New Trends in the Chemistry of Condensed Heteromacrocycles Part B: Macrocyclic Formazans

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This review article, covering the literature from 1979 to 2002, deals with the main strategies for the synthesis of macrocyclic crown formazans as well as their specific syntheses. Reactivities and applications of these compounds are also in focus.

Contents

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Introduction.

Heteromacrocycles are compounds that contain twelve or more members and they are aliphatic rather than aromatic. They generally complex cations internally using four or more donor groups to stabilize the Lewis acid. The major motivation for the synthesis of novel structures of heteromacrocycles has been to develop complexing agents.

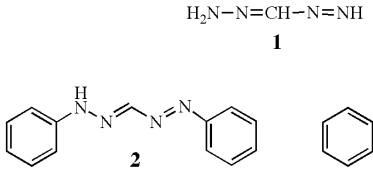
Since Pedersen [1] discovered crown ethers in 1967, which represent a class of heteromacrocycles, there has been great interest in the synthesis of crown compounds in an attempt to find molecules with superior properties and proper applications in various areas. For this purpose, many classes of heteromacrocycles for example, azacrown ethers [2-5], cryptands [6,7], spherands and calixarenes [8], have been prepared and their applications have been studied and reviewed.

Our first review [5] (Part A) focused on the main strategies for the synthesis of condensed azacrown ethers as well as their reactivities and applications. This review cast light on the chemistry and applications of macrocyclic crown formazans. In the last decades crown formazans have attracted much attention due to their wide range of

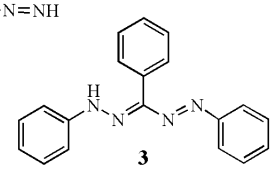
applications in selective metal extraction [9-12] and identification [13-25].

Most of the macrocyclic formazans are dark violet crystalline substances. They are insoluble in water but are readily soluble in organic solvents. Introduction of the crown ether fragments into the molecule increases the solubility in methanol and diethyl ether [26]. Macrocyclic effect was also found to increase the chromatographic mobility and thermal stability of the crown formazans compared with their open chain analogues [26].

Nomenclature.



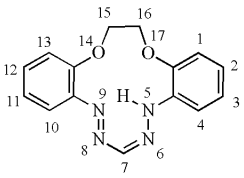
1,5-diphenylformazan



1,3,5-triphenylformazan

The compound **1** is named formazan and its derivatives **2**, **3** are named as substitution products with numerical locants as indicated.

Macroheterocycles that contain a rigid formazan block with one carbon and four nitrogen atoms linked in a cyanine like system and a flexible crown-like bridge, which consists of oligo-oxyethylene or oxypropylene units, are given the name "crown formazans". Crown formazan **5** with a cyano group directly attached to the formazyl carbon is called cyanocrown formazan or TMC-crown formazan [15,16,20]. Crown formazan **6** is called phenylcrown formazan or TMF-crown formazan [27]. On the other hand, crown formazan **7** with two nitro substituents on the benzene rings is called NTM-crown formazan [17-19]. To avoid confusion with literature as for as possible IUPAC names for all the representative examples are also given.

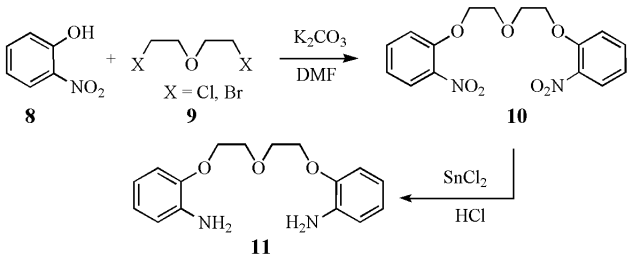


Crown formazan
IUPAC Name: 15,16-Dihydro-5*H*-dibenzo[*b,i*][1,11,4,5,7,8]dioxatetraazacyclotridecine

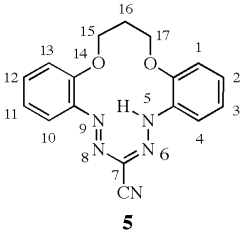
Macrocyclic Crown Formazan Precursors.

The preparation of macrocyclic formazans requires the preparation of the appropriate amine precursors. The nitro group has been used successfully as an amine precursor in the preparation of crown formazans. Thus, 2-nitrophenol (**8**) is treated with diethylene glycol dihalides **9** and K_2CO_3 in DMF [28,29]. The resulting dinitro derivative **10** is subsequently reduced with stannous chloride and acid to give the diamine **11** (Scheme 1).

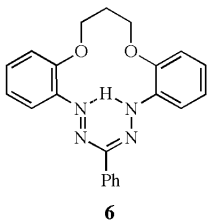
Scheme 1



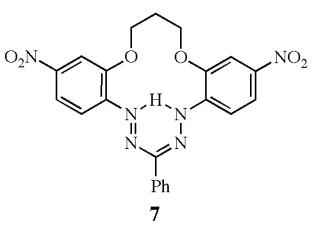
1,ω-Bis(2-aminophenoxy)alkanes **16** needed in the synthesis of macrocyclic crown formazans could be obtained as the dihydrochloride salt by first reacting *o*-acetamidophenol **12** with the appropriate dihalides, ditosylates **13** or epichlorohydrin (**14**) in ethanol containing sodium ethoxide or K_2CO_3 in DMF to give the corresponding bis-acetamido derivatives **15**. Hydrolysis of the latter with



Phenylcrown formazan
TMF-crown formazan
IUPAC Name:
16,17-dihydro-5*H*,15*H*-dibenzo[*b,i*][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile



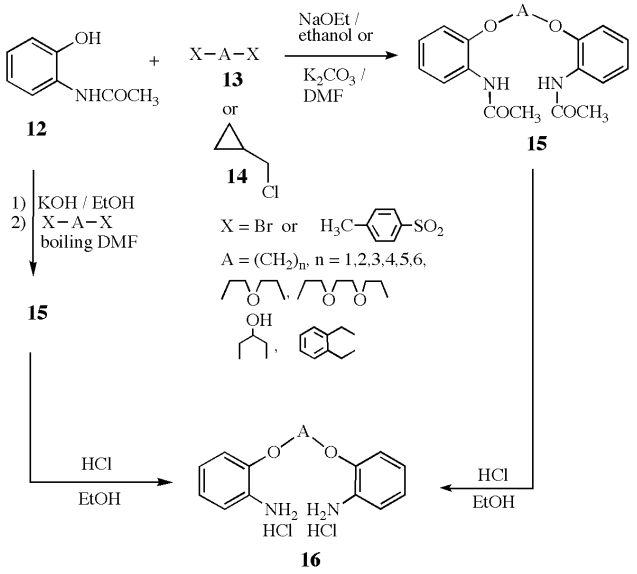
Cyanocrown formazan
TMC-crown formazan
IUPAC Name:
16,17-dihydro-5*H*,15*H*-7-phenyldibenzo[*b,i*][1,11,4,5,7,8]dioxatetraazacyclotetradecine



NTM-crown formazan
IUPAC Name:
16,17-dihydro-2,12-dinitro-5*H*,15*H*-7-phenyldibenzo[*b,i*][1,11,4,5,7,8]dioxatetraazacyclotetradecine

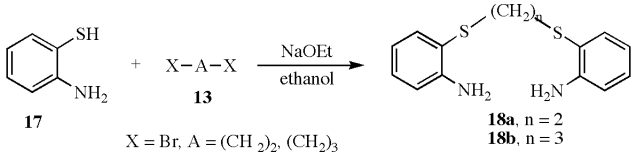
hydrochloric acid in ethanol gave the corresponding dihydrochlorides **16** in quantitative yield. Compounds **15** could also be synthesized by reacting the potassium salt of **12** (obtained upon treatment of 2-acetamidophenol **12** with ethanolic KOH) with dihalides or ditosylates in boiling DMF [16,22,24,30] (Scheme 2).

