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FRAGMENTATION WITH SUPERNUCLEOPHILES—VI[1]

β-HALOALKYL GROUPS AS FUNCTIONAL PROTECTION IN PEPTIDE SYNTHESIS. A KINETIC STUDY OF THE REACTION OF THE COBALT(I)PHTHALOCYANINE ANION WITH ORGANIC HALIDES

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Abstract—The kinetics of the reaction between cobalt(I)phthalocyanine anion and primary alkyl monohalogenides was studied by the use of conductivity measurements. The data agree with an S_N2 mechanism. In the case of geminally polyhalogenated compounds a somewhat different type of mechanism seems to prevail. The alkylation of cobalt(I)phthalocyanine anion by β-haloethyl esters, urethanes, phenolethers, phenolthioethers, amines and amides, followed by reductive fragmentation of the organo-cobalt intermediate, are model experiments related to the extension of an earlier developed protective group technique for peptide synthesis. In the studied cases the rate of the overall reaction is roughly the same as the rate of the initial alkylation step.

Zusammenfassung—Die Reaktion von Kobalt(I)phthalocyanin Anion mit primären Alkylmonohalogeniden wurde mittels der Konduktometrie kinetisch untersucht. Sie verläuft wahrscheinlich nach einem S_N2-Mechanismus. Im Falle geminal polyhalogenierter Verbindungen scheint ein anderer Reaktionsmechanismus vorzuliegen. Die Alkylierung von Kobalt(I)phthalocyanin Anion mittels β-Halogenäthyl-estern, -urethanen, -phenoläthern, -phenolthioäthern, -aminen und -amiden, der sich eine reduktive Fragmentierung der kobaltorganischen Zwischenstufen anschließt, dient als Grundlage der Erweiterung einer küzlich engeführten Schutzgruppentechnik für Peptidsynthesen. Die bei diesen Reaktionen bestimmten Gesamtreaktions-raten stimmen uberein mit den entsprechenden Alkylierungsreaktionsraten.

Recent results indicate that reactions according to the general Scheme 1 may serve as a basis for a new protective group technique of peptide synthesis.[1-3]

In the present paper some model experiments designed to yield information on the scope and limitations of this technique are described. Particular emphasis was put on determining from which functional groups β-haloalkyl groups could be removed by this method. Such information would indicate to what extent the technique is applicable to protecting functional groups in the side-chains of polyfunctional amino acids.

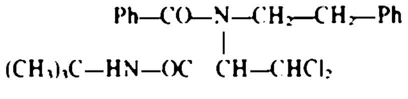
Furthermore, the dependence of the reaction rates on the structure of the alkylating agent 1 was studied. The results of such investigations may not only be useful for the further development of the protective technique mentioned above, but could also lead to evidence concerning the mechanism of the alkylation of the supernucleophilic cobalt(I)phthalocyanine anion 2.

Among the supernucleophiles the cobalt(I)phthalocyanine anion is distinguished by its extraordinary stability under a variety of conditions and its relatively weak reducing power.[4-8] The redox-potential of the cobalt(I) phthalocyanine anion is −0.37 V[9] whereas the other supernucleophiles like the cobaloximes or vitamin B_{12} have redox-potentials in the range −0.7 to −1.1 V.[10]

RESULTS AND DISCUSSION

In some preparative model experiments the reactions according to Scheme 1 were studied in order to find which functional groups could be protected by a β-haloalkyl group. The reactions were run till the evolution of ethylene ceased. The results are listed in Table 1.

