Acta Chemica Scandinavica B 31 (1977) 135—140

A New Synthesis of [2.2.2.2]Cyclophanetetraenes

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[2.2.2.2]Cyclophanetetraenes and some related compounds have been prepared in moderate yields, in a single step Wittig reaction performed at low temperature, from aromatic dialdehydes and bistriphenylphosphonium salts of bis(halomethyl)arenes. Some spectroscopic characteristics of the cyclophanes and their stereochemistry are briefly discussed.

Cyclophanes or more generally phanes [1] are the common names for large ring compounds in which an aromatic nucleus is a part of the ring. The numbers in brackets give the length and number of bridges between the aromatics.

A large number of cyclophanes have been synthesised and studied for various reasons. Much of the work has been concerned with the stereochemistry and dynamic behaviour of small cyclophanes, interactions and deformations of benzene rings in small and strained cyclophanes [2–4] and photoisomerisation of unsaturated cyclophanes to annulenes.[5] Larger cyclophanes have properties as potential cage compounds or multidentate ligands if properly substituted. Size, shape and other properties of the cavity in the center of larger cyclophanes also depend on their stereochemical and conformational behaviour.

Previously we have reported that 1,4-benzenedicarbaldehyde and the bistriphenylphosphonium salt of 1,4-bis(bromomethyl) benzene gave [2.2.2.2]paracyclophanetetraene, *1*, (15 %) in a Wittig reaction at −40 °C in dimethylformamide (DMF) with lithium ethoxide as base.[6] In order to get a total yield of 15 %, statistically 60 % of the double bonds formed must have *cis* configuration.

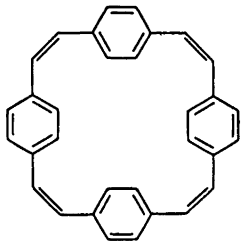
In this paper we describe the application of the above method to the synthesis of some new [2.2.2.2]cyclophanetetraenes and related compounds.

RESULTS AND DISCUSSION

The Wittig reaction has been successfully used for the preparation of a variety of large ring compounds.[7] However, this reaction has some inherent limitations for the synthesis of cyclic compounds. The initial reaction between the ylid and the carbonyl group to form a betain is reversible. Thus the linear unstrained products are favoured over cyclic strained ones. It is also of prime importance to control the *cis*/*trans* ratio. Selective formation of *cis* double bonds, which in part can be achieved by careful control of the reaction conditions, favours the ring formation over open-chain oligomerisation. The yield, however, will always suffer from incomplete *cis*-selectivity.

Substituents in either the dialdehyde or the bisphosphonium salt appear to decrease the yield of [2.2.2.2]paracyclophanetetraenes when prepared by the Wittig reaction. Thus, 1,4-benzenedicarbaldehyde and the bisphosphonium salt of 1,4-bis(bromomethyl)-2-iodobenzene gave diiodo[2.2.2.2]paracyclophanetetraene, *3*, in 10 % yield.[8] The same dialdehyde and the bisphosphonium salt of 1,4-bis(bromomethyl)-2,5-dibromobenzene gave a 10 % yield of tetrabromo[2.2.2.2]paracyclophanetetraene, *2*, whereas 2,5-dibromobenzene-1,4-dicarbaldehyde and the bisphosphonium salt of 1,4-bis(bromomethyl)benzene gave a 9 % yield of the same product, *2*.

Heterocyclic dialdehydes also react with the bisphosphonium salt to form [2.2.2.2]cyclo-



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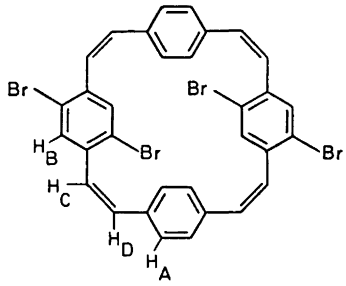

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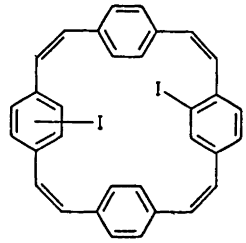

