# Topics in Current Chemistry

113





## Cyclophanes I

Springer-Verlag Berlin Heidelberg NewYork Tokyo

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Editor: F. Vögtle

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With 22 Figures and 19 Tables

Springer-Verlag
Berlin Heidelberg New York Tokyo
1983

This series presents critical reviews of the present position and future trends in modern chemical research. It is addressed to all research and industrial chemists who wish to keep abreast of advances in their subject.

As a rule, contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for "Topics in Current Chemistry" in English.

ISBN 3-540-12397-0 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-12397-0 Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging in Publication Data. Main entry under title: Cyclophanes.
(Topics in current chemistry = Fortschritte der chemischen Forschung; 113)
Bibliography: p. Includes index.
1. Cyclophanes--Addresses, essays, lectures.
I. Boekelheide, V. (Virgil), 1919 —. II. Series:
Topics in current chemistry; 113.
QD1.F58 vol. 113 [QD400] 540s [547'.5] 83-4650


Printed in GDR


2152/3020-543210

# 113 Topics in Current Chemistry

Fortschritte der Chemischen Forschung

Managing Editor: F. L. Boschke

# Introduction

The scientific importance of bridged aromatic compounds — PHANES — has continually increased during the last years, whereas previously they were considered as esoteric substances exclusive for academic interests.

The bridging of molecules using long chains or short clamps can be and has since been usefully applied in many branches of chemistry. This development was encouraged by several factors: New synthetic accessabilities for medium- and large rings were developed, which lead to phanes in up to excellent yields without using complicated techniques. The still widespread prejudice that larger rings generally imply difficult experiments and low yields should finally be eliminated. Besides multi-bridged, multi-layered, multi-stepped and helically wound phanes, compounds can be obtained in which the static and dynamic stereochemistry, steric interactions and electronic effects may be directionally adjusted and varied by bridge length, interior ring substituents and other parameters.

The spectroscopic methods allowed a rapid and detailed study of stereochemistry and electronic effects, among these bent and battered benzene rings, the face-to-face neighbourhood of aromatic nuclei, charge transfer effects and non-benzenoid $\pi$-systems. The availability of more efficient NMR- and mass spectrometers and X-ray analyses will admit more accurate interpretations for the future. Phanes may especially be exploited as model structures for weak intra- and intermolecular interactions.

It was only a small step from pyridinophanes to the complex-chemistry of crown- and cryptand-like ligands. Today it has expanded to ranges like capped cyclodextrins, bridged hem, concave host cavities for guest ions and -molecules as for water soluble enzyme models. In the latter field of receptors containing large cavities, pockets or niches, the development towards new branches of bioorganic and biomimetic chemistry has only just begun.

The present volume enters the field of PHANES with three research surveys, which are intended to fill at least some of the wide gaps since B. H. Smith published the "cyclophane bible" in 1964. The reviews mainly deal with the subgroup of the

CYCLOPHANES, which have been defined as those phanes containing *benzene* nuclei as ring members. Although the individual contributions of this (and following volumes) cannot include the entire phane chemistry, they give, however, a critical insight into actual theoretical and experimental developments, innovations and future trends.

After leaving its earlier isolation, the bridging of molecular skeletons has promoted most fields of chemistry with synthetic, stereochemical, spectroscopic and bioorganic relevancy. The literature quoted could moreover be useful for further interests in relation with phanes, crowns and other medio-/macrocyclic compounds as well as for their open chain analogues.

Bonn, October 1982 F. Vögtle

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# Synthesis of Medio- and Macrocyclic Compounds by High Dilution Principle Techniques

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# I Introduction

Within the last decades the chemistry of medio-[1] and macrocyclic ring systems, such as phanes, polyynes, annulenes, crown compounds, cryptands, ionophores, macrolides etc. has developed rapidly. Progress stems from an increased recognition of the theoretical [1-5] and practical importance [6-10] associated with these compounds and was aided also by a growing insight into general synthetic concepts and strategies for ring closure reactions. Among them, the *dilution principle* [4, 6a], the *template effect* [11], the *rigid group principle* [12], the *gauche effect* [11a], the *caesium effect* [13, 14] and other concepts [15] proved to be most profitable.

