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Nucleophilic reactivity of perhydro-3,6,9,12-tetraazacyclopenteno[1,3-*f*,*g*]acenaphthylene. A unified approach to *N*-monosubstituted and *N*,*N*′′-disubstituted cyclene derivatives

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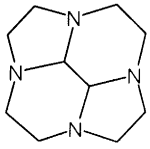
Abstract

Perhydro-3,6,9,12-tetraazacyclopenteno[1,3-*f*,*g*]acenaphthylene is readily mono- and dialkylated on nitrogen with alkyl bromides and iodides giving mono- and bis-quarternary ammonium salts. The title compound is a unified starting material for the preparation of cyclene based chelators.

Cyclene derivatives are widely investigated chelators due to their biomedical applications. The synthesis of derivatives with differentiated sidearms on nitrogen has been addressed so far by stepwise closure of the macrocyclic ring, starting from appropriately alkylated non-cyclic materials,[1] or by pH-controlled *N*-alkylation of an excess of free cyclene with a less than stoichiometric amount of reactive halide,[1,2] with careful pH control. These methods suffer from only moderate yields and long separation steps. Procedures for obtaining monoalkyl-substituted cyclenes are based on the concept of cyclene protection with silicon, phosphoryl or tricarbonylmolybdenum groups, affording *N*-alkylated cyclenes with C_xH_y (x=1,2,3, y=2x+1) groups on nitrogen.[3]



1

Recently, a special case of protection of the cyclene ring by conversion to glyoxal aminal **1** was used by Weisman in the synthesis of 4,10-dibenzyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane,[4] while Baker et al. used this type of protection in the conversion of *N*-monoethyl to *N*-monooctadecyl cyclene.[5] However, the reaction leading to methyl or benzyl derivatives resulted in a mixture of mono- and dialkyl-compounds[5] due to overalkylation. The aminal **1** was also utilised by Handel as a key intermediate in the synthesis

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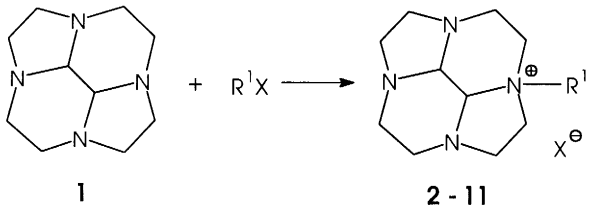
of cyclene.[6] The ready availability of **1** encouraged us to study its use in the synthesis of monoalkyl- or *N*,*N*′′-dialkyl-cyclene derivatives in detail. In the present paper we focused on the nucleophilic reactivity of **1**, as procedures for conversion of cyclic diaminals to cyclene derivatives are well established.[7]

We had observed that compound **1** smoothly reacts with alkyl iodides and bromides and various other alkylating agents in toluene or acetonitrile as solvent at room temperature giving monoquarternary ammonium salts **2**–**10** (Scheme 1, Table 1) in good to excellent yields.



Scheme 1. Reagents and conditions for monosubstitution of **1**

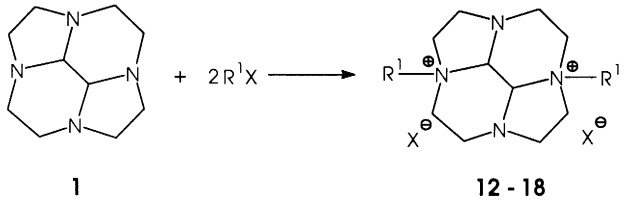
Table 1
Monoquarternary ammonium salts of **1**[a]

Compound[b]	R^1X	Solvent	Yield, %
2	CH_3I	$C_6H_5CH_3$	98
3	CH_3CH_2I	CH_3CN	94
4	$CH_3CH_2CH_2I$	CH_3CN	90
5	$C_6H_5CH_2Br$	$C_6H_5CH_3$	95
6	*p*-$NO_2C_6H_4CH_2Br$	CH_3CN	95
7	$EtOOCCH_2Br$	$C_6H_5CH_3$	88
8	NH_2COCH_2I	$C_6H_5CH_3$	79
9	$BrCH_2CH_2Br$	$C_6H_5CH_3$ or CH_3CN	74
10	$BrCH_2CH_2CH_2Br$	$C_6H_5CH_3$ or CH_3CN	69
11	NH_2COCH_2Cl	$C_6H_5CH_3$; CH_3CN	0; 0

[a] Molar ratios R^1X/ **1** were 1:1; for **3** and **4** 1.1 : 1. [b] Spectroscopic data are given in ref. 9.

