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112. Metal Complexes with Macrocyclic Ligands, IV[1]). Synthesis, Properties and Kinetics of Complexation with Three N-methyl Substituted 1,4,8,11-tetraazacyclotetradecanes

by **Rudolf Buxtorf** and **Thomas A. Kaden**

Institut für Anorganische Chemie, Spitalstrasse 51, CH-4056 Basel

(20. II. 74)

Summary. The synthesis, properties and complexation of 1-methyl-1,4,8,11-tetraazacyclotetradecane (1-MeCyclam-14), 1,5-dimethyl-1,5,8,12-tetraazacyclotetradecane (2-MeCyclam-14) and 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (4-MeCyclam-14) are described.

While the Ni^{2+} and Cu^{2+} complexes of 1-MeCyclam-14 and 2-MeCyclam-14 exhibit square planar geometries, 4-MeCyclam-14 forms Ni^{2+} and Cu^{2+} complexes, whose absorption spectra are best explained by assuming pentaco-ordination of the metal ions.

The complexation rate of the three N-methyl substituted macrocycles with Cu^{2+} and Ni^{2+} is slower than can be accounted for by water exchange and little affected by introducing methyl groups at the nitrogens. Both results are in contrast to what is known for open chain amine ligands. A mechanism for the complexation is proposed, which also explains why the products of the reaction of 4-MeCyclam-14 with Cu^{2+} and Ni^{2+} are pentaco-ordinated.

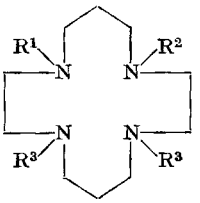
The complexation rate of transition metal ions with macrocyclic ligands is much slower than with analogous open chain compounds [2–4]. Based on such comparisons it has been concluded that the rate determining step of the complex formation with tetraazacyclotetradecanes is not the dissociation of the first co-ordinated water molecule [2–4]. In the meantime *Rorabacher et al.* [5] have shown that N-substitution strongly affects the complexation rate of open chain amines with Ni^{2+} raising the question whether the observed slow reaction with macrocyclic ligands could similarly be explained.

The present investigation was undertaken with a twofold aim. For one we wanted to study systematically the effects of N-methyl substitution on the complexation rate of tetraazacyclotetradecanes, secondly we hoped to prove the hypothesis, that the conjugate base of the pentaco-ordinated [6] blue intermediate plays an important role in the complexation of *meso*-5,7,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (tet a or 1,7-CTH) with Cu^{2+} [3]. Replacement of all the hydrogen atoms of the four amino groups of the ligand by methyl groups should prevent the forma-

[1]) Part III, see [1].

tion of the conjugate base as well as the interconversion of the pentaco-ordinated into the square planar structure.

For these purposes we have synthesized the following three N-methyl substituted macrocycles:



$R^1 = CH_3$, $R^2 = R^3 = H$ 1-MeCyclam-14
$R^1 = R^2 = CH_3$, $R^3 = H$ 2-MeCyclam-14
$R^1 = R^2 = R^3 = CH_3$ 4-MeCyclam-14

Experimental Part. – N,N'-Ditosyl-N,N'-diacetic acid (I) was synthesized according to the literature [7], with the only difference that ethylbromoacetate instead of methylbromoacetate was used. Yield and properties of the product were similar to those described.

1,3-Dimethyl-1,3-ditosyl-1,3-diaminopropane (II). 100 g 1,3-ditosyl-1,3-diaminopropane disodium salt and 77 g methyl iodide were reacted in boiling abs. MeOH. The solvent was evaporated and the resulting oil shaken with 200 ml of water and 400 ml of $CHCl_3$. The $CHCl_3$ phase was twice extracted with 200 ml of water, dried over Na_2SO_4 and evaporated. The residue was crystallized from MeOH and gave 65 g (61%) of white crystals (II), m.p. 110–111° (113° [8]).

1,3-Dimethyl-1,3-diaminopropane (III). 97.2 g of II were hydrolyzed with 80% H_2SO_4 during 6 h at 120°. A concentrated solution of NaOH was added until pH > 12 and the amine separated by steam distillation. After extraction with ether the compound was distilled over sodium yielding 15 g (62%) of III, b.p. 142–145° (142° [8]). III. 2HCl m.p. 255–258° (266° [8]).