Scheme 2



On the other hand, 1,ω-bis(2-aminophenylsulphonyl)-alkanes **18a,b** were obtained by reacting the deprotected 2-aminothiophenol **17** directly with the appropriate dihaloalkanes **13** in ethanol containing sodium ethoxide [31,32] (Scheme 3).

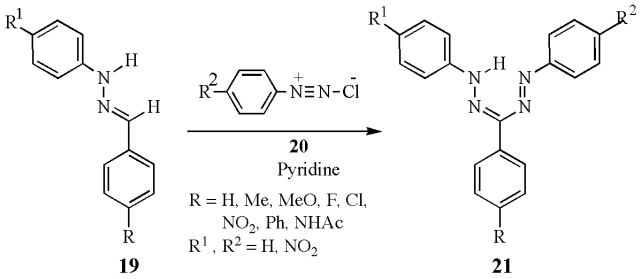
Scheme 3



Main Strategies for Preparation of Crown Formazans.

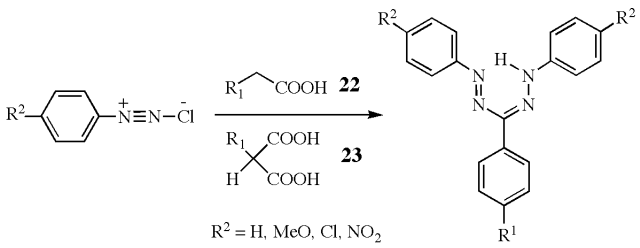
In general, two strategies have been reported for the synthesis of formazans [33]. The first comprises the azo-coupling of diazonium salts **20** with aldehyde arylhydrazones **19** in strongly basic medium. It allows access to both symmetrically and unsymmetrically *N,N'*-disubstituted formazans **21** and is the only general method for preparation of the 1,3,5-triarylformazans. With some exceptions, most yields are poor to moderate and isolation is tedious. The toxicity of the pyridine solvent used seriously limits scale up (Scheme 4).

Scheme 4



The second strategy based on the coupling of diazonium salts **20** with active methylene **22** or methine compounds **23**. This leads to symmetrically *N,N'*-disubstituted formazans **24** (Scheme 5). Yields depend strongly on the type of substituents at the active methylene group (nitro, carboxy or cyano derivatives are often employed).

Scheme 5

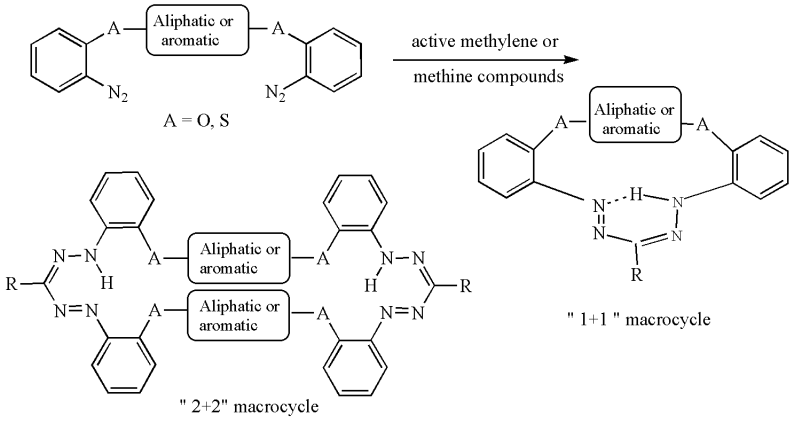


22, R^1 = CN, $COCH_3$, $PhSO_2$, *p*-$CH_3C_6H_4SO_2$, **23**, R^1 = Ph, *p*-$O_2NC_6H_4$

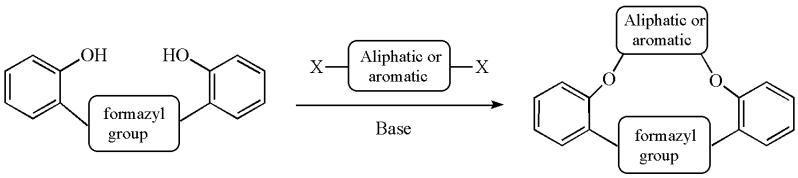
The final products are either arylhydrazones or formazans. The latter is produced if one of the substituents at the reaction center of the hydrazone formed is expelled by a second molecule of the diazonium compound [34]. The basicity of the medium, ratio of reagents and type of substituents play a key role in this reaction. Most of the reported macrocyclic crown formazans have been preparaed using the second strategy. The macrocyclization were performed by coupling of the appropriate bis-diazonium salts with the corresponding active methylene or methine compounds. Reacting species containing heteroatom and aliphatic as well as aromatic fragments (between interacting centers) have been used for cyclization (Scheme 6).

The reaction was carried out either in the absence or presence of metal ions. The latter can serve to direct the coupling reactions preferentially to cyclic rather than hydrazones and/or polymeric products [35]. The reaction proceeds to give "1+1" macrocyclic and/or "2+2" macrocycles [31,36].

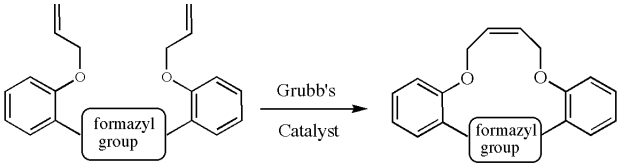
Scheme 6



Scheme 7



Scheme 8



Cyclizations are possible using functional groups at each end where the formazyl groups are in the center of the starting bis-functional materials (Scheme 7,8) [37,38].

The problems encountered in the synthesis of macrocyclic crown formazans are those typical of reaction forming large rings namely low yield and polymerization. In general the yields of the macrocyclic formazans decrease with increase in the size of the macrocycles.

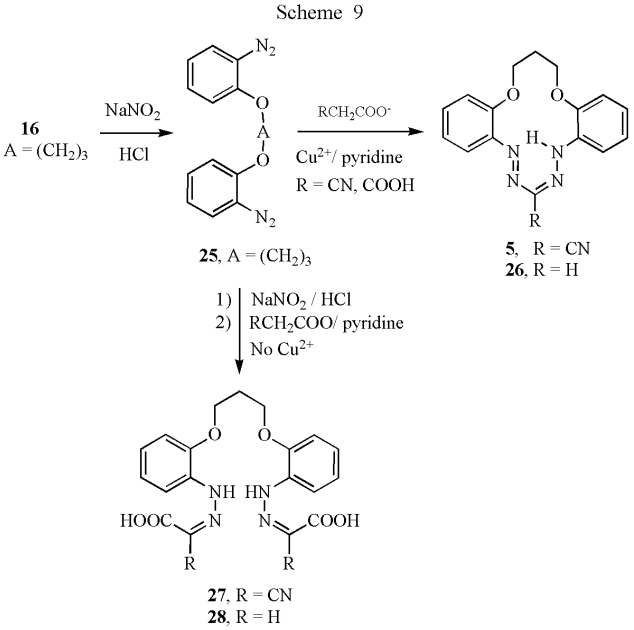
The cyclization yields may be enhanced by using transition metal cations as a "template" to keep the chain together during the coupling reactions [26,35,36], however the non-template method of bis-azocoupling was reported to increase the yields of some phenylcrown formazans with large size by 1.5-2 times [26]. Moreover using in the cyclization step, a rapid reaction under high dilution conditions can minimize the possible formation of polymeric materials. On the other hand, Katritzky and coworkers [39] reported that azo-coupling reactions of bis-diazonium salts with active methylene or methine compounds under mild basic conditions in two phase liquid-liquid media is efficiently promoted by phase transfer catalysis.

Specific Synthesis of Macrocyclic Crown Formazans.

A- Synthesis of Crown Formazans by Coupling the Corresponding Bis-diazonium Salts With Appropriate Active Methylene or Methine Compounds.