A typical procedure is given in Ref. 8. Choice of an appropriate solvent is essential for avoiding dialkylation, which was not studied by Baker.[5] The reaction of **1** with ethyl bromoacetate leads to a valuable product in the synthesis of DOTA (i.e. 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) analogues. Toluene was found to be the solvent of choice for monoalkylation, as the monoquarternary salts **2**–**10** are almost insoluble in the hydrocarbon, thus preventing dialkylation.

Prolonged action of excess of alkylating agents to **1** leads to formation of *N*,*N*′′-disubstituted products, as was known[4] for R^1=$PhCH_2$. We observed that other selected alkylating agents showed the same behaviour, forming products **12**–**18** (Scheme 2, Table 2).



Scheme 2. Reagents and conditions for *N*,*N*′′-dialkylation of **1**

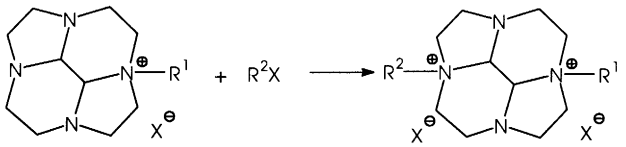
Acetonitrile proved to be a suitable solvent for *N*,*N*′′-dialkylation. Under the reaction conditions used, *N*,*N*′-substitution was not observed in any case, probably due to repulsion of positive charges in adjacent

Table 2
Symmetrical bisquarternary ammonium salts of **1**[a]

Compound[b]	Reagent	Solvent	Yield, %
12	CH_3I	CH_3CN	98
13	CH_3CH_2I	CH_3CN	94
14	$CH_3CH_2CH_2I$	CH_3CN	95
15	$C_6H_5CH_2Br$	CH_3CN	96
16	*p*-$NO_2C_6H_4CH_2Br$	CH_3CN+MeOH	95
17	$EtOOCCH_2Br$	CH_3CN	88
18	NH_2COCH_2I	CH_3CN	84

[a] Molar ratios R^1X/ **1** were 3:1; for **14**,**17** and **18** 5:1.
[b] Spectroscopic data are given in ref. 11.

positions in the macrocyclic ring. The triple alkylation does not proceed, not even with high excesses of highly reactive alkyl iodide (e.g. CH_3I, CH_3I:**1** molar ratio 10:1), at prolonged reaction times (two weeks at room temperature). The room temperature reaction was found to give purer products than the reaction carried out at 60°C. A representative procedure is given in Ref. 10. The products **5**, **6**, and **7** were found to undergo a second alkylation with a different alkylating agent in acetonitrile as a solvent according to Scheme 3 and Table 3, providing that they are at least slightly soluble in the reaction medium. The reaction conditions are the same as for preparation of **12**–**18**.[10]



5 - 7 **19 - 24**

Scheme 3. Reagents and conditions for preparation of unsymmetrical *N*,*N*′′-dialkyl derivatives of **1**

Table 3
Unsymmetrical bisquarternary ammonium salts of **1**[a]

Compound[b]	Starting compound		R^2X	Solvent	Yield, %
19	**5**	$C_6H_5CH_2$	CH_3I	CH_3CN	0
19	**5**	$C_6H_5CH_2$	CH_3I	CH_3CN+MeOH	90
20	**6**	*p*-$NO_2C_6H_4CH_2$	CH_3I	CH_3CN+MeOH	84
21	**7**	$EtOOCCH_2$	CH_3I	CH_3CN	89
22	**7**	$EtOOCCH_2$	CH_3CH_2I	CH_3CN	77
23	**7**	$EtOOCCH_2$	$C_6H_5CH_2Br$	CH_3CN	81
24	**7**	$EtOOCCH_2$	*p*-$NO_2C_6H_4CH_2Br$	CH_3CN	83

[a] Molar ratios R^2X/ **5**,**6** or **7** were 5:1. [b] Spectroscopic data are given in ref. 12.

Deprotection of the salts **2**–**24** upon formation of *N*-monoalkylated or *N*′,*N*′′ dialkylated cyclene derivatives was achieved according to established literature techniques by treatment with aqueous sodium hydroxide, hydrazine monohydrate, or an ethanolic solution of hydroxylamine.[5–7] Representative procedures are described in Ref. 13, together with characterisation of products.

Compounds **5** and **14** were characterised by X-ray diffraction of a single crystal obtained by recrystallisation of **5** from hot H_2O (Fig. 1) or during the alkylation in the case of **14** (Fig. 2).The results fully confirmed the structures of **5** and **14** obtained from ^1H and ^{13}C NMR measurements. Exclusive formation of one isomer with a *cis* arrangement of the aminal bridge was found. Full experimental results, atomic coordinates and e.s.d.s were deposited with the CCDC.