General cyclization procedure. The cyclization was accomplished according to the procedure of *Stetter & Mayer* [7] in a 4 l three necked flask equipped with a stirrer and two 500 ml dropping funnels, with which a constant dropping rate could be maintained. The two cyclization components, a solution of freshly prepared N,N'-ditosyltrimethylenediamine-diacetylchloride in benzene and a solution of two equivalents of the freshly distilled diamine, also in benzene, were slowly added at the same dropping rate within 15–20 h to 1.5 l of abs. benzene. The crude cyclic diamides, which precipitated during the reaction, were isolated after distilling off the solvent and extracting the residue with hot water to dissolve the diaminedihydrochloride formed.

General reduction procedure. The cyclic diamide dissolved in abs. THF was added under stirring to a suspension of 100% excess of $LiAlH_4$ in 400 ml of refluxing abs. THF during 24–60 h. At the end of the reaction the excess of $LiAlH_4$ was decomposed by adding water. The precipitated $Al(OH)_3$ was filtered and extracted in a *Soxhlet* with THF during 48 h. Evaporation of the combined solutions gave the cyclic amines as brown oils.

1-Methyl-4,8-ditosyl-1,4,8,11-tetraaza-2,10-dioxo-cyclotetradecane (IV). The acid chloride prepared from 15 g of I and $SOCl_2$ was cyclized with 5.3 g 1-methyl-1,3-diaminopropane (*Fluka*). The product was crystallized from methanol until thin layer chromatography (H_2O/CH_3COOH/butanol 3:1:2, Rf = 0.7) showed that it was pure. Yield 10 g (60%), m.p. 207–209°.

$C_{25}H_{34}N_4O_6S_2$ Calc. C 54.53 H 6.22 N 10.17% Found C 54.4 H 6.3 N 10.0%

1-Methyl-1,4,8,11-tetraazacyclotetradecane (1-MeCyclam-14). Reduction of 5.5 g of IV in 100 ml abs. THF according to the procedure given above with 2.0 g $LiAlH_4$ produced an oil, which upon treatment with alcoholic HCl gave a crystalline hydrochloride. Recrystallization from MeOH/H_2O gave 1.4 g (35%) of the monohydrate of 1-MeCyclam-14. $(HCl)_4$, dec. 220°.

$C_{11}H_{30}Cl_4N_4 \cdot H_2O$ Calc. C 34.95 H 8.53 N 14.80 Cl 37.45%
Found ,, 35.12 ,, 8.55 ,, 14.85 ,, 37.52%

1,5-Dimethyl-1,5,8,12-tetraazacyclotetradecane (2-MeCyclam-14). 7.5 g of I, which was converted to the acid chloride with $SOCl_2$, and 2.9 g of III were cyclized. The diamide, obtained with 70% yield, could not be crystallized. The crude product was therefore dissolved in 100 ml of abs. THF and reduced with 1.2 g $LiAlH_4$. The amine was purified by distillation at 150° and 10^{-2} Torr and the tetrahydrochloride prepared with alcoholic HCl. Yield 0.8 g (20% for both steps), dec. 210°.

$C_{12}H_{30}Cl_4N_4$	Calc.	C 38.52	H 8.62	N 14.97 Cl 37.89%
	Found	,, 38.40	,, 8.60	,, 14.89 ,, 37.80%

1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane (4-MeCyclam-14). 1 g 1,4,8,11-tetraazacyclotetradecane (Cyclam-14) [7] dissolved in 5 ml of 90% formic acid and 2 ml of 35% formaldehyde was heated for 12 h. 5 ml conc. HCl were added and the mixture evaporated to dryness. The tetrahydrochloride was crystallized from $EtOH/H_2O$. Yield 0.8 g (40%), dec. 230°.

$C_{14}H_{36}Cl_4N_4$	Calc.	C 41.80	H 9.02	N 13.93 Cl 35.25%
	Found	,, 41.57	,, 9.09	,, 14.01 ,, 35.11%

Measurements and equipement. Reagents: analytical grade, used without further purification, except 2,6-lutidine and 2,4,6-collidine which were distilled. Measurements Temp. 25 ± 0.1°, I = 0.5 (KCl).

Potentiometric titrations were obtained with a pH-meter E 353 (*Metrohm*) equiped with a glass electrode UX (*Metrohm*) on 10^{-2} M amine tetrahydrochloride solutions under 99.99% N_2.