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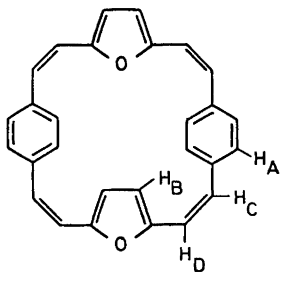
phanetetraenes under the same reaction conditions. 2,5-Furandicarbaldehyde reacts with bisphosphonium salt of 1,4-bis(bromomethyl) benzene to give [2](2,5)furano[2]paracyclo[2]-(2,5)furano[2]paracyclophanetetraene, *4*, in 10 % yield and some larger cyclophanes with three furan and three benzene nuclei bridged by six double bonds in 15 % yield. 2,5-Thiophenedicarbaldehyde reacts analogously to give 4 % of [2](2,5)thiopheno[2]paracyclo[2](2,5)-thiopheno[2]paracyclophanetetraene, *5*, together with some larger cyclophanes. 1,4-Benzenedicarbaldehyde and the bisphosphonium salt of 2,5-bis(chloromethyl)thiophene give a somewhat better yield, 10 %, of the same cyclophane, *5*, under similar conditions. The cyclophanetetraenes *4* and *5* are light-sensitive and must be protected from light. The relatively poor yields of the cyclophanetetraenes *4* and *5* may be due in part to their decomposition



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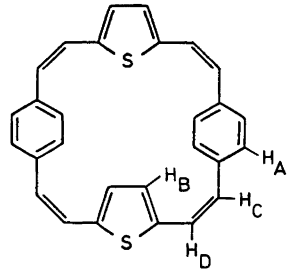

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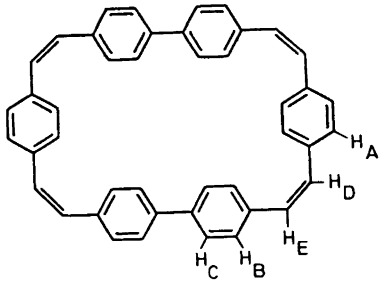

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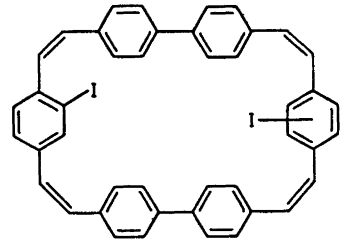

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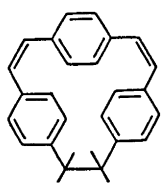
during workup.

The method has also been extended to the synthesis of larger cyclophanes. 4,4′-Biphenyldicarbaldehyde reacts with the usual bisphosphonium salt of 1,4-bis(bromomethyl)benzene under the standard conditions to give 15 % of [2.2.0.2.2.0]paracyclophanetetraene, *6*. The product shows an intense fluorescence on irradiation with UV light. The corresponding reaction with the bisphosphonium salt of 1,4-bis-(bromomethyl)-2-iodobenzene gave a lower yield (4.5 %) of diiodo[2.2.0.2.2.0]paracyclophanetetraene, *7*.[9]

In an attempt to prepare smaller cyclophanes we reacted 4,4′-bibenzyldicarbaldehyde with the bisphosphonium salt of 1,4-bis(bromomethyl)benzene. No [2.2.2]paracyclophanediene, *8*, was observed among the products. Instead a high-melting solid which showed the simple NMR spectrum expected from [2.2.2]paracyclophanediene, was isolated in 9 % yield. Combined information from mass and NMR spectra showed it to be [2.2.2.2.2.2]paracyclophanetetraene, *9*, with four *cis* double bonds. The cyclophane *9* was hydrogenated to [2.2.2.2.2.2]-paracyclophane, *10*. This route to [2.2.2.2.2.2]-paracyclophane gives an improved yield over the previous method [10b] and should allow some variation of substituents in the product. Known methods for the synthesis of [2_n]cyclophanes ($n \geq 3$) use a bis(chloromethyl)benzene and sodium in the presence of tetraphenylethylene.[10] The isolation of the products involves a tedious separation of cyclophanes of different ring sizes. The method is also of limited use for the preparation of substituted cyclophanes. A few attempts to prepare [2.2.2.2]cyclophanetetraenes by the Wittig reaction from simple starting materials have also been reported.[11–13]