Dziomko *et al* [35] reported the synthesis of metal free dibenzo[*b*,*i*][1,11,4,5,7,8]dioxatetraazacyclotetradecines **5** and **26** by the double azocoupling of bis-diazotized bis(2-aminophenoxy)-1,3-propane **25** (obtained by diazotization of **16** [A = $(CH_2)_3$] with sodiu m nitrite in HCl) with

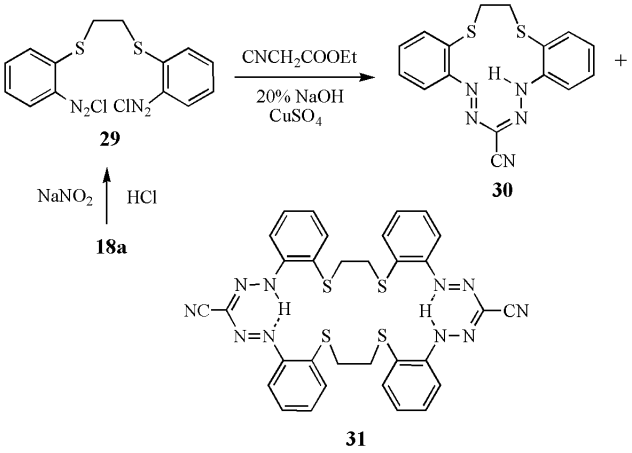
Scheme 9



cyanoacetic acid or malonic acid in pyridine in the presence of copper sulfate. In the absence of Cu^{2+} the main products are dihydrazones **27** and **2 8**, respectively (Scheme 9).

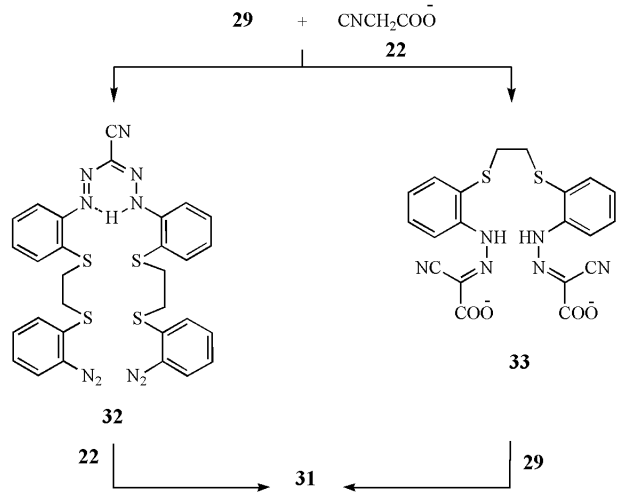
Ostrovskaya and Palilova [31] reported the synthesis of "2+2" macrocyclic formazan **31** in 10% yield along with 26% of "1+1" macrocyclic formazan **30** by treating the bis-diazonium salt **29** (obtained by treatment of **18a** with $NaNO_2$ in HCl) with ethyl cyanoacetate in pyridine containing $CuSO_4 \cdot 5H_2O$ followed by hydrolysis with 20% NaOH (Scheme 10).

Scheme 10



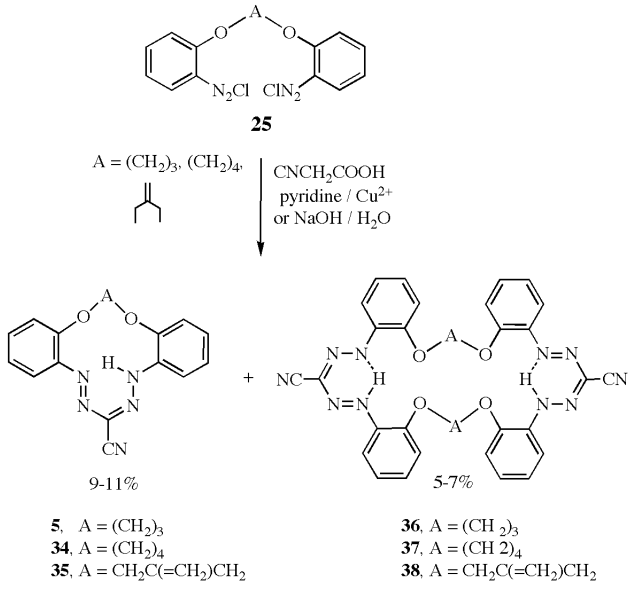
The same authors reported that compound **31** may be obtained by first coupling two moles of **29** with one equivalent of cyanoacetic acid to give the bis-diazonium salt **32** and subsequent coupling with cyanoacetic acid. The reaction can also proceed *via* initial formation of the bis-hydrazone **33** by coupling **29** with two moles of cyanoacetic acid followed by reacting **33** with one equivalent of **29** [31] (Scheme 11).

Scheme 11



Abbas [36] also isolated 5-7% yields of cyanocrown formazans with two formazyl moieties **36**-**38** by the azocoupling of the appropriate bis-diazonium salts **25** with cyanoacetic acid in aqueous NaOH or in pyridine containing $CuSO_4$. In addition to **36**-**38** the reaction afforded also 9-11% yields of the corresponding 7-cyanoformazans **5**, **34** and **35**, respectively (Scheme 12).

Scheme 12



Many authors [13,16,22,24,26,27,39,40-42] have reported the synthesis of crown formazans **40a-jj** (Table 1) in 3-46% yield by coupling of the appropriate bis-diazonium salts **39** with the corresponding active methylene or methine compounds **22** or **23** (Scheme 13). In most cases pyridine containing $CuSO_4$ or aqueous sodium hydroxide were used as the basic media. Malonic acid, arylmalonic acid, cyanoacetic acid, acetylacetic acid, nitroacetic acid or arenesulfonylacetic acid were used as the active methylene or ethane compounds.