Absorption spectra were measured on a *Bausch & Lomb* Spectronic 600 E with a *Walz & Walz* recorder or on a *Cary* 14 spectrophotometer in 1 or 4 cm cells.

The kinetics of complexation with Ni^{2+} was followed spectrophotometrically on a *Cary* 14 spectrophotometer with automatic sample changer at 459 nm ($\varepsilon = 62.5\,M^{-1}cm^{-1}$) for 1-MeCyclam-14, 467 nm ($\varepsilon = 40\,M^{-1}cm^{-1}$) for 2-MeCyclam-14 and at 510 nm ($\varepsilon = 62.5\,M^{-1}cm^{-1}$) for 4-MeCyclam-14 at 40° in 1 cm cells. Typical concentrations: $8 \cdot 10^{-4}$ M ligand, 10^{-2} M $NiCl_2$, 0.1 M 2,6-lutidine or 2,4,6-collidine buffer with KCl.

The rate of complexation of the macrocycles with Cu^{2+} was followed by pH-stat measurements on a Combititrator 3 D (*Metrohm*). Typical concentrations: $3 \cdot 10^{-4}$ M ligandhydrochloride, $3 \cdot 10^{-3}$ M $CuSO_4$ and 0.5 M KCl. The temperature dependence of the reaction rates was measured between 15° and 60°.

Computation of the pK^H values of the tetraazacyclotetradecanes was accomplished with the program VARIAT [9] on a PDP 9 computer. Rate constants, calculated on an *Olivetti* Programma 101 desk computer with appropiate programs for first or second order reactions, were generally accurate to ± 5%.

Results and Discussion

pK^H values. – The pK^H values of the macrocyclic tetramines are given in Table 1. As previously observed for Cyclam-14, the N-substituted macrocycles add

Table 1. *pK^H values of 1-MeCyclam-14, 2-MeCyclam-14 and 4-MeCyclam-14 at 25° and I = 0.5*

	pK_4^H	pK_3^H	pK_2^H	pK_1^H
1-MeCyclam-14	~2.3	2.8	10.35	11.40
2-MeCyclam-14	~2.3	3.05	9.90	10.90
4-MeCyclam-14	~2.7	3.45	9.35	10.10

two protons in two well separated steps. This observation has led *Bosnich et al.* [10] to postulate for Cyclam-14 a structure with two intramolecular hydrogen bonds, which leaves two of the nitrogen lone pairs easy accessible and the two others hidden. If the postulated structure is the reason for the two groups of pK^H values, one would expect that 4-MeCyclam-14, which cannot form any hydrogen bonds as a free base, should behave differently from the other tetraazacyclotetradecanes. A glance at the results of Table 1, however, shows that the pK^H values of 4-MeCyclam-14 are

quite similar to those of the other macrocycles, the slight differences originating from the fact that tertiary amines are less basic than secondary ones. Therefore the proposed structure for the amines with two intramolecular hydrogen bonds cannot be the explanation for the two groups of differently basic nitrogens. However, it can be noted, that the diprotonated form (4-MeCyclam-14)H_2^{2+} could assume such a structure.

Structure of the Ni^{2+} and Cu^{2+} complexes. – The absorption spectra of the Cu^{2+} and Ni^{2+} complexes of 1-MeCyclam-14, 2-MeCyclam-14 and 4-MeCyclam-14, shown in Fig. 1a and b, exhibit striking differences. The spectra of the complexes

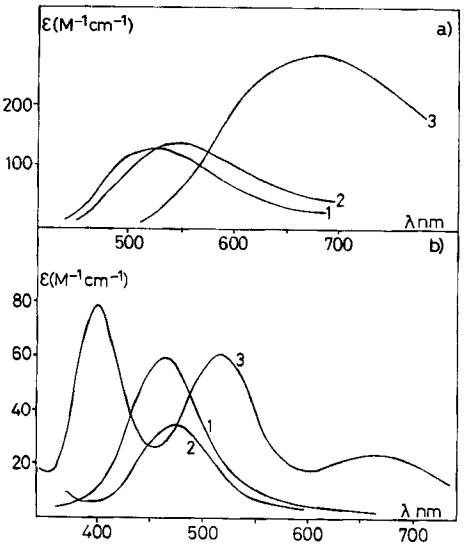


Fig. 1. *Absorption spectra of the complexes of 1-MeCyclam-14, 2-MeCyclam-14 and 4-MeCyclam-14 with a) Cu^{2+} and b) Ni^{2+} at pH = 7 in 2,6-lutidine buffer*