Planarity and stereochemistry. [2.2.2.2]Paracyclophanetetraene, *1*, can be regarded as a cyclooctatetraene with benzene rings inserted into the single bonds. Simple molecular models of [2.2.2.2]paracyclophanetetraene show the molecule to be non-planar as is cyclooctatetraene. However, because of the size of the molecule, small distortions in bond angles and bond lengths could flatten the molecule. If the molecule is close to planar and exposed to a strong magnetic field, an induced paramagnetic shielding of the outer protons and deshielding of the inner protons would be expected.[14] As the outer and inner aromatic protons are equivalent on the NMR time scale, the net effect of an induced paramagnetic "ring current" over the entire molecule would only affect the chemical shift for the olefinic protons. These are expected to be located outside the ring.



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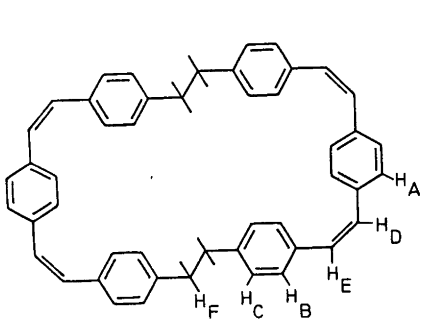

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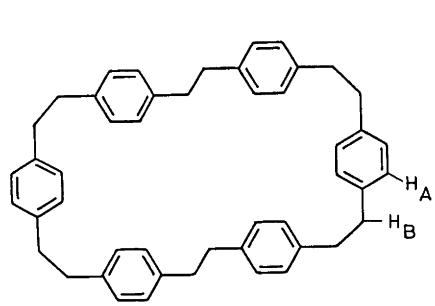

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The experimental value for the chemical shift, δ 6.45, is quite close to that of the olefinic protons in *cis*-stilbene, δ 6.53.[15] The UV spectrum of [2.2.2.2]paracyclophanetetraene does not give any conclusive information about planarity, although the maximum shows a red shift of 23 nm relative to that of *cis*-stilbene.[16] A full solution of the problem must await a complete structural determination. This is being done by an X-ray method.

A non-planar structure of [2.2.2.2]paracyclophanetetraene with rapidly rotating benzene rings, still has two mirror planes and three perpendicular C_2-axes of symmetry, one of which coincides with an S_4-axis. The non-planar molecule thus belongs to symmetry point group D_{2d}. The cyclophanes *2*, *4*, *5*, and *6* in which the aromatic rings are pairwise identical have no mirror planes of symmetry of S_4-axes but still three perpendicular C_2-axes. They all belong to the rare symmetry point group D_2.

The hetero[2.2.2.2]cyclophanetetraenes *4* and *5* can adjust towards more planar conformations than cyclophane *1*, with the heteroatoms pointing outwards from the center of the ring. This is even more pronounced in [2.2.2.2](2,5)-thiophenophanetetraene and [2_4(2,5)furano[2]-(2,5)thiopheno[2] (2,5)furano[2] (2,5)thiophenophanetetraene.[17] The NMR spectra of these cyclophanes indicate that a small paramagnetic shielding of the outer protons and deshielding of the inner protons occur in a strong magnetic field and thus the molecules can attain near planar conformations. The UV spectra show a red shift of the maxima on changing the benzene rings for thiophene or furane rings in [2.2.2.2]paracyclophanetetraenes. This is also consistent with existence of near planar conformations with delocalisation of π-electrons in hetero[2.2.2.2]cyclophanetetraenes.

Mass spectra. The mass spectra of [2.2.2.2]-cyclophanetetraenes and related compounds show the high stability of the ring systems on ionisation. The typical fragmentation reactions are the loss of hydrogens and halogens, if present. This could occur accompanied by the formation of new six-membered rings, equivalent to the photochemical ring closure of *cis*-stilbenes. Doubly charged and sometimes triply charged ions are frequent and contribute substantially to the total ion current.