The compound **6** obtained by four component condensation (4CC)[11] was fragmented analogously, giving the amide **7** in 40% isolated yield.



$$\begin{array}{l} \qquad\qquad\quad \mathrm{Ph{-}CO{-}N{-}CH_2{-}CH_2{-}Ph} \\ \qquad\qquad\qquad\qquad\quad | \\ \mathrm{(CH_3)_3C{-}HN{-}OC\ \ CH{-}CHCl_2} \end{array}$$

6

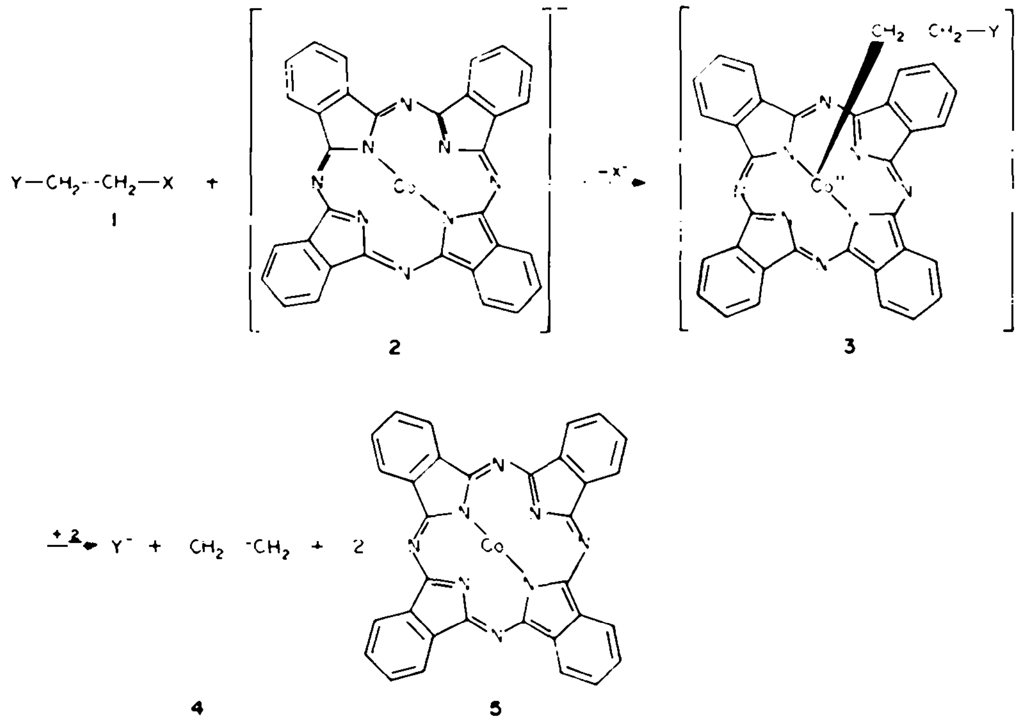
$\mathrm{Ph{-}CO{-}NH{-}CH_2{-}CH_2{-}Ph}$

7

The preparative studies were supplemented by a corresponding kinetic investigation of some reactions according to Scheme 1.

Rate data for these reactions were obtained by measuring the time-dependence of the conductivity of the reactants in methanol solutions and/or by gas-volumetric determination of the ethylene evolution. The conductivity measurements were carried out under pseudofirst order conditions (halide excess > 20-fold) while in the gas-volumetric measurements second-order conditions were observed.

The change in the electrical conductivity during the reaction is due to the difference in ionic mobility between cobalt(I)phthalocyanine anion **2** and the ions X⁻ and Y⁻ formed by the reaction.



Scheme 1.

Table 1. The reaction of β-halogenalkyl compounds 1 with cobalt(I)phthalocyanine anion 2 according to Scheme 1

Y	X	Reaction time	Yield (%) of isolated Y-H
$C_6H_5-CO_2$	Br	[illegible] min	[illegible]
$C_6H_5-CO_2$	Cl	[illegible] h	[illegible]
$C_6H_5-NH-CO_2$	Br	45 min	[illegible] a)
$C_6H_5-NH-CO_2$	Cl	[illegible] h	83 a)
C_6H_5-O	Br	[illegible] min	[illegible]
C_6H_5-S	Br	[illegible] min	[illegible]
$C_6H_5-N-CH_3$	Br	– b)	[illegible]

a) $C_6H_5-NH_2$ was isolated.

b) No evolution of ethylene was observed.

In a given case the conductometrically determined rate and the gas-volumetrically measured rate of ethylene evolution, corresponding to the overall reaction, do not differ much (Table 2). This indicates that the fragmentation step is as fast as, or faster than, the alkylation step, which seems to be rate-determining.