Scheme 13

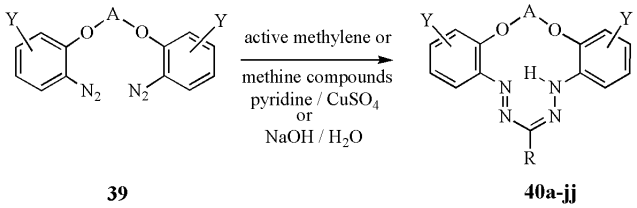


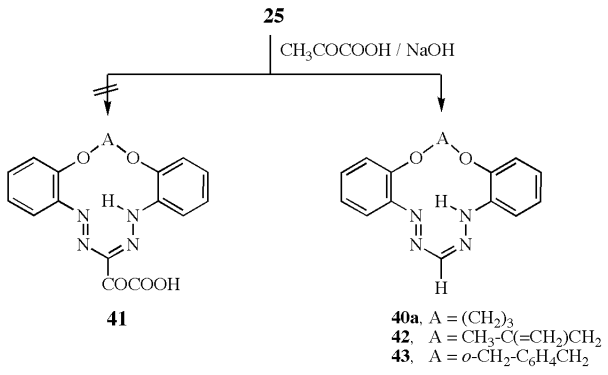
Table 1

No	A	R	Y	No	A	R	Y
40a	$(CH_2)_3$	H	H	**40s**	$(CH_2)_3$	Ph	NO_2
40b	$(CH_2)_3$	H	NO_2	**40t**	$(CH_2)_4$	Ph	H
40c	$CH_2(CH_2OCH_2)CH_2$	H	H	**40u**	$(CH_2)_5$	Ph	H
40d	$CH_2(CH_2OCH_2)_2CH_2$	H	NO_2	**40v**	$(CH_2)_6$	Ph	H
40e	$CH_2(CH_2OCH_2)_2CH_2$	H	NO_2	**4w**	CH_2OCH_2	Ph	H
40f	$(CH_2)_3$	$COCH_3$	H	**40x**	$CH_2(CH_2OCH_2)CH_2$	Ph	H
40g	$CH_2(CH_2OCH_2)CH_2$	$COCH_3$	NO_2	**40y**	$CH_2(CH_2OCH_2)CH_2$	p-$NO_2C_6H_4$	H
40h	$CH_2(CH_2OCH_2)_2CH_2$	$COCH_3$	H	**40z**	$CH_2(CH_2OCH_2)_2CH_2$	Ph	H
40i	$(CH_2)_3$	$COCH_3$	NO_2	**40aa**	$CH_2(CH_2OCH_2)_2CH_2$	p-$NO_2C_6H_4$	H
40j	$(CH_2)_3$	CN	NO_2	**40bb**	$(CH_2)_3$	$PhSO_2$	H
40k	$CH_2(CH_2OCH_2)CH_2$	CN	H	**40cc**	CH_2-$C(=CH_2)CH_2$	$PhSO_2$	H
40l	$CH_2(CH_2OCH_2)CH_2$	CN	NO_2	**40dd**	o-$CH_2C_6H_4CH_2$	$PhSO_2$	H
40m	$CH_2(CH_2OCH_2)_2CH_2$	CN	H	**40ee**	CH_2-$CH(OH)CH_2$	$PhSO_2$	H
40n	$CH_2(CH_2OCH_2)_2CH_2$	CN	NO_2	**40ff**	$(CH_2)_3$	$CH_3C_6H_4SO_2$	H
40o	o-$CH_2C_6H_4CH_2$	CN	H	**40gg**	CH_2-$C(=CH_2)CH_2$	$CH_3C_6H_4SO_2$	H
40p	CH_2	Ph	H	**40hh**	o-$CH_2C_6H_4CH_2$	$CH_3C_6H_4SO_2$	H
40q	$(CH_2)_2$	Ph	H	**40ii**	CH_2-$CH(OH)CH_2$	$CH_3C_6H_4SO_2$	H
40r	$(CH_2)_3$	p-$NO_2C_6H_4$	H	**40jj**	$(CH_2)_3$	NO_2	COOH

B- Synthesis of Crown Formazans from Pyruvic Acid Derivatives.

Ibrahim *et al* [30] reported on the use of pyruvic acid as active methylene compound in an attempt to obtain macrocyclic crown formazylglyoxalic acid **41**. They reacted the bis-diazonium salts **25** with pyruvic acid in aqueous sodium hydroxide solution. Instead of the expected glyoxalic acid derivatives **41**, they obtained only 4-6% of the crown formazans **40a**, **42** and **43**. The coupling reactions were unsuccessful in ethanolic sodium acetate solution or pyridine containing Cu^{2+} (Scheme 14).

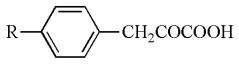
Scheme 14



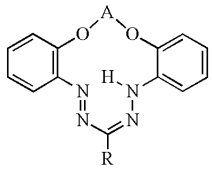
41

40a, A = $(CH_2)_3$
42, A = CH_3-$C(=CH_2)CH_2$
43, A = o-CH_2-$C_6H_4CH_2$

Crown formazans substituted with aryl groups in the formazyl carbon **6**, **40r**, **45a-k** (Table 2) could also be obtained in 5-6% yields when the appropriate bis-diazonium salts **25** were coupled with the corresponding arylpyruvic acid **44** [22,30].



44



6, **40r**, **45a-k**

R = H, OMe, NO_2, CN

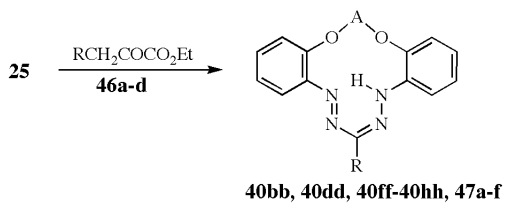
In an attempt to increase the yields of these macrocycles LiOH was added to the reaction mixture during the coupling reaction. This was found to raise the yield of compounds **6** and **40r** to 10%, however with compounds such as **45i**, **45j** LiOH has no detectable effect upon the yield [30]. This can be explained by the template effect of Li^+, which is consistent with the formation of 1:1 complex between 14-crown formazan and lithium [15].

Table 2

No	A	R	No	A	R
45a	$(CH_2)_3$	OMe	**45g**	$CH_2C(=CH_2)CH_2$	OMe
45b	$(CH_2)_3$	CN	**45h**	$CH_2C(=CH_2)CH_2$	CN
45c	$(CH_2)_4$	CN	**45i**	o-$CH_2C_6H_4CH_2$	H
45d	$CH_2CH(OH)CH_2CN$	CN	**45j**	o-$CH_2C_6H_4CH_2$	OMe
45e	$CH_2(CH_2OCH_2)CH_2$	CN	**45k**	o-$CH_2C_6H_4CH_2$	CN
45f	$CH_2C(=CH_2)CH_2$	H			

The same authors [22,42] obtained crown formazans with methylsulphonyl, arylsulphonyl or pyridine *N*-oxide in the formazyl carbon **40bb**, **cc**, **dd**, **ff**, **gg**, **hh**, **47a-f** (Table 3) in 4-20% yield by coupling the corresponding bis-diazonium salts **25** with the appropriate pyruvate derivatives **46a-d** (Scheme15).

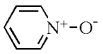
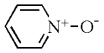
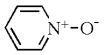
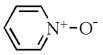
Scheme 15



40bb, 40dd, 40ff-40hh, 47a-f

aminophenoxy)propan-2-ol **25** (A= $CH_2CH(OH)CH_2$, Y= H) to a vigorously stirred mixture containing tetrabutylammonium bisulfate (PTC), sodium hydroxide, methylene chloride and water. Apparently, the intermediate hydrazone **49**, which exists in equilibrium with the related azo compounds **48**, first affords a 12-membered macrocyclic triazene **50** as a result of intramolecular azo-coupling, which is consistent with the suggested mechanism of formazan formation. Intramolecular cyclization is

Table 3

No	A	R	No	A	R
47a	$(CH_2)_3$	CH_3SO_2	**47d**	$CH_2CH(OH)CH_2$	
47b	$(CH_2)_3$		**47e**	*o*-$CH_2C_6H_4CH_2$	CH_3SO_2
47c	$CH_2C(=CH_2)CH_2$		**47f**	*o*-$CH_2C_6H_4CH_2$	

In all of the above cases the yields of the crown formazans obtained from coupling of bis diazonium salts with pyruvate derivatives did not exceed 10%.

C- Synthesis of Crown Formazans Under Phase Transfer Conditions.

Hashida *et al* [43] found that azocoupling of arenediazonium salts with compounds having either an activated methylene group or an activated position in an arene moiety to give the corresponding formazans occurs readily in liquid-liquid systems and is significantly accelerated by tetraalkylammonium salts.

When this synthetic approach was used, the following important experimental details should be noted [44,45]:

1- The reaction proceeds at temperatures which are higher than normally required for azo-coupling.

The reaction is not as exothermic as in the case of azo-coupling in pyridine.

The basicity of the aqueous phase is lower than in the traditional pyridine synthesis.

A reduced excess of the diazonium component compared with the traditional method decreases the likelihood of side reactions.

By this methodology the disadvantage of diazonium salt such as instability and insolubility in low polar media have been overcome.

Katritzky *et al* [39] applied the phase transfer catalysis methodology to synthesize the crown formazan **51** in 30% yield (Scheme 16). The reaction was carried out by addition of an aqueous solution of β-phenylpyruvic acid **44** simultaneously with a solution of tetrazotized 1,3-di(2-

accompanied by loss of the hydrophilic portion of the triazine, which forces the transfer of the macrocycle into the organic phase with subsequent rearrangement into formazan **51**.

Cyclization of diazonium salt **25** with phenylmalonic acid using an equimolar ratio of reagent at high dilution under basic conditions gave only 13% yield of **51**. A considerable amount of deeply colored side products was also formed, apparently, as a result of a preferable linear azo-coupling that stops the reaction at the azo-compound stage, *i.e.*, decarboxyaltion of the diazo derivatives of phenylmalonic acid, followed by Japp-Klingemann rearrangement into the phenylhydrazone derivatives, does not proceed easily in this particular case.