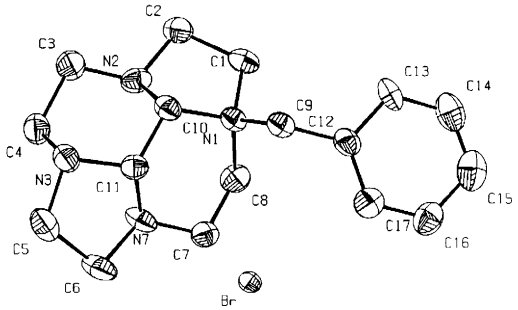


Fig. 1. X-Ray structure of **5**·H_2O in $P2_1$, the final *R* value was 0.043

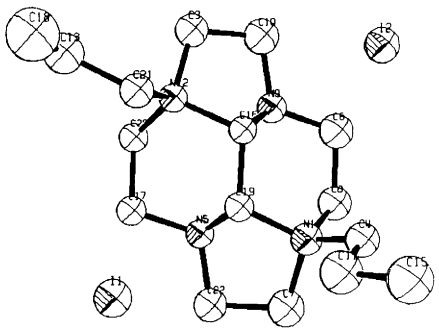


Fig. 2. X-Ray structure of **14** in $C2/_c$, the final *R* value was 0.042

The driving force for the alkylation reaction discussed is separation of insoluble mono- or bis-quarternary ammonium salts from solution during the course of the alkylation. The procedure described represents a unified, easily accomplished and cheap route to mono- or *N*,*N*′′-disubstituted cyclene derivatives with various pendant arms. Starting from easily accessible **1**, this procedure makes it possible to obtain a variety of new of DOTA-type ligands.