In two cases the characteristic alkylation products 3 of the first step of Scheme 1 were isolated. This may be interpreted as evidence for the assumed reaction mechanism. Further, the rate of the reductive cleavage of the compound 3 (Y = PhCOO) by Cobalt(I)phthalocyanine anion was measured gas-volumetrically. In Table 3 the time after which the reaction had proceeded to 50%, 90% and 100% completion are recorded for the reactions according to scheme 1 of the β-haloethyl esters 1(Y = PhCOO, X = Br, Cl), in which the compound 3(Y = PhCOO) would be the intermediate, as well as the reductive cleavage by 2 of isolated 3(Y = PhCOO). These results are further evidence that the first step of scheme 1 is rate-determining.

Since the alkylation step can be assumed to be rate-determining in reactions according to Scheme 1, it was of interest to measure the rates of the reaction between cobalt(I)phthalocyanine anion and a variety of organic halides in order to determine the reactivity of the latter as a function of their structural features. The results are listed in Table 4.

The reason why only primary alkyl halides were investigated is that secondary halides tend to eliminate hydrogen halide when reacted with 2, e.g. butene-1 was

Table 2. The second order overall rate constants of some reactions according to Scheme 1 in methanol at 25°

Y	X	Coulometrically determined rate const. (l/mol·sec)	Gas-volumetrically determined rate const. (l/mol·sec)
[illegible]	Br	[illegible]	[illegible]
[illegible]-Phe-Ala-	Br	-	[illegible]
[illegible]	[illegible]	[illegible]	-
[illegible]-Val-[illegible]	Br	-	[illegible]
[illegible]-Ala-Val-Ala-[illegible]	Br	-	[illegible]
[illegible]	Br	[illegible]	[illegible]
[illegible]	Br	-	[illegible]
Br	Br	[illegible] a)	[illegible] a)

a) Corrected for a statistical factor [illegible].

Table 3. Gas-volumetrically determined time for 50, 90 and 100% completion of the reactions according to Scheme 1 of the listed benzoic acid esters with 2[1]

Reactant	$t_{50\%}$ (min)	$t_{90\%}$ (min)	$t_{100\%}$ (min)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]Co(III)Pc a)	[illegible]	[illegible]	[illegible]

a) Co(III)Pc = cobalt(III)phthalocyanine

produced in the reaction of 2-bromobutane with cobalt(I)phthalocyanine anion.[8] In several cases the measurements included a variation of the halide concentration by a factor 2–10. The fact that under these conditions constant values for the calculated second order rate constants were obtained, indicates that the alkylation reaction proceeded by a second-order rate law.

The relative alkylation rate of n-butyl halides increases in the series Cl < Br < I from 1 via 300 to 6000 in a manner which is typical for an S_N2 reaction. Similarly, the reaction rate was found to increase by the factor 5×10^4 when an α-phenyl substituent was introduced, and by the factor 6×10^4 in the case of an α-oxo substituent. Further, with monohalides the change of the group Y in 1 (Scheme 1) showed, in general, negligible influence on the reaction rate. Note also the practically identical reaction rates of the 2-bromoethyl benzoate and the BOC-dipeptide 2-bromoethyl ester. Branching in β-position, however, leads to a decrease in alkylation rate. This is in accordance with an assumed S_N2 mechanism. These results are similar to those observed by Schrauzer and Deutsch[12] concerning the alkylation of Cobaloximes(I). Steric hindrance does not seem to be relevant to the 2,2,2-trichloro-t-butyl benzoate, which reacts at approximately the same rate as the 2,2,2-trichloroethyl benzoate. In these cases, however, the rates could not be measured accurately due to the limitations of the equipment available.