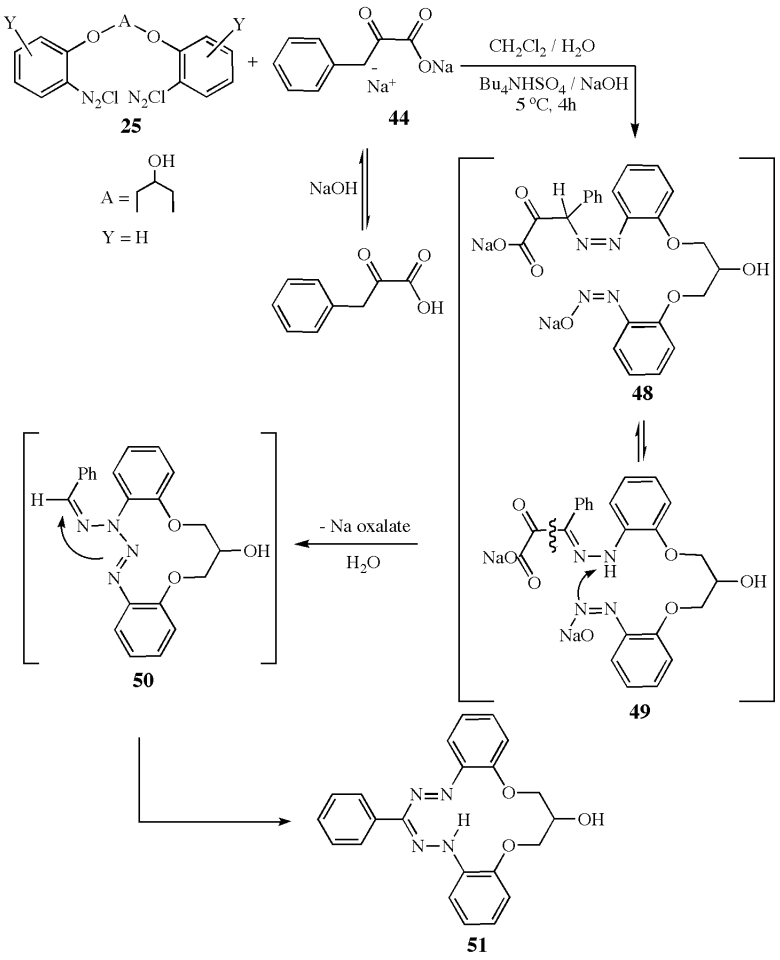
The template method, employing Cu^{2+} as an assembling cation, gave a still smaller yield of **51**, probably because of the unfavorable competitive involvement of the pendant hydroxy group of **25** in complex formation leading to linear products. Ibrahim *et al* [22] used a similar approach to increase the yields of some macrocyclic formazan derivatives.

D- Synthesis of Allyl-substituted Macrocyclic Crown Formazans.

The use of crown formazans on a large scale for industrial purpose is still inhibited by their expense as a result of the low yields obtained from the coupling reactions. A preferentially useful way around this problem lies in attracting the complexing agent to a polymeric backbone and then facilitating its retrieval.

Very recently Abbas and Elwahy [37] reported on the synthesis of macrocyclic formazans with allyl moiety that can be subsequently utilized as promising monomers for

Scheme 16



the synthesis of polymer-supported macrocycles. Two methods were described for the synthesis of allyl-substituted macrocyclic formazans **56**:

i) Coupling Reaction Methodology.

The synthetic pathway is outlined in Scheme 17. Alkylation of acetamidophenol **12** with allyl bromide in ethanolic sodium hydroxide afforded allyloxyacetamidophenol **52** which underwent Claisen rearrangement to give the corresponding phenol **53**. Treatment of the latter with the appropriate dihaloalkane in basic medium gave **54**. Hydrolysis of **54** with ethanolic solution containing hydrochloric acid led to the formation of the bis-amine hydrochlorides **55**. Diazotization of **55** and subsequent coupling with the appropriate active methylene compounds furnished the allyl-substituted macrocyclic crown formazans **56a-d** in 7-35% yield.

ii) Alkylation Methodology.

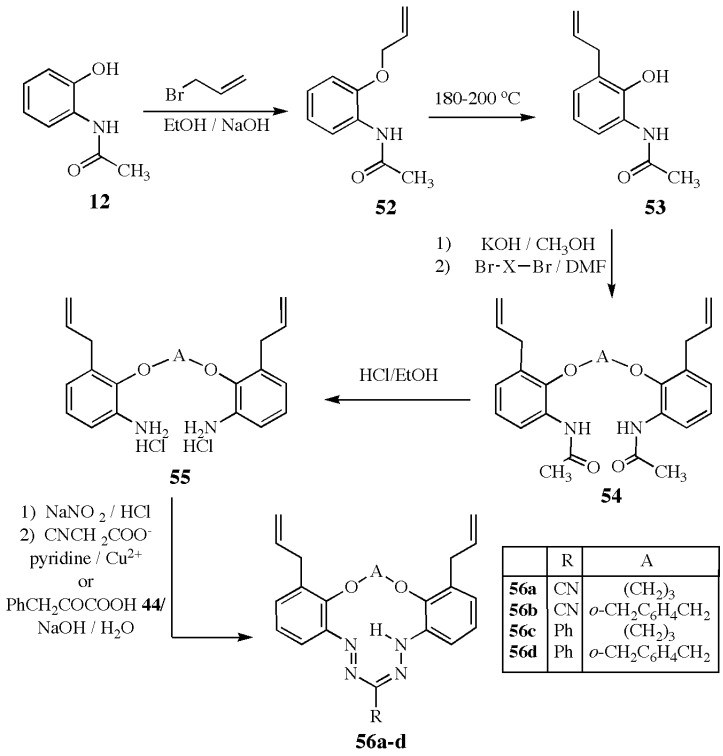
The same authors [37] reported the synthesis of compound **56a** but in a very low yield (2-3%) using a new strategy as shown in Scheme 18. Compound **53** was chosen as the precursor for **57** *via* initial hydrolysis with ethanolic solution containing hydrochloric acid to give the corresponding amine hydrochloride followed by diazotization with $NaNO_2$ in hydrochloric acid and subsequent coupling with cyanoacetic acid in aqueous sodium hydroxide solution. The bis-phenol **57** was then reacted with 1,3-dibromopropane in ethanolic solution containing sodium ethoxide under high dilution conditions to give **56a**.

E- Synthesis of Macrocyclic Formazans *Via* Ring Closure Metathesis.

Ring closure metathesis (RCM) is a versatile technique used for the formation of cyclic olefins. In the last decade RCM and its wide range of applications have been the subject of many reviews [46]. Very recently, Ibrahim *et al* [38] reported the synthesis of some crown formazan derivatives **61a-g** using ring closure metathesis with Grubb's Catalyst as the key macrocyclization step as outlined in Scheme 19.

The diene **59** [37] was obtained from **52** by first hydrolysis with ethanolic solution containing hydrochloric acid

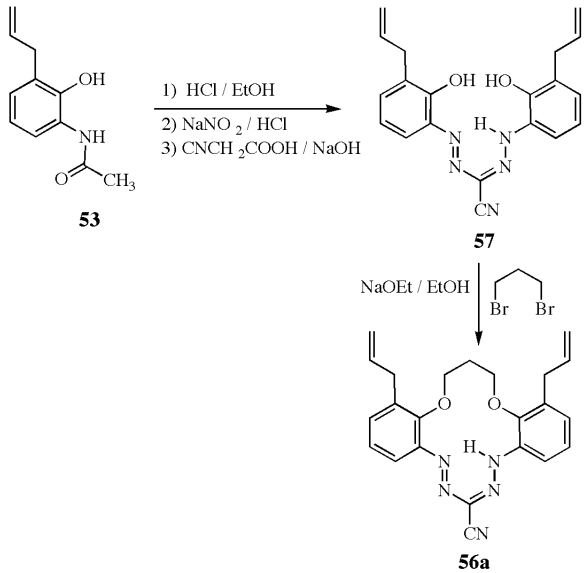
Scheme 17



	R	A
56a	CN	$(CH_2)_3$
56b	CN	*o*-$CH_2C_6H_4CH_2$
56c	Ph	$(CH_2)_3$
56d	Ph	*o*-$CH_2C_6H_4CH_2$

followed by diazotization with $NaNO_2$ in HCl to give the diazonium salt **58**. Subsequent coupling of **58** with the appropriate active methylene compounds led to the formation of **59a-g**. RCM of the diene **59a-g** proceeded under mild conditions using 2-7.5% mole of Grubb's Catalyst **60** in refluxing CH_2Cl_2 to give 60-95% yields of the corresponding formazans **61a-g**.