Acknowledgements

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8. Compound **2** (representative procedure): To a stirred solution of 0.19 g of **1** (1 mmol) dissolved in 1 ml of dry toluene a solution of 0.14 g (1 mmol, 1 equivalent) of CH_3I in 0.5 ml of dry toluene was added during 1 min. An exothermic reaction proceeded and a precipitate was formed. After stirring for 1 h, the product was filtered off.
9. ^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) **2**: CH_2 47.10, CH_3 50.47, CH_2 50.66, 50.84, 51.15, 51.30, 54.27, 64.15, 68.49, CH 74.61, 86.54; **3**: CH_3 11.09, CH_2 46.68, 50.64, 50.68, 51.21, 51.43, 54.26, 56.96, 59.13, 64.40, CH 74.73, 86.43; **4**: CH_3 13.12, CH_2 19.45, 46.71, 50.67, 50.81, 51.23, 51.45, 54.27, 59.87, 62.84, 65.04, CH 74.76, 86.57; **5**: CH_2 46.93, 50.61, 50.70, 51.30, 51.38, 54.36, 60.27, 64.36, 64.69, CH 74.79, 85.63, CH_{Ar} 132.66, 134.15, 135.57, C_{Ar} 129.91; **6**: CH_2 46.82, 50.63, 50.67, 51.27, 51.37, 54.38, 60.29, 63.26, 64.73, CH 74.72, 86.38, CH_{Ar} 127.61, 136.85, C_{Ar} 152.19; **7**: CH_3 16.23, CH_2 47.01, 50.70, 51.26 (double), 51.35, 54.29, 60.09, 62.37, 66.89, 67.53, CH 74.69, 87.64, CO 168.25; **8**: CH_2 47.02, 50.67, 51.31, 51.32, 51.39, 54.28, 60.28, 62.38, 67.67, CH 74.72, 87.40, CO 169.27; **9**: CH_2 24.18, 46.79, 50.68, 50.93, 51.23, 51.37, 54.29, 64.50, 61.45, 65.77, CH 74.70, 86.72; **10**: CH_2 21.08, 46.62, 50.54, 50.71, 51.11, 51.30, 54.23, 57.20, 60.23, 60.35, 65.27, CH 74.53, 87.29. All the compounds gave satisfactory elemental analysis.
10. Compound **12** (representative procedure): To a stirred solution of 0.19 g of **1** (1 mmol) in 1 ml of dry acetonitrile, 0.45 g (3 mmol, 3 equivalents) of CH_3I was added in one portion. An exothermic reaction proceeded and a precipitate was formed. The product was filtered off after 1 h. For less reactive bromides and long chain alkyl iodides, prolonged reaction times were used.
11. ^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) **12**: CH_2 46.02, CH_3 49.78, CH_2 49.45, 62.09, 67.94, CH 80.99; **13**: CH_3 11.06, CH_2 45.72, 49.31, 56.67, 57.36, 64.04, CH 81.35; **14**: CH_3 13.08, CH_2 19.41, 45.74, 49.41, 58.21, 62.34, 64.61, CH 81.31; **15**: CH_2 45.86, 49.10, 57.87, 63.98, 64.15, CH 80.67, CH_{Ar} 135.48, 132.80, 134.41, C_{Ar} 129.25; **16**: CH_2 45.37, 48.96, 58.03, 62.94, 64.49, CH 81.30, CH_{Ar} 127.57, 136.05, 136.63, C_{Ar} 152.29; **17**: CH_3 16.04, CH_2 45.83, 49.86, 59.35 (double), 60.27, 66.93, CH 81.94, CO 167.7; **18**: CH_2 46.07, 50.09, 59.83, 60.59, 67.23, CH: 81.94, CO 168.67. All the compounds gave satisfactory elemental analysis.
12. ^{13}C NMR (D_2O, 25°C, ref. *t*-BuOH int.) **19**: CH_2 45.77, 46.04, 49.12, 49.41, CH_3 49.56, CH_2 57.85, 62.11, 63.89, 64.17, 67.93, CH 80.41, 81.99, CH_{Ar} 132.78, 134.35, 135.47 C_{Ar} 132.14; **20**: CH_2 45.55, 45.92, 49.15, 49.31, CH_3 49.77, CH_2 60.39, 62.04, 62.54, 64.17, 67.87, CH 80.81, 80.96, CH_{Ar} 127.72, 136.88, C_{Ar} 136.08, 151.98; **21**: CH_3 16.28, CH_3N 49.73, CH_2 45.89, 46.01, 49.45, 49.99, 59.67, 60.55, 61.95, 67.05, 67.10, 67.96, CH 80.90, 82.16, CO 167.59; **22**: CH_3 16.25, 49.67 CH_2 45.90, 46.13, 49.46, 50.01, 59.65, 60.58, 61.96, 67.10, 67.12, 67.15, 67.99 CH 80.97, 82.21, CO 167.65; **23**: CH_3 16.25 CH_2 45.95 (double), 49.17, 50.01, 57.79, 59.53, 60.67, 63.98, 64.21, 67.13 (double), CH 80.36, 82.42, CH_{Ar} 132.80, 134.43, 135.48, C_{Ar} 129.20, CO 167.77; **24**: CH_3 16.23 CH_2 45.77, 45.85, 49.18, 49.95, 57.69, 60.61, 62.74, 64.35, 67.02, 67.08, 67.15, CH 81.19, 82.23, CH_{Ar} 127.71, 136.79 C_{Ar} 136.13, 152.33, CO 167.74. All the compounds gave satisfactory elemental analysis.
13. Monomethylcyclene tetrahydrochloride (representative procedure, deprotection with NH_2OH): Compound **2** (0.25 g, 0.75 mmol) was dissolved in 10 parts of 2 M solution of NH_2OH in dry EtOH. A slightly exothermic reaction proceeded. After refluxing for 2 h, the solution was mixed with an equal volume of 10% KOH and extracted five times with dichloromethane. Evaporation of the extracts and acidification with aqueous HCl gave a product identical with the authentic sample prepared by the Ritchman–Atkins procedure (0.22 g, 89%). ^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) CH_3 44.96, CH_2 45.27, 46.11, 46.73, 55.43. Similarly, 1,7-dimethylcyclene tetrahydrochloride (0.14 g, 77%,^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) CH_3 45.35, CH_2 45.47, 55.09) and 1,7-dibenzylcyclene tetrahydrochloride (0.20 g, 86%,^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) CH_2 45.51, 50.98, 60.65, CH_{Ar} 131.67, 132.80, 133.08, C_{Ar} 138.55) from **12** and **15** were prepared. Monobenzylcyclene tetrahydrochloride (representative procedure, deprotection with NH_2NH_2): Compound **5** (1,15 g, 3.14 mmol) was dissolved in 6 ml of hydrazine monohydrate and heated (100°C) for 24 h. The excess of hydrazine was evaporated, the product was extracted four times with hexane. Evaporation of the extracts and acidification with azeotropic HCl gave a crude product, which was purified by crystallisation from water (0.77 g, 60%) ^{13}C NMR (D_2O 25°C, ref. *t*-BuOH int.) CH_2 37.48, 37.57, 39.31, 43.72, 52.73, CH_{Ar} 124.16, 124.51, 125.63, C_{Ar} 129.28.