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MACROCYCLES FROM BIFUNCTIONAL 1,2-BIS(STYRYL)BENZENES AND SOME AZA ANALOGUES [1)]

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Dedicated to Professor T.Nozoe
on the occasion of his 77th birthday

The diamines 1-3 and the dialdehyde 4 have been synthesized. From these compounds the macrocycles 6, 7, 9, 10, 14 and 15 have been obtained. Fundamental aspects of cyclisation reactions of this type are discussed.

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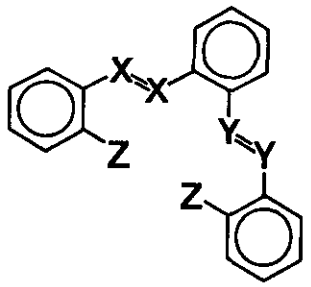
1) Macrocyclic Aza Compounds VI. Part V: Ehrensperger, Heberlein and Skrabal [1].

1. Introduction

Our interest in macrocyclic aza compounds, such as 5, has been discussed in previous papers [2] [3]. For the synthetic approach to such macrocycles, the cyclisation of bifunctional phenylazo- and styrylbenzene derivatives was chosen. To this end we have synthesized the diamines 1-3 and the dialdehyde 4 [1] [2]. In the present paper we discuss fundamental aspects of the cyclisation of these compounds.



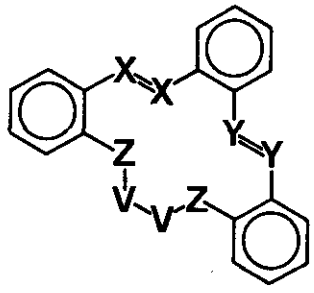
	1	2	3	4
X	N	CH	CH	CH
Y	N	N	CH	CH
Z	NH_2	NH_2	NH_2	CHO

2. Cyclisation Reactions

We found that 1,2-bis(2-aminophenylazo)benzene (1) does not cyclise to 5 with either aqueous or monomeric glyoxal (in anhydrous solvents), but rearranges or decomposes [2]. Cyclisation of 1 with 1,2-cyclohexadione was also unsuccessful. However, with the more reactive oxalyl chloride the macrocycle 6 is obtained in 18% yield. These results indicate a low reactivity of the amino groups in 1 which we attribute to deactivation by the phenylenebisazo group [4].

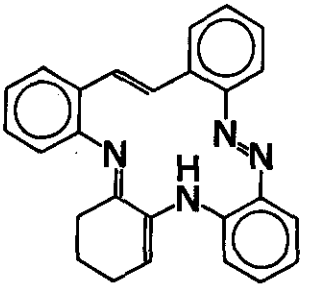
In the template reaction of diamine 1 with glyoxal in the presence of Ni^{II}-, Co^{II}- or Cu^{II}-salts a fast and quantitative formation of the complexes with the diamine is observed. The complexes of 1 do not cyclise under mild conditions, and decompose under vigorous conditions. This is likely to be due to the expected lower reactivity of the amino functions in the complexes vs. the free diamine.

In an alternative route to 5 the tetrahydro derivative 7 can be obtained from the reaction of 1 with 1,2-dibromoethane in 6% yield [5]. However, our attempts to oxidize 7 to 5 have so far been unsuccessful.



	5	6	7	8	9
X	N	N	N	CH	CH
Y	N	N	N	CH	CH
Z-V	N=CH	NH-CO	$NH-CH_2$	N=CH	CH=N

Similar to the situation found for 1, 2-amino-2'-(2-aminophenylazo)stilbene (2) does not cyclise with glyoxal and derivatives, but decomposes. Nevertheless, from its reaction with 1,2-cyclohexadione the macrocycle 10 and the 1:1 condensation product 11 have been obtained [1]. Since 11 could not be cyclised to 10 we propose that cyclisation to 10 proceeds via the intermediate 12. Since the amino group in position ortho to the vinyl group is the more reactive one in diamine 2, compound 11 is probably formed to a larger extent than 12. On the other hand, 12 - whenever formed - will cyclise more readily than 11.