This contribution aims to give a detailed presentation of the different types of ring closure reactions used for the formation of medio- and macrocycles where the principle of high dilution plays a dominant role. Nevertheless, it should be kept in mind that in many cases discussed here, there is no strong decision hitherto between the effect arising from high dilution techniques and other concepts mentioned above.

Although the dilution principle approach plays the most important role in the synthesis of phanes, it is not restricted to them. In this survey in order to gain insight into the method and its detailed applications, we shall not limit the scope to phanes, but shall for the sake of comparison, include the other types of macro rings [16].

Cyclizations taking advantage of the dilution principle, usually start with open chained educt compounds bearing two or more functional groups, and, as a rule, only one of the possible oligomers, in most cases the monomeric cyclization product, is wanted as the main product. The formation of oligo- or polycondensation products usually is wished to be suppressed. The preference of the monomer formation is not simply based — as sometimes taken for granted — on the use of a large solvent volume and/or addition of highly diluted reagents. Contrarily, in "dilution principle reactions" not the total amount of the solvent volume is decisive, but instead the establishment of a stationary concentration of the educts in the reaction flask that is as low as necessary, to steer the cyclization reaction in such a way that ideally the same amount of starting material is flowing into the reaction flask per time unit as is reacted to yield the optimum of the target cyclization product [3, 4, 6a]. This flow equilibrium of educt influx and product outcome may be achieved with small volumes as well. We therefore use the expression "dilution principle reaction" ("DP-reaction") instead of simply speaking of "high dilution reaction" (DP = *D*ilution *P*rinciple).

The total amount of solvent may be diminished additionally by recycling the boiling solvents, which can be condensed to (pre-) dilute the starting components prior to their addition to the reaction flask. The simultaneous addition of components is facilitated by precision dropping funnels [6], pumps or syringes (s.b.).

Even today, the dilution principle is very often used empirically. Investigations into its theoretical and physico-chemical fundamentals have been undertaken much more rarely than synthetic and preparative studies. Nevertheless, there have been some

1 Regarding the term mediocyclic see: Thulin, B., Vögtle, F.: J. Chem. Res. (S) **1981**, 256 and references [33d, 34a, 65a, 232].

developments in theoretical directions [1-3], exceeding the former works of Ziegler [4] and Ruggli [5].

Recently Galli and Mandolini [1a] made the proposal of a classification of cyclization reactions, based on physico-chemical evidences resulting from e.g. lactonization reactions of ω-bromoalkanolates. Thereafter, the fundamental measure in cyclization reactions is the effective molarity EM. This molarity is defined as *the* reactant concentration, at which the intramolecular cyclization ($k_{intra}$) and the intermolecular formation of oligo-/polymeric products ($k_{inter}$) occur at the same rate ($k_{intra}/k_{inter} = 1$; k = rate constant). The course of the reaction depends on the initial concentration. If this concentration is small enough, the cyclization will dominate. In this case the educts can be put forward in the reaction mixture (batch-wise cyclization procedure).

As very dilute solutions are almost valueless in synthetic work, an "*influxion procedure*" is usually practical in preparative syntheses, where the reactant(s) is/are introduced slowly into the reaction medium over a longer period of time. The rate of feed $v_f$ is the critical parameter now, which must be adjusted to make cyclizations dominant over polymerisation/polycondensation. This is achieved when $v_f < EM \cdot k_{intra}$. The rate of feed $v_f$ substantially controls the duration of the process and it is a measure of its efficiency. This procedure corresponds to the Ruggli/Ziegler high dilution technique [4].

This review is mainly concerned with those reactions which yield preparative amounts of medium- and large ring systems and which therefore are generally carried out according to the influxion (DP-) procedure. In this study those reactions which were carried out according to the batch-wise technique and which are rare in the literature, are marked with the corresponding literature note [1a].