with Cyclam-14, 1-MeCyclam-14 and 2-MeCyclam-14 are typical for square planar co-ordinated metal ions, whereas those of 4-MeCyclam-14 clearly indicate that a different geometry is present. The absorption band of Cu(4-MeCyclam-14)$^{2+}$ with $\lambda_{max} = 675$ nm ($\varepsilon = 271$ M^{-1} cm^{-1}) strongly resembles that of the blue intermediate observed in the reaction of Cu^{2+} with tet a with $\lambda_{max} = 620$ nm ($\varepsilon = 206$ M^{-1} cm^{-1}) [3], for which trigonal bipyramidal geometry has been proved by X-ray structure analysis [6]. In addition both Cu(4-MeCyclam-14)$^{2+}$ and Cu(tet a)$^{2+}$ (blue) react as weak acids when titrated with NaOH, since the water molecule co-ordinated in the fifth position can be deprotonated [1] [3]. Similarly the absorption spectrum of Ni(4-MeCyclam-14)$^{2+}$ with three bands in the visible region was rationalized assuming pentaco-ordination of the metal ion [1] [11].

Kinetics and mechanism of complexation. – In the pH region between 5 and 9 the stoichiometry of the complexation of the macrocycles with Cu^{2+} and Ni^{2+} can be described by (1). The metal ion reacts with the diprotonated form of the ligand

$$M^{2+} + LH_2^{2+} \rightarrow ML^{2+} + 2\,H^+ \qquad (1)$$

LH_2^{2+} giving the product ML^{2+} and releasing two protons. The observed rate of reaction (1) is directly proportional to $[M]_{tot}$, $[LH_2]_{tot}$ and inversely proportional to $[H^+]$ (2) (Fig. 2 and 3)

$$\frac{d[ML]}{dt} = k \cdot [M]_{tot} \cdot [LH_2]_{tot}/[H^+] \quad (2)$$

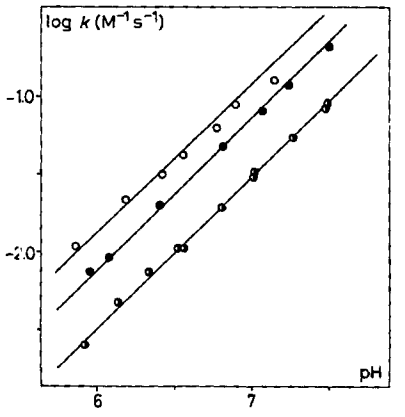


Fig. 2

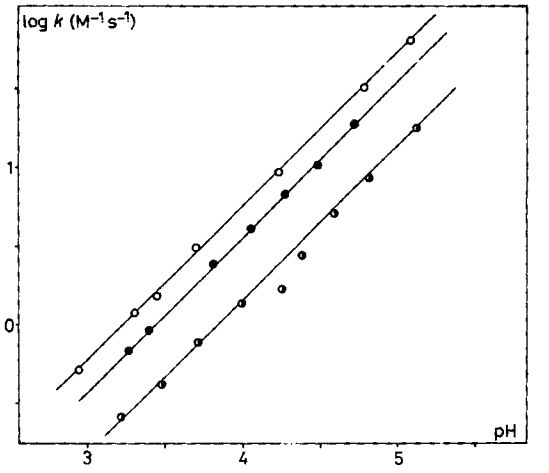


Fig. 3

Fig. 2. *pH dependences of the rate constant for the formation of the Ni^{2+} complexes with 1-MeCyclam-14* (○), *2-MeCyclam-14* (●) *and 4-MeCyclam-14* (◑) *at 40°*

Fig. 3. *pH dependences of the rate constant for the formation of the Cu^{2+} complexes with 1-MeCyclam-14* (○), *2-MeCyclam-14* (●) *and 4-MeCyclam-14* (◑) *at 25°*

The experimentally determined rate constants k, the activation energies ΔE^* and *Arrhenius* constants A for the reactions of 1-MeCyclam-14, 2-MeCyclam-14 and 4-MeCyclam-14 with Cu^{2+} and Ni^{2+} are reported in Table 2.