Scheme 18



The main product in all RCM reactions was shown to be the *Z*-isomer with the characteristic ^{13}C-NMR signal of the OCH_2 (of the OCH_2CH=CH) at *Ca* δ = 63. On the other hand ^{13}C-NMR signal of the OCH_2 of the *E*-isomer appears more downfield around δ = 70. Moreover, the OCH_2 chemical shift of the *Z*-isomer appears further downfield in the ^{1}H NMR than that of the *E*-isomer. In case of pyridyl-*N*-oxide derivative **59f** RCM macrocyclization afforded in addition to the expected product **61f**, the corresponding deoxygenated compound **62**. Although RCM of 1,5-bis-*o*-allyloxyphenylformazans led to an efficient highly stereoselective synthetic approach towards macrocyclic crown formazan, this methodology is limited only to 15-membered crown formazans.

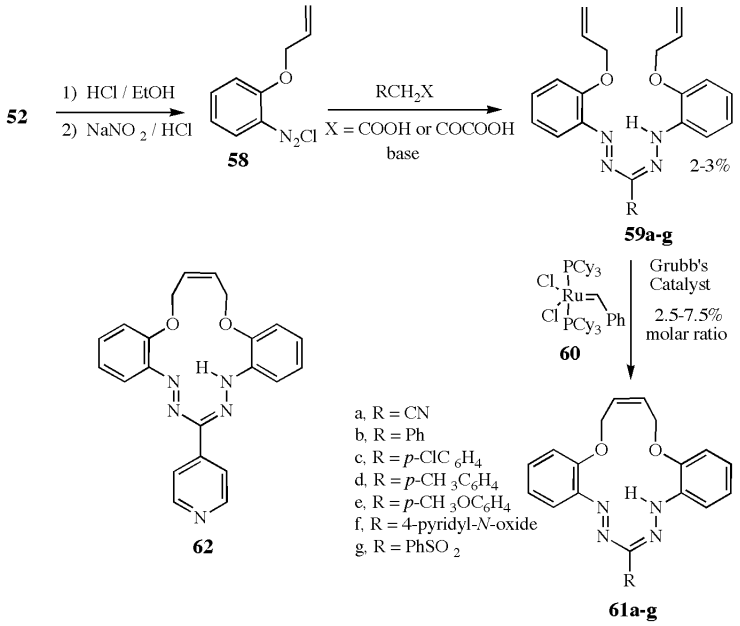
Reactions of Macrocyclic Crown Formazans.

A- Reactions of the Formazyl Groups.

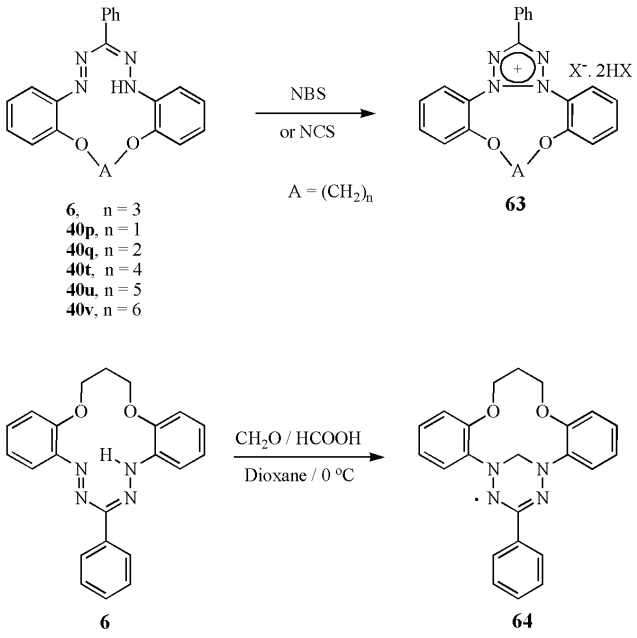
Chlorination or bromination of crown formazans **6**, **40p**, **40q**, **40t**, **40u**, **40v** by *N*-chloro or *N*-bromosuccinimide gave 20-90% yield of the macrocyclic tetrazolium salts **63** [47]. Treating the macrocyclic formazan **6** with CH_2O-HCO_2H in dioxan for 3 h at 0 °C afforded the crown tetrazinyl radical **64** (verdazyl radical) (Scheme 20) [48].

Mechanism for the formation of verdazyl are not well established. However Katritzky *et al* [49] reported a mechanism for the formation of 2,4,6-triphenylverdazyl from 1,3,5-triphenylformazan by first reaction with protonated

Scheme 19



Scheme 20



formaldehyde in two phase liquid-liquid (chloroform-water) medium to give the corresponding verdazylium salt followed by reduction.

B- Side Chain Reactions.

Katritzky [39] reported the synthesis of the first lariat crown formazan **66** from **51** by first reaction with 2-chloroacetyl chloride in DMF to give the corresponding ester **65**. Subsequent reaction of **65** with an excess of dimethyl amine in acetone under high dilution conditions afforded 52% of the dimethylamino derivative **66** (Scheme 21).

Abbas [36] obtained 16-oxocrown formazan **67** by ozonolysis of **35** in CH_2Cl_2 at –80 °C. The structure of compound **67** was confirmed by its reduction in methanolic solution containing $NaBH_4$ to give the corresponding crown formazan **45d**. Reaction of **67** with 1,3-diaminopropane in methanolic solution gave the corresponding bis-macrocycle formazan **68** in 70% yield (Scheme 22).

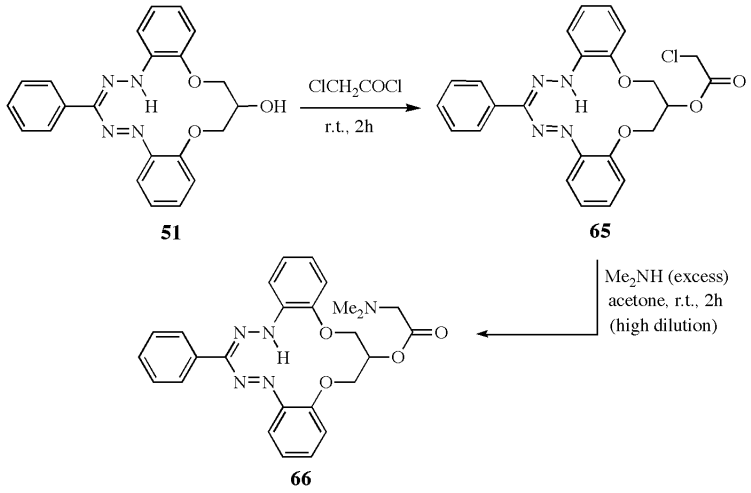
Ibrahim [50] prepared triazolium crown formazan **70** by addition of the crown cyanoformazan **5** to 2-aza-1-azoniaallene salts **69** (Scheme 23).

Structural Methods.

A- X-ray Diffraction.