Further, the comparison of the reactivities of the mono-, 1,1,-di-and 1,1,1-trichloroalkanes show a rate increase in the order $ClCH_2{-}R < Cl_2CH{-}R \ll Cl_3C{-}R$ with a remarkable jump in rate between the dichloro and the trichloro compounds. These results, in combination with the known slight tendency of gem-poly-haloalkanes to participate in S_N2 reactions, indicate that at least the gem-trichloro compounds react with 2 by a mechanism which is different from that of the corresponding monochloro-alkanes. It is not clear from the available data whether 1,1-dichloroethane reacts by S_N2 mechanism or like the 1,1,1-trichloroethane.

EXPERIMENTAL

All operations involving cobalt(I)phthalocyanine derivatives were carried out under N_2.

Solvents and starting materials. The solvents used (MeOH where not otherwise stated) were deoxygenated by refluxing in a N_2 atmosphere and subsequent distillation.

The supernucleophile lithium cobalt(I)phthalocyanine was prepared by reduction of cobalt(II)phthalocyanine with dilithium benzophenone in THF,[6,8] from which it crystallized with 4.5 crystal THF. The simple alkyl halides were all commercially available. They were purified and deoxygenated by distillation in a N_2 atmosphere. The purity was confirmed by comparing the b.ps with the corresponding literature values.

The 2-bromoethyl, 2-chloroethyl, 2,2,2-trichloroethyl and 2,2,2-trichloro-tert-butyl esters of benzoic acid were prepared from benzoyl chloride and the corresponding alcohol.[7,8] The urethanes N-(2-chloroethoxycarbonyl)- and N-(2-bromoethoxy-car-

Table 4. The conductometrically determined second order rate constants of the reaction between cobalt(I)phthalocyanine anion and various organic halides in methanol at 25°

Substrate	Rate const. (l/mol·sec)
$CH_3CH_2CH_2CH_2Cl$	[illegible]
$C_6H_5CH_2Cl$	[illegible]
$CH_3CH_2OCOCH_2Cl$	[illegible]
CH_3CHCl_2	[illegible]
CH_3CCl_3	[illegible]
$C_6H_5COOCH_2CCl_3$	[illegible]
$C_6H_5COOC(CH_3)_2CCl_3$	[illegible]
CH_3CH_2Br	[illegible]
$CH_3CH_2CH_2Br$	[illegible]
$CH_3CH_2CH_2CH_2Br$	[illegible] a)
$(CH_3)_2CHCH_2Br$	[illegible]
$HOCH_2CH_2Br$	[illegible]
$BrCH_2CH_2Br$	[illegible] b)
$BrCH_2CH_2CH_2Br$	[illegible] b)
$BrCH_2CH_2CH_2CH_2Br$	[illegible] b)
CH_3I	[illegible]
$CH_3CH_2CH_2CH_2I$	[illegible]
CH_3OTs	[illegible]
$CH_3CH_2CH_2CH_2OTs$	[illegible]

[a] Erroneously given as 2.9×10^{-3} l/mol.sec in Ref. 2.
[b] Corrected for a statistical factor 2.
[c] from Ref. 2.

bonyl)aniline respectively were obtained by the reaction of aniline with 2-chloroethoxycarbonyl and 2-bromoethoxycarbonyl chloride respectively.[6,8]

The peptide derivatives MeO–Val–CO–OCH_2CH_2Br,[6,8] t-BuO–Ala–Val–Ala–CO–OCH_2CH_2Br[6,8] and BOC–Phe–Ala–OCH_2CH_2Br[7,8] were prepared according to known methods.

The purity of these compounds (after distillation or recrystallization) was verified by IR and ^1H NMR spectroscopy and by satisfactory elemental analyses. n-Butyl tosylate,[11] 2-bromoethylphenyl ether,[14] 2-bromoethylphenyl thioether[14] and N-(2-bromoethyl)-N-methylaniline[14] were all prepared according to published procedures. Their purity was confirmed by comparing the b.ps with literature values and by ^1H NMR spectroscopy.