Conclusions. The new method described above for the synthesis of [2.2.2.2]cyclophanetetraenes and related compounds from the readily available dialdehydes and bisphosphonium salts is simple. It can conveniently be employed for the synthesis of many cyclophanes which are interesting intermediates for the preparation of circulenes, annulenes, helicenes, and aromatic cage compounds. Some cyclophanes may also be used as ligands for transition metals.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage apparatus. UV spectra in cyclohexane were recorded with a Beckman DK-2A, MS with a AEI MS 902, IR spectra in KBr with a Beckman IR 9 and NMR spectra in $CDCl_3$ with a Varian A 60 or a Bruker WH 270.

Phosphonium salts. The bistriphenylphosphonium salt from 1,4-bis(bromomethyl)benzene was prepared by the standard procedure.[18] The bistriphenylphosphonium salt from 1,4-bis(bromomethyl)-2,5-dibromobenzene was prepared from triphenylphosphine and 1,4-bis-(bromomethyl)-2,5-dibromobenzene. The latter was prepared by bromination of 2,5-dibromo-1,4-dimethylbenzene with bromine in tetrachloromethane (30 %, m.p. 161–162 °C). ^{1}H NMR: δ 7.75 (2 H, s) and 4.55 (4 H, s). Analysis: C, H and Br. The bisphosphonium salt from 2,5-bis(chloromethyl)thiophene was prepared by the standard procedure from triphenylphosphine and 2,5-bis(chloromethyl)-thiophene [19] in dry dimethylformamide (DMF) at 110 °C. All phosphonium salts were carefully dried under vacuum at 110 °C before use.

Aldehydes. Commercial 1,4-benzenedicarbaldehyde was recrystallised before use. 2,5-Furandicarbaldehyde was prepared from sucrose and hydrochloric acid which gave 5-chloromethylfuran-2-carbaldehyde. A Sommelet reaction gave the desired 2,5-furandicarbaldehyde.[20] 2,5-Thiophendicarbaldehyde was prepared from 2,5-dibromothiophene, butyllithium and DMF or conveniently from 2,5-bis(chloromethyl)thiophene.[21] 2,5-Dibromobenzene-1,4-dicarbaldehyde was prepared by tetrabromination of 2,5-dibromo-1,4-dimethylbenzene with *N*-bromosuccinimide in tetrachloromethane to give 1,4-bis(dibromomethyl)-2,5-dibromobenzene which on mild hydrolysis gave 2,5-dibromobenzene-1,4-dicarbaldehyde (m.p. 170 °C). 4,4′-Biphenyldicarbaldehyde [22] was prepared from 4,4′-dibromobiphenyl,[23] butyllithium and DMF (55 %, m.p. 142–144 °C). 4,4′-Bibenzyldicarbaldehyde was prepared from 4,4′-dibromobibenzyl [23], butyllithium and DMF (62 %, m.p. 125–127 °C).

Wittig reaction, general procedure. The Wittig reactions were run in a three-necked flask equipped with a mechanical stirrer, a nitrogen inlet tube and a dropping funnel with a pressure-equalising side arm. The flask was immersed into a thermostated cold bath. The aldehyde and the phosphonium salt were dissolved or suspended in dimethylformamide, purified by azeotropic distillation with 10 % benzene and then from calcium hydride. The reaction vessel was flushed with nitrogen and a slow stream of nitrogen was maintained during the reaction which was usually conducted at −35 or −40 °C. A freshly prepared solution of lithium ethoxide in ethanol (0.2–0.3 M) was added dropwise in such a way that the coloured ylid was allowed to be consumed between successive additions. The total reaction time varied from a few hours to several days. When no colour change was observed on addition of the base, the reaction mixture was warmed to room temperature and diluted with an equal volume of water. A yellow sticky precipitate was usually formed. The mixture was extracted with diethyl ether three times and the ether extract was then washed with water several times, dried over sodium sulfate and the solvent distilled. The yellow to red residue contained, besides the desired cyclophanes, a large proportion of triphenylphosphine oxide which in a few cases was removed by extraction with warm ethanol. The cyclophanes were separated by chromatography on silica gel (Merck Kieselgel 60, 70–230 mesh ASTM) with tetrachloromethane as eluent. The first fractions usually gave pure [2.2.2.2]cyclophanetetraenes on evaporation and recrystallisation from tetrachloromethane/methanol. The subsequent fractions gave a mixture of *cis* and *trans* isomers of [2.2.2.2.2.2]cyclophanehexaenes as apparent from their simple MS and complex ^{1}H NMR spectra.