Though this theoretical progress is of general value, it is often of minor use in answering distinct preparative synthetic questions because in a cyclization reaction, the influence of several different, decisive reaction parameters must be taken into account (reactivity of the reactants, reaction temperature, reaction time, dilution ratio, solvent parameters, apparative factors). Such influences have seldom been studied in a systematic way by physico-chemical methods with respect to modern synthetic reactions [1, 2g, 3].

For reasons of limited printing space, full experimental description of characteristic reactions have, unfortunately, to be omitted here apart from some exceptions. Instead, only a few typical experimental parameters are sketched out informing solely on educts, products, type of reaction, solvent, dilution/predilution, time of addition, additional reaction time, reaction temperature, yield and references, data which should be useful in planning analogous and new DP-reactions as well especially for comparisons of substrate concentrations, solution ratios, yields etc.

One of these parameters, the type of reaction, may need some explanation [6a]: All DP-reactions are formally characterized according to the number of the educt components to be added (n-component DP-reactions, n = 1, 2, 3). If, for example, two educt solutions are dropped separately out of two dropping funnels or syringes into a certain solvent volume stirred in the reaction flask, we characterize this as a two-Component *DP*-reaction (2C-DP-reaction) [6a]. n in the nC-DP-reaction signifies only the number of the educt solutions dropped from each other independently into the reaction flask, and does not mean the total number of educts. Therefore, in the

above example, even if an additional component has been dissolved in the reaction solvent in the reaction flask prior to the addition of the two components, or if it is mixed with one of the two educts in one of the dropping funnels, we nevertheless call this a 2C-DP-reaction, thus characterizing the technical procedure rather than chemical details. The latter may be noted in addition [6a].

The apparative handling of high dilution reactions is described elsewhere and can be omitted here; for up-to-date information see l.c. [6-10,23,24].

The following contribution attempts, therefore, to present a critical summary of the hitherto known facts and results on high dilution reactions; in addition it endeavours, as far as possible, to set up rules by comparative regard of reactions carried out according to the dilution principle, with respect to the type of reactions, dilutions and techniques applied. Such general comparisons and conclusions should be helpful in planning ring closure reactions. The philosophy of this report does not consist of a systematic presentation of all known DP reactions. It is, rather, a selection of characteristic cyclization reactions which allow a comparison with other synthetic methods and conditions in such a way that the generalizations and conclusions may help synthetic chemists to estimate the parameters, chances and yields of hitherto unknown cyclizations. Other publications, in which the synthesis of medio/macrocyclic compounds is described without remarks or details on the dilution conditions, are not considered in this text.

Hopefully, this — the first review on specific DP-reactions since Ziegler's [4] — may lead in future to a better calculation of this synthetic procedure, enabling scientists to carry it out in an optimal and standardized way and thereby saving time, needed otherwise for empirical testing.

## II Nucleophilic Substitutions at Saturated C-Atoms

DP-reactions (DP = *D*ilution *P*rinciple) may be divided into sections according to the demand that they should proceed quickly, unambiguously and with high yield, at least with respect to the noncyclic model reaction using substrates exhibiting only one function each.

Such reactions are found in nucleophilic substitutions at saturated and unsaturated C-atoms. Apart from these, only few reaction types have been applied to the synthesis of medium/large membered ring systems in diluted solution. They will be discussed later, as the aforementioned are considered more important.

The nucleophilic substitution reactions can be further split according to the type of the attacking nucleophile (S, O, N and C-nucleophile). Most of the many DP-reactions can be systematically ordered according to this scheme. We start with C—S-bond forming DP-reactions, because many detailed studies have been carried out in this field and so comparisons between reactions, dilutions and yields can be drawn easier than with other reaction types.

### II.1 Synthesis of Medio- and Macrocyclic Compounds by Formation of C—S-Bonds

Regarding ring closure reactions according to the dilution principle, including C—S-bond formation, only two sulphur delivering reagent types seem to have been

used: *sulfide ions* generated from $Na_2S \cdot 9\ H_2O$ or from thioacetamide, and on the other side, organic *thiols*. The latter are applied either as metal thiolates or as free thiols, which in situ form their metal salts in basic solutions. These methods have been used very often for the preparation of thiacycloalkanes, crown ether sulfides and thiaphanes.