Although LH_2^{2+} is the predominant species in the pH range, in which the reaction was studied, the pH dependence of k indicates that LH^+ is the reactive form of the ligand. With pK_2^H one can then calculate the bimolecular rate constant $k_{LH} = k/K_2^H$ (Table 2). From Table 2 it is clearly apparent that Cu^{2+} and Ni^{2+} react with these macrocycles more slowly than with open chain amines, for which water substitution is the rate determining step. Several possible explanations for the slow reaction with tetraazacyclotetradecanes have been proposed: a) a high potential energy barrier for internal rotation [2], b) multiple desolvation of the metal ion [4] and c) steric effects due to N-substitution [5].

By analogy to the results obtained by *Rorabacher et al.* on steric effects in the complexation with amines [5] one would expect that by succesive methylation of Cyclam-14 the reactivity towards metal ions would first slowly decrease by the statistical factor, given by the number of secondary amino groups available for complexation (Cyclam-14 ≥ 1-MeCyclam-14 ≥ 2-MeCyclam-14) and then abruptly fall when all four nitrogens are methylated (4-MeCyclam-14). However, the results in Table 2 show that the expected trend is not observed. Thus, a) either steric effects are not important in first-bond formation with these macrocycles, because the ring

Table 2. *Rate constants, activation energies and* Arrhenius *constants for the complexation of* Cyclam-14, *1-MeCyclam-14, 2-MeCyclam-14, and 4-MeCyclam-14 with* Cu^{2+} *and* Ni^{2+}

	Cu^{2+}				Ni^{2+}			
	Cyclam[a])	1-MeCyclam	2-MeCyclam	4-MeCyclam	Cyclam[b])	1-MeCyclam	2-MeCyclam	4-MeCyclam
$k(s^{-1})$ at 40°					4.0×10^{-9}	1.2×10^{-8}	7.6×10^{-9}	3.1×10^{-9}
$k(s^{-1})$ at 25°		5.3×10^{-4}	3.6×10^{-4}	1.3×10^{-4}	9.3×10^{-10}	2.5×10^{-9}	1.3×10^{-9}	6.3×10^{-10}
k_{LH} $(M^{-1}s^{-1})$	2.6×10^{5}	1.2×10^{7}	2.8×10^{6}	2.9×10^{5}	7.4[c])	55	10	1.4
ΔE^* (kcal/mol)		19.4	19.2	19.6	18.7	20.3	19.1	18.4
$A(M^{-1}s^{-1})$		2.3×10^{21}	3.8×10^{20}	7.7×10^{19}	4.3×10^{14}	4.8×10^{16}	1.1×10^{15}	4.8×10^{13}

a) *Th. Kaden*, unpublished results.

b) see [2].

c) calculated with $pK_2 = 9.9$, *D. B. Rorabacher*, personal communication.

already induces such a high steric hindrance that any further change can little affect the reactivity, or b) the expected decrease in complexation rates from Cyclam-14 to 4-MeCyclam-14 is compensated by some other effect, for example, by a different conformation of the ligand, or c) no steric effects are observed, because the rate determining step for the macrocycles is not the same as for the open chain amines. Another interesting point is the observation, that 4-MeCyclam-14 forms with Cu^{2+} and Ni^{2+} either square pyramidal or trigonal bipyramidal complexes [1] [11], which cannot be coerced to give the square planar compounds expected by analogy from results with other tetraazacyclotetradecanes. We have previously in the case of Cu^{2+} and tet a suggested that this interconversion must go through the conjugate base, formed by deprotonation of one of the co-ordinated amino groups of the pentaco-ordinated complex (Fig. 4) [3]. If our hypothesis is right and if the complexation with

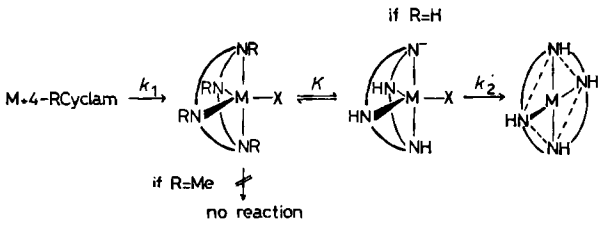


Fig. 4. *Reaction scheme for the complexation of tetraazacyclotetradecanes with Ni^{2+} and Cu^{2+}*

tetraazacyclotetradecanes always goes through such intermediates, one would expect that 4-MeCyclam-14 reacts with metal ions to give pentaco-ordinated complexes since no conjugate base can be formed in this case.