Tetrabromo[2.2.2.2]paracyclophanetetraene, 2. To a suspension of 2,5-dibromobenzene-1,4-dicarbaldehyde (3 mmol) and the bistriphenylphosphonium salt from 1,4-bis(bromomethyl)-benzene (3 mmol) in DMF (250 ml) at −40 °C, was added lithium ethoxide in ethanol. The addition required *ca.* 24 h. Subsequent to work-up and purification as described under general procedure, there was obtained tetrabromo-[2.2.2.2]paracyclophanetetraene, *2*, (100 mg, 9 %, m.p. 284–286 °C) as the first yellow compound. IR: cm^{-1} 1503 (m), 1460 (m), 1410 (m), 1340 (m), 1052 (s), 960 (m), 890 (s) and 738 (m). ^{1}H NMR: δ 7.43 (4 H, s), 6.96 (8 H, s), 6.59 (4 H, d) and 6.50 (4 H, d, J 12 Hz). MS (70 eV): *m/e* 728 (20 %), 727 (22), 726 (70), 725 (35), 724 (100), 723 (25), 722 (67), 566 (15), 564 (30), 562 (15), 484 (12), 482 (12), 405 (25), 404 (73), 403 (18), 402 (22), 401 (18), 400 (20), 399 (12), 398 (15), 202 (40), 201.5 (15), 201 (30), 200.5 (20), 200 (40), 199.5 (12) and 199 (25). UV: nm 295 (log ε = 4.71).

The analogous reaction between 1,4-benzenedicarbaldehyde (3 mmol) and the bis triphenylphosphonium salt from 2,5-dibromo-1,4-bis-(bromomethyl)benzene (3 mmol) in DMF (250 ml) at −40 °C gave the same product, tetrabromo[2.2.2.2]paracyclophanetetraene, *2*, (110 mg, 10 %) after the usual work-up procedure.

[2](2,5)Furano[2]paracyclo[2](2,5)furano[2]-paracyclophanetetraene, 4. To a suspension of 2,5-furandicarbaldehyde (35 mmol) and the bis triphenylphosphonium salt from 1,4-bis-(bromomethyl)benzene (35 mmol) in DMF (600 ml) at −40 °C was added lithium ethoxide in ethanol. The addition required *ca.* 55 h. The usual work-up followed by purification by column chromatography gave cyclophane *4* (710 mg, 10.5 %, m.p. 242 °C) as the first yellow compound. IR: cm^{-1} 1182 (m), 1030 (s), 960 (s), 800 (s). ^{1}H NMR: δ 7.08 (4 H, s, H_A), 6.41 (2 H, s, H_B), 6.34 (2 H, d, H_C) and 6.21 (2 H, d, H_D, J_{CD} 12.7 Hz). MS (70 eV): *m/e* 388 (100 %), 196 (12.5). UV: nm 385 (sh), 345 (sh), 320 (log ε = 4.68) and 250 (4.60). Analysis: C, H, O.

Later fractions from the column gave an orange solid (1.04 g, 15 %) believed to be a mixture of larger cyclophanes, mainly isomers of [2](2,5)furano[2]paracyclo[2](2,5)furano[2]-paracyclo[2](2,5)furano[2]paracyclophanehexaene. The ^{1}H NMR spectrum was very complex but the MS showed the base and parent peak at *m/e* 582. The IR spectrum was similar to that of cyclophane *4* with broadened peaks at 1022 (s), 958 (s), 810 (sh) and 795 (s) cm^{-1}.

