Allyl-Substituted Macrocyclic Crown Formazans: Promising Precursors for Polymer-Supported Macrocycles

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Abstract: The bisphenol 1 was obtained by reacting the amine hydrochloride 11 with cyanoacetic acid in aqueous sodium hydroxide solution. Thermal rearrangement of 1,5-bis(allyloxyphenyl)formazan (7) failed to give 1. Alkylation of the bis phenol 1 with 1,3-dibromopropane in basic solution under high dilution conditions gave the corresponding allyl-substituted macrocyclic formazan 2a in a very low yield. On the other hand, diazotization of the new bis amine hydrochloride 3a,b with NaNO₂ in hydrochloric acid followed by coupling with the appropriate active methylene compounds furnished the corresponding macrocyclic formazans 2a–d. Compounds 3a,b were obtained by first reacting the K-salt of 12 with the appropriate dihalides to give the corresponding bis acetamides 13 and 14, respectively. Subsequent acid hydrolysis of the latter afforded 3a,b in good yield.

Key words: alkylation, thermal rearrangement, diazotization, coupling, macrocyclic formazans

The chemistry and diverse applications of formazans have been the subject of a large number of reviews that have been cited previously.¹ Moreover, there is recent growing interest in the synthesis of macrocyclic crown formazans² due to their useful applications in selective metal extraction³–⁶ and determination.⁷–¹⁶ Such applications depend mainly on the cavity size of the macrocyclic crown formazans as well as on the substituents in the macrocycle. In this respect, we recently reported the synthesis of some macrocyclic formazans ¹ (Figure) and studied their evaluation in spectrophotometric determination of lithium as well as carriers in cesium ion selective electrode.¹,¹⁷–²¹

The use of such compounds on a large scale for industrial purposes is inhibited by their expense. A potentially useful way around this problem lies in attracting the complexing agent to the polymeric backbone and then facilitating its retrieval. In the last decades, large numbers of both soluble and insoluble polymers containing crown compounds have been developed and have been the subject of many reviews²²–²⁷ In connection with this finding and in continuation of our interest in the chemistry and application of formazans, we report here on the synthesis of the first macrocyclic formazans with allyl moiety, which can be subsequently utilized as promising monomers for the synthesis of polymer-supported macrocycles.

We planned to construct the allyl-substituted macrocyclic formazans 2 by two strategies as shown in Scheme 1. In the first strategy, we studied the formation of 2 by reacting
the corresponding 1,5-bis(3-allyl-2-hydroxy)formazan 1 with the appropriate dihalo compound in basic solution under high dilution conditions. The second strategy depends firstly on the formation of the bisamine hydrochlorides 3 followed by diazotization with NaNO₂ in hydrochloric acid and subsequent coupling with the appropriate active methylene compounds.

Two routes were attempted to synthesize the new allyl-substituted formazans 1 as outlined in Schemes 2, 3. In the first route (Scheme 2), our attention focused on the synthesis of 1,5-bis(2-allyloxy)formazan 7, which should then undergo thermal rearrangement to give 1. Unfortunately, heating 7 in an oil bath at 180°C for 2 hours did not lead to the formation of 1. Instead, the reaction gave an oily residue that could not be easily handled nor characterized. Compound 7 was obtained in 65% yield by diazotization of the corresponding 2-allyloxyaniline hydrochloride, and subsequent coupling with cyanoacetic acid in aqueous sodium hydroxide solution. The latter was obtained from 2-acetamidophenol (4) by first alkylation with allyl bromide to give 5 followed by hydrolysis with ethanolic solution containing hydrochloric acid. In the second route (Scheme 3), the 6-allyl-2-aminophenol 11 was chosen as the precursor for 1 (R = CN) via initial diazotization with NaNO₂ in hydrochloric acid followed by coupling with cyanoacetic acid in aqueous sodium hydroxide solution. Compound 11 was obtained in 70% yield by reacting N-(3-allyl-2-hydroxyphenyl)phthalimide (10) with hydrazine hydrate in ethanolic solution containing hydrochloric acid. The latter was obtained from N-(2-hydroxyphenyl)phthalimide (8) by first alkylation with allyl bromide to give 70% of 9. Subsequent thermal rearrangement of 9 upon heating in an oil bath at 180°C for 2 hours furnished 55% of 10. Compound 11 was alternatively obtained in 75% yield upon treatment of 2-acetamido-6-allylphenol (12) with ethanolic solution containing hydrochloric acid. Tiffany reported the synthesis of 12 in 50% yield by heating 2-allyloxyacetamidophenol (5) at 190°C in N,N-dimethylaniline. It is noteworthy to mention here that repeating the above reaction under the same condition described by Tiffany gave only 20% of 12.