In addition *Barefield et al.* [12] have been able to synthesize a square planar Ni^{2+} complex of 4-MeCyclam-14 by direct alkylation of Ni(Cyclam-14)$^{2+}$, thus showing that this complex can be obtained by a different synthetic route. This and our kinetics results indicate that the formation of the pentaco-ordinated Cu^{2+} and Ni^{2+} complexes with 4-MeCyclam-14 must be kinetically controlled.

In general, when no excessive steric hindrance is present, as for Cyclam-14, 1-MeCyclam-14 and 4-MeCyclam-14, the pentaco-ordinated complex rapidly reacts to the square planar compound and cannot be observed. In cases, where the energy barrier of rotation is high as in tet a with six methyl groups, the second step is slow and the pentaco-ordinated complex becomes a reaction intermediate. Finally when no conjugate base can be formed as for 4-MeCyclam-14 the pentaco-ordinated complex is the final product of the complexation, no other reaction path being available to reach the square planar structure.

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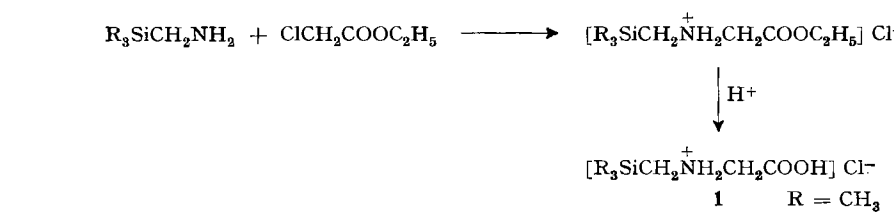
113. Notiz zur Darstellung von N-Trimethylsilylmethyl-glycin und einiger seiner Derivate

von **Walter Fink**
Monsanto Research S.A., Eggbühlstrasse 36, 8050 Zürich

(24. IV. 74)

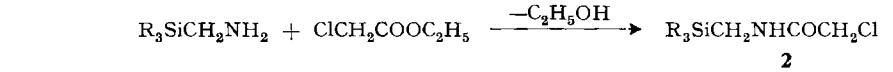
Zusammenfassung. Es wird eine einfache Darstellung von N-Trimethylsilylmethyl-glycin durch Hydrolyse von N-Trimethylsilylmethyl-glycinamid beschrieben.

Kürzlich berichteten *Duffaut et al.* [1] über die Darstellung von N-Trimethylsilylmethyl-glycin-hydrochlorid (**1**). Sie setzten Trimethylsilylmethylamin in siedendem Benzol mit Chloressigsäureäthylester zum Silylderivat des Sarcosinäthylesterhydrochlorids um und erhielten durch dessen Hydrolyse **1** in 30proz. Ausbeute.



1 $R = CH_3$

Im Rahmen einer Arbeit über biologisch aktive Siliciumverbindungen [2] wurde das freie, bisher nicht beschriebene N-Trimethylsilylmethyl-glycin benötigt. Bei Versuchen das entsprechende Salz (**1**) nach obiger Methode zu gewinnen[1]) stellten wir jedoch fest, dass die Kondensation von Trimethylsilylmethylamin mit Chloressigsäureäthylester nicht wie angegeben abläuft, also unter Abspaltung von HCl zu N-Trimethylsilylmethyl-glycin-äthylester-hydrochlorid, sondern im Wesentlichen unter Aminolyse der Estergruppe zu N-Trimethylsilylmethyl-chloracetamid (**2**) [Sdp. 118°/12 Torr, $n_D^{20} = 1{,}4733$, Ausb. 78%. – NMR. ($CDCl_3$)[2]): $\delta = 0{,}10$ (*s*, Si-CH_3); 2,8 (*d*, $J = 5{,}5$ Hz, N–CH_2); 4,03 (*s*, Cl–CH_2)][3]).



2

[1]) Herrn *N. Duffaut* danken wir für die Überlassung experimenteller Unterlagen.

[2]) ^{1}H-NMR.-Spektren (60 MHz): δ = chem. Verschiebung in ppm (Multiplizität, Zuordnung); δ-Werte bezogen auf Tetramethylsilan ($\delta = 0$).

[3]) $C_6H_{14}ClNOSi$ (179,7) Ber. C 40,10 H 7,85 Cl 19,73 N 7,79%
Gef. ,, 40,05 ,, 7,92 ,, 19,56 ,, 7,58%