analytical error will obviously increase with storage and increase in temperature. Vinczue and Gefen<sup>11</sup> have particularly stressed the possible fallacies when analyzing amines in solutions of dichloromethane by means of mass spectrometers with heated direct interprobe.

The chemistry of weakly basic and sterically hindered amines may well be examined in dichloromethane as solvent. In the case of aromatic amines, however, care has to be exercised to

avoid direct sunlight.<sup>23</sup> Dichloromethane seems also to be a most useful solvent for the study of reactions of trialkylphosphines; the rate of formation of chloride ions,  $\text{Cl}^-$ , and chloromethyl carbanions,  $\text{ClCH}_2^-$ , appears to be very low for all trialkylphosphines. It should be emphasized, however, that if the solvent is not carefully dried, the rate of formation of hydrochloric acid will equal that of the main substitution reaction.

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