The bisphenol 1 was then reacted with 1,3-dibromopropane in ethanolic solution containing sodium ethoxide under high dilution conditions. The 1H NMR spectrum of the reaction products indicated the presence of the macrocyclic formazan 2a together with other reaction products whose structures could not be determined so far. The formation of 2a was also supported by the presence of the correct molecular ion peak in the mass spectrum. After successive purifications on preparative TLC, a pure sample of 2a was isolated in only 2.5% yield. Repeated attempts to enhance the yield of 2a by performing the alkylation reaction under different basic conditions were also unsuccessful.

In anticipation of the low yield of the macrocyclic formazan 2a, we applied the second strategy as outlined in Scheme 4. Thus, reaction of the K-salt of 12 with 1,3-dibromopropane or 1,4-dibromo-2-xylene in DMF afforded 65% and 68%, respectively, of the corresponding bis(acetamido) ethers 13 and 14. The latter underwent acid hydrolysis upon treatment with ethanolic solution containing hydrochloric acid to give 70% and 72%, respectively, of the corresponding bis amine hydrochlorides 3a, 3b. Diazotization of 3a, 3b with NaNO₃ in hydrochloric acid followed by coupling with cyanoacetic acid in pyri-
dine containing CuSO₄ yielded 35% and 30%, respectively, of the corresponding macrocyclic formazans 2a,b. Moreover, the macrocyclic formazans 2c,d substituted with phenyl group in the formazyl carbon were obtained in 10% and 7% yields, respectively, by diazotization of 3a,b with NaNO₂ in hydrochloric acid followed by coupling with phenylpyruvic acid in aqueous sodium hydroxide solution.

In conclusion, we have prepared the first macrocyclic formazans with allyl substituents in the macrocycles. Further studies on the attachment of the new macrocycles to a polymeric backbone are now in progress and will be described in due course. Although our first strategy for constriction of 2 did not yield considerable amount of the product, this method led to the formation of the new allyl-substituted formazans 1 and 7, which should also be good precursors for the synthesis of new polymeric formazans of expected useful applications.

All mps are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian GEMINI 200 spectrometer (200 MHz, ¹H NMR) for compounds 1, 2a-d, 9, 10, 13 and 14 or with a Bruker WM-300 instrument (for compounds 1 and 7). Mass spectra were recorded on a GCMS-QP 1000 EX or a Varian 311A instrument. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 1,3-Dibromopropane and α,α′-dibromo-o-xylene were used as purchased from Aldrich.

Formazans 1, 7 and Macrocyclic Formazans 2a,b; General Procedure
A solution of the appropriate amine hydrochloride 6, 11 (2 mmol) or diamine dihydrochloride 3a,b (1 mmol) in H₂O (5 mL) and concd HCl (3 mL) was diazotized at −5°C with a solution of NaNO₂ (0.23 g in 5 mL water) during 30 min. Stirring was continued for 1 h at −5°C, and then the reaction mixture was added dropwise with stirring to a solution containing cyanoacetic acid (1 mmol) [in H₂O (10 mL) containing NaOH (1.2 g)] for compounds 1 and 7 or in pyridine (150 mL), CuSO₄·5H₂O (0.5 g) and H₂O (20 mL) for compounds 2a,b] over 1 h. The reaction mixture was kept in the freezer overnight. The solid, which precipitated by adding concd HCl, was collected and crystallized from the proper solvent (for 1 and 7) or purified on preparative TLC using silica gel (60 F₂₅₄) [CH₂Cl₂–petroleum ether (40–60), 2:1] (for 2a,b).
3-Cyano-1,5-bis(3-allyl-2-hydroxyphenyl)formazan (1)
Application of the general procedure (using 11) gave crude 1, which was crystallized from toluene as deep red crystals. Yield: 60%; mp 175°C.
IR: \( \nu = 3352.1 \text{ (OH)}, 2233.4 \text{ (CN)} 1639 \text{ (C=C)} \).  