[2](2,5)Thiopheno[2]paracyclo[2](2,5)thiopheno[2]paracyclophanetetraene, 5. To a suspension of 1,4-benzenedicarbaldehyde (10 mmol) and the bistriphenylphosphonium salt from 2,5-bis(chloromethyl)thiophene (10 mmol) in DMF (250 ml) at −35 °C was added a solution of lithium ethoxide in ethanol over a period of 75 h. After the usual isolation and separation operations, cyclophane *5* (160 mg, 8 %, m.p. 257–259 °C) was obtained as a yellow compound. The corresponding Wittig reaction between 2,5-thiophenedicarbaldehyde (5 mmol) and the bis triphenylphosphonium salt from 1,4-bis(bromomethyl)benzene (5 mmol) in DMF (200 ml) at −40 °C with lithium ethoxide as base gave, after the usual isolation and separation, the same cyclophane *5* (40 mg, 4 %). IR: cm^{-1} 1617 (m), 1402 (m), 1392 (m), 1200 (m), 882 (s) and 797 (s). ^{1}H NMR: δ 7.24 (4 H, s, H_A), 6.80 (2 H, s, H_B), 6.55 (2 H, d, H_C or H_D) and 6.38 (2 H, d, H_D or H_C, J_{CD} 11.8 Hz). MS (70 eV): *m/e* 420 (100 %). UV: nm 335 (log ε = 4.49) and 276 (4.59). Analysis: C, H, S.

[2.2.0.2.2.0]Paracyclophanetetraene 6. To a suspension of 4,4′-biphenyldicarbaldehyde (5 mmol) and the bistriphenylphosphonium salt from 1,4-bis(bromomethyl)benzene (5 mmol) in DMF (250 ml) at −40 °C was added a solution of lithium ethoxide in ethanol. The addition required *ca.* 50 h. After the usual isolation, the solvent was distilled and the pale yellow residue

was extracted with warm ethanol to remove triphenylphosphine oxide. The residue was recrystallised from tetrachloromethane to give [2.2.0.2.2.0]paracyclophanetetraene *6* (208 mg, 15 %, m.p. 246–248 °C). IR: cm^{-1} 1600 (m), 1495 (s), 1412 (m), 892 (s), 830 (s), 748 (s). ^1H NMR: δ 7.50 (4 H, d, H_B or H_C), 7.39 (4 H, d, H_C or H_B, J_{BC} 8 Hz), 7.24 (4 H, s, H_A) and 6.60 (4 H, s, H_D and H_E). MS (70 eV): *m/e* 560 (100 %), 559 (2), 281 (4), 280.5 (4), 280 (8), 279 (4), 278 (4), 277 (4) and 276 (4). UV: nm 312 (log $\varepsilon = 4.79$).

[*2.2.2.2.2.2*]*Paracyclophanetetraene* 9. To a suspension of 4,4'-bibenzyldicarbaldehyde (10 mmol) and the bistriphenylphosphonium salt from 1,4-bis(bromomethyl)benzene (10 mmol) in DMF (250 ml) at −40 °C was added a solution of lithium ethoxide in ethanol. The addition required *ca.* 30 h. The usual isolation and separation gave the pale yellow all-*cis* [2.2.2.2.2.2]paracyclophanetetraene *9*, (280 mg, 9 %, m.p. 262–264 °C) as the first compound. ^1H NMR: δ 7.21 (4 H, d, H_C or H_B), 7.17 (4 H, s, H_A), 7.08 (4 H, d, H_B or H_C, J_{BC} 8 Hz), 6.57 (2 H, d, H_D or H_E), 6.52 (2 H, d, H_E or H_D, J_{DE} 12.5 Hz) and 2.85 (4 H, s, H_F). MS (70 eV): *m/e* 616 (100 %), 512, 308, 205. UV: nm 337 (log $\varepsilon = 4.50$), 280 (4.29, sh) and 237 (4.43). Analysis: C, H.

The cyclophane *9* was quantitatively hydrogenated over palladium on charcoal in benzene (1 atm., 25 °C, 24 h) to give [2.2.2.2.2.2]-paracyclophane,[10b] *10*, (m.p. 211–213 °C). ^1H NMR: δ 6.83 (1 H, s, H_A) and 2.85 (1 H, s, H_B).

Acknowledgements. We thank the Swedish Natural Science Research Council for financial support and one of us, B.C., the UNESCO and the Swedish Institute for a generous scholarship and support.

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Received September 6, 1976.