Compound **6** which was obtained by four component condensation of dichloroacetaldehyde, t-butyl isonitrile, benzoic acid and phenylethylamine was kindly provided by Mr. Hasso v. Zychlinsky and showed satisfactory IR- and ^1H NMR-data.[21]

n-Butyl-cobalt(III)*phthalocyanine* 3(R = CH_3CH_2. Lithium cobalt(I)phthalocyanine (2.5 g, 2.77 mmol) and n-butyl bromide (2 ml, *ca.* 20 mmol) in MeOH (20 ml) were stirred at 20° for 1 hr. The blue ppt was filtered off and was washed consecutively with MeOH, water and MeOH. Recrystallization from THF/pentane yielded violet crystals of n-butyl-cobalt(III)phthalocyanine (1.05 g, 61%). (Found: C, 68.83; H, 4.02; N, 18.00 for $C_{36}H_{25}CoN_8$: C, 68.79; H, 4.01; N, 17.83).

2-*Hydroxyethyl-cobalt*(III)*phthalocyanine* 3(Y = OH) was prepared analogously by the reaction of lithium cobalt(I)phthalocyanine with 2-bromoethanol.[4,8]

2-*Benzoyloxyethyl-cobalt*(III)*phthalocyanine* 3(Y = PhCOO) was obtained by the reaction of 2-hydroxyethyl-cobalt(III)phthalo-cyanine with benzoyl chloride in pyridine.[4,8]

Fragmentation of 2-bromoethylphenyl ether. Lithium cobalt(I)phthalocyanine (27.0 g, 29.9 mmol) and 2-bromoethylphenyl ether (2.0 g, 10 mmol) in MeOH (150 ml) were stirred at 20° for 80 min. During the reaction ethylene (138 ml, 62%) was evolved. Water (100 ml) was added at 0° to the deep-green suspension and the mixture was aired for 5 min. The violet ppt of cobalt(II)phthalocyanine was filtered off and the filtrate was washed with diethyl ether. The aqueous phase was acidified using conc HCl and was extracted with dichloromethane. Evaporation of the solvent yielded phenol (0.58 g, 62%), which was characterized IR- and ^1H NMR-spectroscopically.

Fragmentation of 2-bromoethylphenyl thioether. Lithium cobalt(I)phthalocyanine (4.75 g, 5.3 mmol) and 2-bromoethylphenyl thioether (0.435 g, 2.0 mmol) in MeOH (30 ml) were stirred at 20° for 95 min. During the reaction ethylene (33.5 ml, 75%) was evolved. To the deep-green suspension water (30 ml) was added at 0° and the mixture was aired for 5 min. The deep-blue ppt was removed by centrifugation and the centrifugate was washed with diethyl ether. After 5 days colourless needles of diphenyl disulfide (0.13 g, 60%) were obtained by filtration of the aqueous phase, m.p. 60° (lit. m.p. 61°).

Fragmentation of N-*(2-bromoethyl)*-N-*methylaniline.* Lithium cobalt(I)phthalocyanine (6.3 g, 7.0 mmol) and N-(2-bromoethyl)-N-methylaniline (0.43 g, 2.0 mmol) in MeOH (40 ml) were stirred at 20° for 16 hr. No gas-evolution was observed. The deep-green suspension was acidified at 0° using 1 N HCl. The deep-blue ppt was filtered off and the filtrate was washed with diethyl ether. The aqueous phase was made alkaline using NaOHaq and was extracted with dichloromethane. Evaporation of the solvent yielded N-methyl-aniline (0.12 g, 53%), which was characterized IR- and ^1H NMR-spectroscopically.

Fragmentation of the 4CC product **6**. Lithium cobalt(I)phthalocyanine (2.6 g, 2.9 mmol) and the 4CC product **6** (0.441 g, 1.0 mmol) in MeOH (20 ml) were stirred at 20° for 24 hr. The deep-green mixture was then acidified at 0° using 1 N HCl. The deep-blue ppt was filtered off and was washed with acetone and the filtrate was evaporated. The residue was dissolved in dichloromethane, washed consecutively with 1 N HCl, water and $NaHCO_3$aq, then the solvent was evaporated. The crude product thus obtained was chromatographed on silica gel using dichloromethane as eluent. After recrystallization from dichloromethane/pentane, colourless crystals of IR and ^1H NMR spectroscopically characterized compound **7** (0.09 g, 40%) were obtained, m.p. 114°.