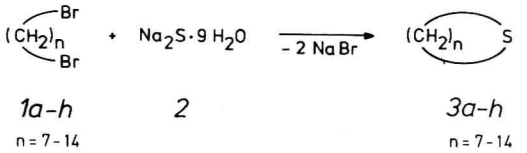
The one starting component (substrate) not containing sulphur in most cases is a mono- or oligohalogeno compound. Often preferably bromo compounds have been used instead of the chloro compounds, because the C—Br-bonds are usually more reactive and bromide is a better nucleofuge than chloride. There seem, however, to exist exceptions in which chlorides lead to higher yields than bromides (cf. references at the appropriate place in the text below).

## II.1.1 C—S-Bond Formation with $Na_2S \cdot 9\ H_2O$

### *II.1.1.1 Thiacycloalkanes*

The synthesis of thiacycloalkanes following the sodium sulfide method has been investigated only by a few groups [17–21] who prepared the eight- to fifteen-membered polymethylene sulfides principally according to the same two-component dilution principle reaction (2C-DP) [6a]:

Long-chain 1,ω-dibromo alkanes as a rule are cyclized with $Na_2S \cdot 9\ H_2O$ [21]:




Earlier works of Müller et al. [18] and Friedman and Allen [19, 20] show that this cyclization leading, e.g., to *3a–3h* can be carried out advantageously in a boiling solvent mixture (ethanol/water) of 2–5 l volume. The two starting components are dissolved in the same solvent mixture. Despite long addition times (15 hrs–2 days) and additional reaction times (2 hrs–11 days), the yields of the medium- and many-membered thiacycloalkanes *3a–3h* are rather low: 3–34% [18–20].

Today, thiacycloalkanes can be obtained in substantially higher yields [21], if dipolar aprotic solvents as e.g. DMF, DMSO or HMPT are used as reaction medium. Especially HMPT has turned out to be favourable for the synthesis of *3a–3h*. As an example, we here give in detail a typical experimental procedure for the preparation of thiacyclopentadecane *3h*:

Into a stirred solution of 70 ml HMPT, 2.00 g (5.61 mmole) of 1,14-dibromotetradecane (*1h*) and equimolar amounts of $Na_2S \cdot 9\ H_2O$ (*2*), dissolved in 15 ml of methanol each, are dropped by means of two dosing syringes. The addition is carried out over 2 hrs at 55 °C. At the same temperature, stirring is continued for 10 more minutes. After addition of 150 ml of $H_2O$, the reaction mixture is extracted with pentane for some hrs. The pentane extract is washed with $H_2O$ and the organic layer dried over $Na_2SO_4$. After evaporation of the solvent, the raw product is purified by chromatographing on a column filled with silica gel. A 1:9 mixture of $CHCl_3$/petroleum ether is used for elution. The thiacycle *3h* is obtained in 43% yield (mp = 71 °C) [21].

Due to lack of space, in all further examples below we cannot give a detailed description of typical experimental procedures. Instead, a short insight into the essentials of the procedure with data in the following abbreviated manner will be given:

*Experimental procedure for 1-thiacyclopentadecane (3h)* [21]:
starting components: a) 1,14-dibromotetradecane (*1h*) (5.61 mmole) in 15 ml of methanol
b) $Na_2S \cdot 9\,H_2O$ (*2*) (5.61 mmole) in 15 ml of methanol
reaction type: 2C-DP-reaction [6a]
reaction medium: HMPT (70 ml)
reaction temperature: 55 °C
time of addition: 2 hrs
additional reaction time: 10 min
yield: 43% of *3h*

The other thiacycloalkanes *3a–3g* also are obtained in higher yields in HMPT: 78% for *3a*, 48% for *3b*, 28% for *3c*, 22% for *3d*, 25% for *3e*, 27% for *3f* and 55% for *3g* [21]. Not only the change of the solvent, but also the more refined technical experimental procedure seems to be responsible for the raised yields.