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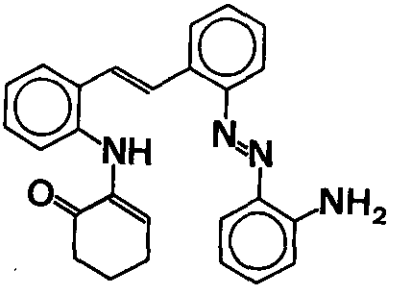

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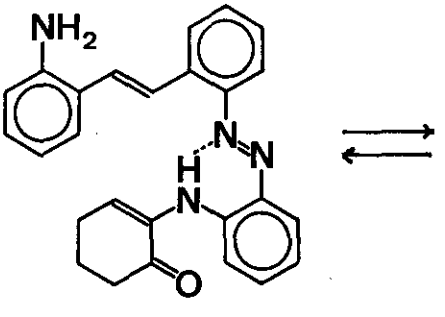

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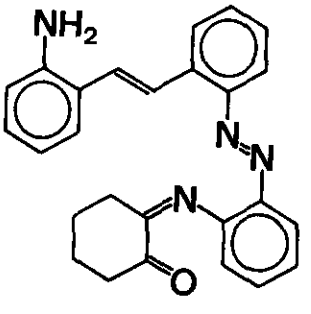

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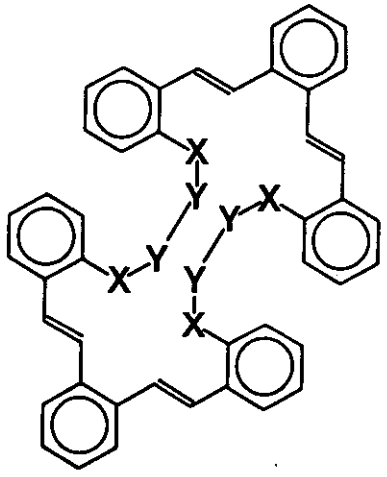
From the reaction of 1,2-bis(2-aminostyryl)benzene (3) and monomeric glyoxal in toluene the 28-membered macrocycle 14 is obtained in ca. 80% yield. Several experiments - inter alia addition of o-phenylenediamine to the reaction mixture or to isolated 14 under reaction conditions gives a quantitative yield of quinoxaline - suggest that 14 is formed by a thermodynamically controlled reaction. By reduction of 14 with lithium aluminium hydride the octahydro derivative 15 can be obtained.

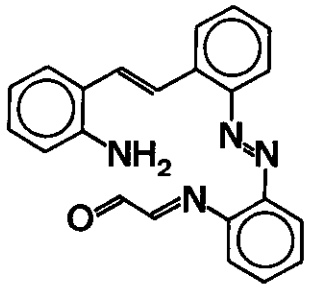
Condensation of 1,2-bis(2-formylstyryl)benzene (4) with hydrazine hydrate gives 82% of the 14-membered macrocycle 9 and only traces of the 28-membered 2:2 reaction product 16.



	14	15	16
X-Y	N=CH	$NH-CH_2$	CH=N

3. Conclusions

The cyclisations of diamine 2 with 1,2-cyclohexadione and diamine 3 with glyoxal demonstrate the enhanced reactivity of 2 and 3 compared to diamine 1.



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In the comparison of glyoxal with cyclohexadione as cyclisation reagents for diamine 2, a point of interest concerns the accessibility of the trajectory for the nucleophilic addition of the amino to the carbonyl group [6] in the intermediates 12 (or 11) and 17. Molecular models demonstrate that in 12 as well as in 17 the amino group can approach the carbonyl group in nonplanar conformations. In 12, however, there is considerable steric hindrance between the cyclohexadienone moiety and the benzene rings. Thus, not only from the point of view of reactivity, but also for steric reasons, cyclisation should be favoured with glyoxal. Among numerous reasons to account

for the opposite observation, the predominance of the hydrogen bonded conformation 12 in the tautomeric equilibrium 12 ⇌ 13 may be invoked.

The cyclisation results with diamine 3 and dialdehyde 4 - formation of the 28- and 14-membered macrocycles 14 and 9, respectively - are likely to be consequences of the thermodynamically and kinetically controlled reactions of 3 and 4, respectively. In contrast to azomethine bonds the azine bonds in 9 are stable under reaction conditions.

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