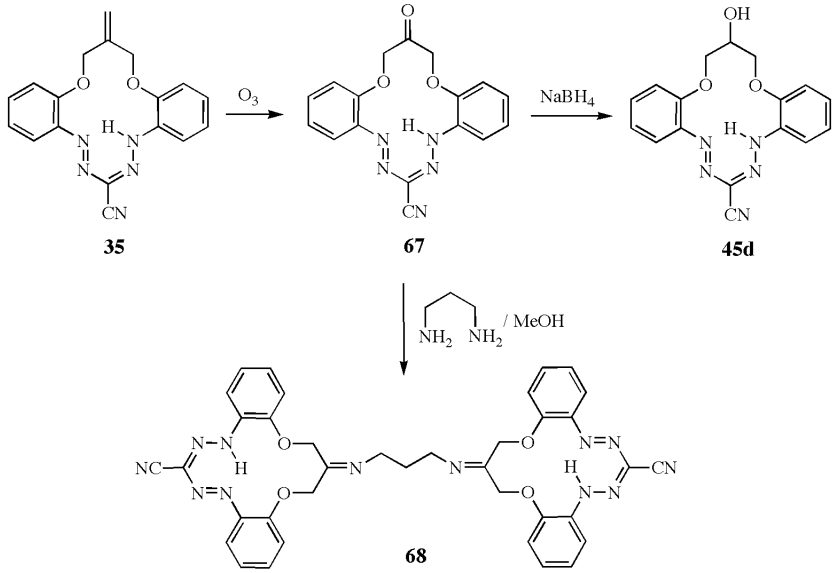
An X-ray crystallographic investigation was undertaken for single crystals of two macrocycloformazans **40o** and **40m** differing in the size of the oligoalkane chain and standing at the beginning and at the end of the obtained series of macrocycles [26]. The crystals of **40o** are constructed of two discrete crystallography independent molecules A and B.

Scheme 21



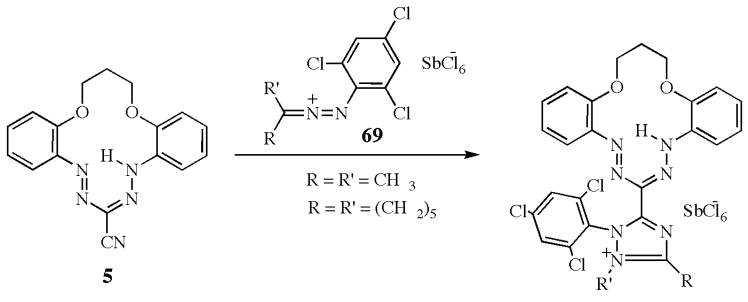
51 65 66

Scheme 22

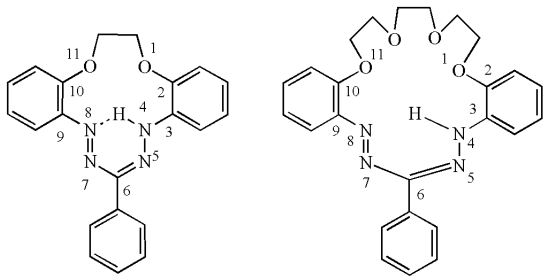


35 67 45d 68

Scheme 23



5 69 70



40o **40m**

The formazan fragment in **40o** and **40m** has the *E,Z,Z*-conformation

Analysis of the bond orders in the formazan ring shows that delocalization of the π-electron density is reduced with increase in the size of the macrocycle and the bond orders are accordingly equalized. Thus, the order of the N^4-N^5, N^5-C^6, C^6-N^7, N^7-N^8 bonds of the formazan ring are 1.45, 1.66, 1.24 and 1.55 (for compound **40o**, molecule A), 1.26, 1.39, 1.31 and 1.34 (for compound **40o**, molecule B) and 1.35, 1.71, 1.17 and 1.75 (for compound **40m**). The intramolecular hydrogen bond in the formazan ring is also weakened with increase in the size of the macrocycle [the N^4-N^8 distance for **40o** and **40m** are 2.51 and 2.63 Å respectively]. This weakening is evidently due to the steric effect of repulsion of the 1,5-phenyl rings with increase in the size of the oligooxaalkane chain. The O^1- O^{11} distance in the molecule of **40m** is increased to 4.615 Å compared with corresponding distance of 2.737 Å for molecule A and 2.641 Å for molecule B in compound **40o**. The coplanarity of the formazan ring decreases in parallel with the decease in π-electron delocalization and the weakening of the intramolecular hydrogen bond during transition from compound **40o** to compound **40m**.

The 13-membered macrocycle **40o** is relatively planar with small deviation of the atoms (maximum 0.48 Å), whereas the maximum deviation from the average plane of the macrocycle for the 19-membered macrocycle **40m** amount to 1.68 Å and the structure is characterized by significant bending (16°) along the N^4-N^8.

B- IR Spectroscopy.

The absence of absorption band characteristic for NH group in the IR spectra of most crown formazans obtained confirms the existence of such compounds in a chelate structure [35].

Ostrovskaya *et al* [51] studied the effect of change in the length of dioxaalkane chain on the IR spectra of a series of *C*-arylcrownformazans **6**, **40p-z**. From this study the following conclusions were inferred:

1. Increase in the length of the dioxaalkane chain O-$(CH_2)_n$-O, (n =1-6) does not give rise to any regular frequency shift but leads to characteristic changes in the relative intensity of the bands.
2. The increased in the non-coplanarity of the *C*-Ph ring and the formazan ring with increase n is accomplished by a decrease in the intensity of the band at ≈ 1580 cm^{-1} as a result of the decrease in the resonance interaction between the monosubstituted benzene ring and the formazan substituent.
3. For compounds with n < 3 the strengthening of the intramolecular hydrogen bond is accomplished by significant planarity and by the delocalization of the π-electron density in the formazan ring. The greater the delocalization in the formazan substituent, the smaller the electron-withdrawing effect it has on the *N*-azophenyl rings and the lower will be the intensity of the bands at ≈ 1600 cm^{-1} for the o-disubstituted benzene rings.
4. On the other hand, the IR spectra of crown formazans with n > 3 show increased intensity of ν (C=C) band at 1595 cm^{-1} as a result of the increased electron withdrawing effect of the formazan ring on the *N*-azophenyl rings, this is due to the weakness of the intramolecular hydrogen bond and the increased localization of the π-electron density in the formazan ring.

C- UV Spectroscopy.

In the electronic absorption spectra of the investigated crown formazans **6**, **40p-z**, two long wave transitions are observed at about 500 nm and 550 nm which are usually assigned to the π-π^* transition in the *N,N*-diarylhydrazone conjugated system [51]. The dependence of the wave length of the stronger electronic transition at about 500 nm on the length of the dioxaalkane chain shows a maximum for compound **6**. This agrees with the conclusion reached on the bases of study of the ^{1}H NMR and IR spectra about the maximum coplanarity of the *N*-Ph rings and the formazan moiety in the tetradecyne macroheterocycle in the series of investigated compounds.

In compound **40p**, the destruction of the coplanarity of the molecule is also accompanied by destructive of the conjugation between the *N*-phenyl rings and the OR substituents. This leads to a marked weakening of the intensity of transition at about 500 nm and in disappearance of the band at 550 nm.

For compound **5**, **40k** (the *C*-CN analogs of compounds **6**, **40x**) [41] on account of the increased in the electron withdrawing characteristics of *C*-substituents, the transitions at about 500 and 550 nm undergo hypsochromic shifts of 27 and 42 nm, respectively.

On the other hand, significantly smaller hypsochromic shifts are brought about by the increase in the electron withdrawing characteristics of *C*-phenyl during its *p*-NO_2 substitution as in compound **40r**. The introduction of NO_2

substituent into the *N*-phenyl rings (compound **40s**) leads to bathochromic shift of ≈ 50 nm in both transitions.

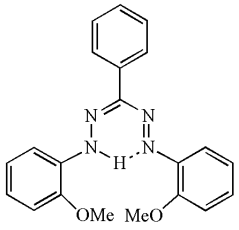
D- NMR Spectroscopy.

Proton NMR spectra have been used extensively to elucidate the structure of crown formazan. The PMR spectra of crown formazans are characterized by the presence of narrow signal for the NH proton in the downfield region, which confirm the existence of an intramolecular hydrogen bond [51]. The upfield of NH proton indicates weakening of the intramolecular hydrogen bond.

Comparison of the position of the NH proton in the PMR spectra of compound **71** (δ = 14.96 ppm) and the macrocycle **40q** (δ = 16.92 ppm) indicates that fixing of the phenyl rings causes a downfield shift of 2.0 ppm.