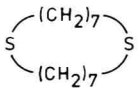
In the early 1950's, a dropping device had been developed specifically for ring closure reactions of thiacycloalkanes. It consisted of a lever made from a piece of yarn ("Wollfadenheber" [18b, 22]), with which the dropping rate could be regulated roughly under inert conditions. This proved to be necessary for $Na_2S$ solutions, as the sulfur containing precipitate, which is formed during the often very long dropping times leads to irregularities or to a standstill of dropping. 10–20 years later, more satisfying precision dropping funnels [6b, 23] and/or syringe apparatus [8, 24] were used widely in high dilution reactions as they allow a comfortable and safe continous and synchronous inlet of one or more components.

It has long been general knowledge that the ring formation tendency is dependent upon the number of ring members [4] and that this is reflected in the yields. In addition to the entropy effects [1b, c, f] in the formation of medium rings, a yield minimum is often observed, for which transanular interactions [1d, f, 25] can be made responsible. This phenomenon known as "medium ring effect" [1f, 26, 27], is revealed clearly in the synthesis of oligothiacycloalkanes *3d–3f* containing 11–13 ring members: The corresponding yields are 22, 25 and 27% [21].

In this context, studies of Friedman and Allen [19, 20] are interesting in which negative influences of the medium ring effect are intended to be suppressed by the so-called "geminal dimethyl effect" [19, 20, 28].

The geminal dimethyl substituents at the C(5)- and C(6)-atoms of the 1,9-dibromo-5,5-dimethylnonane, 1,10-dibromo-5,5-dimethyldecane and 1,11-dibromo-6,6-dimethylundecane should bring the long-chain alkanes into conformations favourable to cyclization. Compared with the unsubstituted cycloalkanes, synthesized under the same conditions, the yields of the substituted rings show remarkable yield increases: from 5.7 [20], 13.0 and 3% [19] to 34 [20], 22 and 23% [19]. The geminal dimethyl effect hence has a decisive influence on the tendency of formation for the medium membered polymethylene sulfides.

In ring closure reactions leading to 1-thiacyclooctane (*3a*) and -nonane (*3b*) carried out by A. Müller and coworkers [18b], besides the monomeric products also the dimeric ones *4* and *5* have been isolated. The former were obtained in yields of 34 and 6.6%, the dimers of 3.9 and 6.7% [18b].



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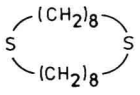

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It should be pointed out here that by use of the caesium effect [13,14], a breakthrough in the field of the synthesis of mediocyclic sulfides has been achieved.

*II.1.1.2 Crown Ether Sulfides*

Of the large number of crown ether sulfides [29,30,32] only a few have been synthesized by use of $Na_2S \cdot 9\ H_2O$. Detailed experimental discriptions have been worked out for the crown ether sulfides *6–10* [30–32]:

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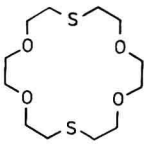

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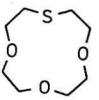

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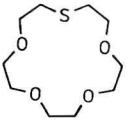

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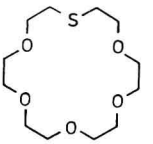

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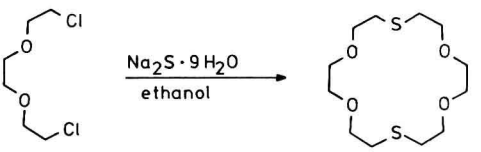
The cyclization reactions leading to these thiapolyethers exhibit some remarkable differences compared with the ring closure reactions yielding the thiacycloalkanes described in the previous Section II.1.1.1 [17–21]. In all syntheses of these medio/macrocyclic compounds open chained 1,ω-dichloro compounds are used as starting material, which is the only component. Dissolved in ethanol it is dropped into a certain volume of the same solvent [30,32]. This proceeding has been called one component dilution principle reaction (1C-DP) [6a]. One mole $Na_2S \cdot 9\ H_2O$ is used for one mole of dichloro compound and predissolved in a volume of 600–1000 ml of ethanol together with a small amount of base (e.g. NaOH). The latter is intended to neutralize the weak acidic reaction of the sulfide anion [32b] to prevent a possible splitting of labile ether bonds.