Fragmentation of 1,2-dibromoethane. Lithium cobalt(I)phthalocyanine (5.15 g, 5.7 mmol) and 1,2-dibromoethane (0.376 g, 2.0 mmol) were stirred in MeOH (30 ml) at 20° for 2 min. During the reaction ethylene (33 ml, 74%) was evolved. Water (30 ml) was added at 0° to the deep-green suspension, then air and CO_2 were bubbled through the mixture. The deep-blue ppt was removed by centrifugation, the centrifugate was washed with dichloromethane and then filled up with water to 50.0 ml. The amount of bromide ion present (3.52 mmol, 88%) was determined by Mohr-titration of two aliquots.

The preparative fragmentation of the β-haloethyl esters and urethanes was carried out in a similar manner.[6,8]

Fragmentation of the isolated 2-benzoyloxyethyl-cobalt(III)*phthalocyanine* 3(Y = PhCOO). Lithium cobalt(I)phthalocyanine (1.60 g, 1.77 mmol) and 3(Y = PhCOO) 1.28 g, 1.77 mmol) were stirred in deoxygenated acetone (15 ml) at 20° for 45 min. During the reaction ethylene evolution was measured (44.5 ml, 111%). Water (15 ml) was then added to the mixture at 0° and the deep-blue ppt of cobalt(II)phthalocyanine (1.87 g, 93%) was filtered off. The filtrate was washed with diethyl ether, the aqueous phase was acidified using 1 N HCl and subsequently extracted with dichloromethane. Evaporation of the solvent yielded benzoic acid (0.141 g, 66%), m.p. 118–119° (lit. m.p. 122°C).

Determination of rate constants by gas-volumetric measurements. In the fragmentation experiments the concentration of organic halide was *ca.* 0.1 M. The halides were added as a methanolic solution (volume *ca.* 5 ml) through a dropping funnel, which was connected with a gas-burette; thus the evolution of gas as a function of time could be followed. In the case of the fragmentations involving 2-bromoethoxycarbonylaniline and 2-benzoyloxyethyl-cobalt(III)phthalocyanine the gas evolved consisted, according to analysis, quantitatively of ethylene.

The eqn (1) is the basis for the calculation of the second order rate constant k_2 for the overall reaction out of the gas-volumetrically determined data.

$$\underline{1} + 2 \times \underline{2} \longrightarrow Y + \underline{4} + 2 \times \underline{5} + X \qquad (1)$$

$$\frac{1}{[\underline{2}]_0 - [\underline{1}]_0} \ln \frac{[\underline{1}]_0[\underline{2}]}{[\underline{2}]_0[\underline{1}]} = k_2 t$$

$$[\underline{2}] = [\underline{2}]_0 - 2[\underline{1}]_0 \frac{V}{V_{total}}$$

$[\underline{1}]$ = concentration of organic halide
$[\underline{2}]$ = concentration of cobalt(I)phthalocyanine anion
V – gasvolume of ethylene.

The inaccuracy of the fragmentation rate constant k_2 is estimated to be 15–20%.

General procedure for the determination of rate constants by conductometric measurements. A conductivity cell was filled with 25.0 ml of a MeOH soln of lithium cobalt(I)phthalocyanine, whose concentration varied between *ca.* 10^{-3} M and 10^{-4} M depending on the respective reaction rate, and thermostatized at 25 ± 0.1°. The organic halide, either neat or as a soln of the halide in MeOH, was injected with a syringe. In all experiments the organic halide was in more than 20-fold excess *vs* the supernucleophile, in order to ensure pseudo first order reaction conditions. The conductivity was measured as a function of time using a Wayne Kerr Autobalance Universal Bridge B 642. The pseudo first order rate constants were obtained from the conductivity data with the computer program LSKIN 1.[16] The second order rate constants were then calculated from these values and the known concentrations of the halides. The specific rate constants reported in Tables 2 and 4 are the average of 2–4 determinations. The average deviation was always less than ±9% and generally less than ±5%.

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