The δ (NH) values and consequently the strength of the intramolecular hydrogen bond in the series of *C*-Ph and *C*-CN crown formazans [41] with small di(oligo)oxaalkane chain lengths practically coincide.

On the other hand, the difference in the chemical shifts of the NH proton of compounds **40x**, **40z** compared with their *C*-CN analogs **40k**, **40m** are 0.35 ppm and 2.52 ppm, respectively. This means that the effect of the *C*-substituents on the intramolecular hydrogen bond in the crown formazans only begins to appear on the attainment of a di(oligo)oxaalkane chain length at which there is no steric approach of the *N*-Ph rings compared with the corresponding linear formazans.



71

The change in the polarity of the solvent in the transition from $CDCl_3$ to DMSO-d_6 affect the δ (NH) value of the heteromacrocycloformazans much less than the δ (NH) value of the linear 1,3,5-triarylformazans [26]. For example, the δ (NH) value for **40z** in $CDCl_3$ ≈ 14.4 and in DMSO-d_6 ≈ 14.08 while for compound **71** the δ (NH) in $CDCl_3$ ≈ 14.96 and in DMSO ≈ 12.74. This is explained by the steric screening by the intramolecular hydrogen bond which hinders solvation by the solvent in the rigidly fixed *E,Z,Z* conformation of crown formazans.

The chemical shift of the phenyl protons adjacent to the formazan ring can serve as an indicator of the coplanarity of the phenyl rings with the formazan ring, since the greater their coplanarity the greater the deshielding of these protons on account of the magnetic anisotropy of the formazan ring or the double bonds included in it.

The fact that the shielding of the 5,5'-protons in the *N*-phenyl rings in the transition from compound **40q** to **40z** is larger than for the 2,6-protons in the *C*-phenyl ring (0.30 and 0.10 ppm, respectively) agrees with the more significant loss of coplanarity of the formazan ring with the *N*-phenyl rings (average angle of rotation 45°) than with the *C*-phenyl ring (angle of rotation 29°), observed in the crystalline state [26].

E- Mass Spectrometry.

Ostrovskaya *et al* [26] recorded the molecular ion peaks in the mass spectra of a series of phenyl crown formazans. The stability of crown formazans to electron impact, which is a characteristic of the total energy of the molecule in the gas phase, depends on the length of di(oligo)oxaalkane chain.

The 14-membered macrocyclic formazan **6** was the most stable to molecular impact and this evidently corresponds to the most favorable conformation. The stability of the molecular ion decreases sharply both with the increase and decrease in the size of the dioxaalkane chain.

Crown formazan fragments by loss of a nitrogen molecule and formation of the crown hydrazone [M-28]. Further fragmentation involves cleavage of the =N-NH and =N-C bonds as in the open chain aryl and heteroarylformazans.

Applications of Macrocyclic Formazans.

The applications of crown formazans in selective metal extraction and determination depend mainly on their ability to form complexes with metal cations. The cavity size of crown formazans as well as the substituents on the macrocyclic ring play an important role in their complexing abilities and should then effect on the stability of their metal complexes.

A disadvantage of azacrown ethers is the decreased hydrolytic stability of their metal complexes compared to non-nitrogen containing related structures which was explained by the rapid inversion of the nitrogen atoms in macrocycle rings [52]. On the other hand crown formazans are characterized by the presence of rigid formazan block with one carbon and four nitrogen atoms linked in a cyanine-like system that is incapable of inversion.

A- Spectrophotometric Determination of Lithium.

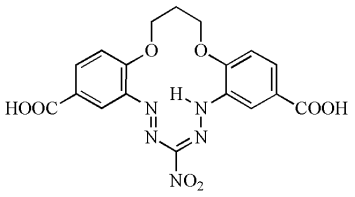
Lithium is used in treatment of manic depression psychosis. The lithium level in blood must be maintained between 0.5 and 2 mM. A higher level is toxic and a level of 5 mM can be lethal [53]. Hence the level of lithium in the patient's blood must be frequently monitored [53,54]. The determination of lithium is performed by the use of flame photometry or atomic absorption spectrophotometry

[53,54]. Also several ion selective electrodes were reported for determination of lithium. The difficulty in determining lithium in blood or serum is their high content of sodium (ca. 140 mM).

The success of any method of such determination is assessed by the possibility of accurate microdetermination in the presence of high concentration of sodium and other interfering ions present in blood serum. Christian and others [14-16,20,21,23,25] reported a spectrophotometric method for determination of Li^+ in blood serum and plasma. This method based on complex formation between Li^+ and TMC-crown formazan and measuring the absorption of the medium.

To increase the sensitivity of Li determination other groups [17-19] reported a spectrophotometric method based on a Li chelate formation in the alkaline medium with NTM-macrocycloformazan **7**.

Lin and Pirio [13] succeeded to determine Li spectrophotometry in a sample without removing protein by combining the sample and solubilized derivative macrocyclic crown formazan **40jj** in an aqueous assay medium and measuring the absorbance of the medium.



40jj

Recently, Ibrahim *et al* [22] investigated a number of crown formazans **5**, **6**, **35**, **40o**, **40bb-40ee**, **40ff**, **40hh**, **40ii**, **45b**, **45f**, **45h**, **45i**, **45k**, **47b**, **47c**, **47d**, **47f** as selective spectrophotometric chelating agents for lithium. Among the investigated chelating agents, only compounds **47b**, **47c** and **47d** with pyridyl-*N*-oxide substituent showed the highest sensitivity for Li determination compared with those reported for the cyano derivatives. The substituent A at the ether part of the investigated crown formazans has almost no effect on the sensitivity for lithium. However, with A= CH_2-(C=CH_2)-CH_2, the highest sensitivity for lithium was obtained in each case.

B- Microdetermination of Cesium.

More stringent requirements are needed for the monitoring and microdetermination of cesium in mineral rocks, thermal water in nuclear and industrail wastes, soil, plants, biological and botanical samples. The methods reported for cesium ion microdetermination in aqueous and nonaqueous solutions include spectrophotometric [55], atomic absorption [56,57], radio-analysis [58] and potentiometric methods [59].

Attiyat *et al* and Ibrahim *et al* [23] investigated a series of macrocyclic crown formazans as ionophores in cesium ion selective electrodes. The aim was to study the effect of two structural factors, namely the ether part of these macrocycles and the substituent at the formazyl carbon on enhancing the selectivity of the crown formazans in cesium ion selective electrodes.

Among the investigated crown formazans the 14-crown formazan **47d** containing 4-pyridine-*N*-oxide at the formazyl carbon exhibit high selectivity in cesium ion selective electrodes especially towards the two low selectivity monovalent ions K^+ and NH_4^+.

C- Selective Metal Extraction.

Zolotov *et al* [11] studied the extraction of several metal ions using macrocyclic formazans **40g**, **40x**, **40z** and **40m**. Of all the 22 elements studied [Na, K, Mg, Ca, Sr, Ba, Sc, Mn(II), Fe(III), Co(II), Ni, Cu(II), Ag, Zn, Cd, Hg(II), Pd(II), Tl(I), Pb, Bi, Eu, U(V)] 10^{-3} M solution of cycloformazans **40g**, **x**, **z**, **m** extract only Hg and Cu.

The mechanism of extraction of these metal ions from water to organic solvent [$CHCl_3$ or methyl-isobutyl ketone (MIBK)] was studied and extraction constants were determined. After extraction mercury was determined spectrophotometry at 568 nm. On the other hand, Cu was determined after extraction by atomic absorption. The detection limit was 0.14 μg/ml and 0.015 μg/ml for Hg and Cu, respectively.

From the investigated crown formazan series it was obvious that mercury and copper extraction depends much more on the nature of substituents in the meso-position (the formazyl carbon) than on the length of the crown like chain that alters the cavity size.

Many authors [9,10,12] have reported similar studies on the selective extraction of Cu and Hg using crown formazans.

Acknowledgements.

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