Without attention to the dilution principle [1a], Dann et al. [32a] isolated in the ring closure reaction of 1,8-dichloro-3,6-dioxaoctane (*11*) in ethanol/water (1:1) with $Na_2S \cdot 9\ H_2O$ exclusively the dimeric product 1,10-dithia-4,7,13,16-tetraoxacyclooctadecane (*7*) in 2.6% yield. The monomeric 4,7-dioxa-1-thiacyclononane (*6*) has not been found in this cyclization reaction. Carrying out this reaction with consideration of the dilution principle, the isolation of *6* (5%) is possible. Also the dimeric product *7* was found in 12% yield [30].

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The three other products have been isolated after a reaction time of 7–14 hrs in the following yields: *8*: 14%, *9*: 29%, *10*: 36% [30,32b].

A discussion and comparison of the yields of sulfur containing crown compounds will be given below, following the description of a further synthetic method, in Section II.1.4.1.

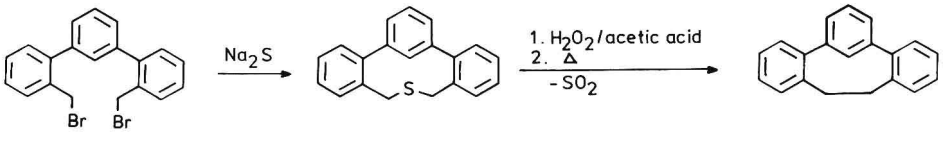
### *II.1.1.3 Thiaphanes*

Phane systems of all ring types have been synthesized with the goal to study their stereochemistry and ring strain [1e,33], the interaction between π-systems and the steric demand of intraanular substituents [34]. The importance of the synthesis of thiaphanes lies in the fact that they are easily available and in relatively high yields by ring closure reactions according to the dilution principle and that they are at the same time the cyclic precursors of the corresponding cyclophane hydrocarbons (carbaphanes). This can be achieved by extrusion of the sulfide sulfur which proceeds more easily than the extraction of N- and O-ring members. Several methods for sulfur extrusion are available: Stevens rearrangement [35], photo reaction of the sulfide in the presence of thiophilic phosphorous compounds [36] and the pyrolysis of the sulfone [37] which is easily obtained by oxidation of the sulfide.

Only a small number of the numerous thiaphane systems known today have been synthesized according to the $Na_2S$ method. This is due to the fact that only intramolecular ring closure reactions to monosulfides or only symmetrical many-membered oligosulfides [38] are possible through intermolecular reactions. The attempted synthesis of unsymmetric thiaphanes starting with two different 1,ω-dihalogeno compounds would necessarily yield a mixture of products (cf. Sect. II.1.4.2).

Nevertheless, different structural types of thiaphanes have been prepared using $Na_2S$: hetero- and heteracyclic [33,39] as well as single and morefold bridged [33,39] ring compounds are known. The synthesis can be divided into IC-DP- and 2C-DP-reactions [6a]. In most cases, dibromo compounds have been used as one of the starting components, the other being $Na_2S \cdot 9\,H_2O$, which is mostly dissolved in 50–95% ethanol/water; higher boiling apolar solvents have also been used.

2-Thia[3](2,2″)metaterphenylophane (*13*) [40a] was the first medium-membered monosulfide, which was submitted to the sulfone pyrolysis for ring contraction yielding the sulfur-free, strained[2](2,2″)metaterphenylophane (*14*) [40b].




*12* *13* *14*

The ring closure reaction yielding the sulfide *13* has been carried out in ethanol as reaction medium and as the solvent for the raw viscous fluid dibromo starting material. 11% of the wanted monomeric thiaphane *13* were isolated after 5 hrs addition time and 12 hrs additional reaction time [40a].

In the framework of studies on steric interactions in the interior of ring systems,