1H NMR (CDCl₃): \( \delta = 3.47 \text{ (d, } 4\text{H, } J = 6.4 \text{ Hz, } \text{C}_2\text{H}_2-\text{CH}═\text{CH}_2 \), 5.18 \( \text{ (d, } 2\text{H, } J = 11.4 \text{ Hz, } \text{CH}═\text{CH}_2 \), 5.19 \( \text{ (d, } 2\text{H, } J_{\text{trans}} = 16.2 \text{ Hz, } \text{CH}═\text{CH}_2 \), 6.94-7.56 \( \text{ (m, } 6\text{H, } \text{Ar-H}) \).  

13 C NMR (CDCl₃): \( \delta = 114.3 \text{ (CN), 116.8, 121.1, 128.6, 131.5, 136}\text{ (Ar-CH, } \text{C}_2\text{H}_2-\text{CH}═\text{CH}_2 \), 133.2, 136.3, 147.9 \( \text{ (Ar-C, } \text{C}═\text{N}) \).  

MS: \( m/\text{z} (%) = 361 (\text{M}^+, 12), 360 (58), 198 (52.5), 104 (100), 76 (55) \).  


1,5-Bis(2-allyloxyphenyl)-3-cyanoformazan (7)
Application of the general procedure (using 6) gave crude 7, which was crystallized from MeOH as deep red crystals. Yield: 65%; mp 85°C.
IR: \( \nu = 2225.7 \text{ (CN)}, 1642 \text{ (C=C)}, 1240, 1050 \text{ (N=N)} \).  

1H NMR (CDCl₃): \( \delta = 4.69 \text{ (d, } 4\text{H, } J = 6.4 \text{ Hz, } \text{CH}_2\text{CH}_2\text{O} \), 3.48 \( \text{ (d, } 2\text{H, } J = 4.9 \text{ Hz, } \text{CH}_2\text{CH}_2\text{O} \), 4.17 \( \text{ (t, } 4\text{H, } J = 5.0 \text{ Hz, } \text{CH}_2\text{CH}_2\text{O} \), 5.89-6.09 \( \text{ (m, } 2\text{H, } \text{CH}═\text{CH}_2 \), 7.14-7.79 \( \text{ (m, } 6\text{H, } \text{Ar-H}) \).  

13 C NMR (CDCl₃): \( \delta = 70.2 \text{ (CH}_2\text{O), 115 \text{ (CN), 114, 116.7, 117.9, 121.8, 129.9, 132.9 \text{ (Ar-CH, } \text{CH}═\text{CH}_2 \), 126.8, 136.7, 151.9 \text{ (Ar-C, } \text{C}═\text{N}) \}.  

MS: \( m/\text{z} (%) = 361 (\text{M}^+, 12), 360 (58), 198 (52.5), 104 (100), 76 (55) \).  


1,13-Diallyl-16,17-dihydro-5H,15H-dibenz[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile (2a)
(a) Application of the general procedure (using 3a) gave deep red crystals of 2a. Yield: 35%; Rₖ = 0.89; mp 195-196°C.
IR: \( \nu = 2225 (\text{CN}, 1641 \text{ (C=C), 1255, 1047 (N=N)} \).  

1H NMR (CDCl₃): \( \delta = 2.26 \text{ (quintet, } 2\text{H, } J = 4.6 \text{ Hz, } \text{OCH}₂ \text{C}_2\text{H}_2 \), 3.48 \( \text{ (d, } 4\text{H, } J = 6.4 \text{ Hz, } \text{C}_2\text{H}_2-\text{CH}=\text{CH}_2 \), 4.17 \( \text{ (t, } 4\text{H, } J = 5.0 \text{ Hz, } \text{OC}₂\text{H}_2 \), 5.09-5.20 \( \text{ (m, } 4\text{H, } \text{CH}═\text{C}_2\text{H}_2 \), 5.89-6.09 \( \text{ (m, } 2\text{H, } \text{CH}═\text{CH}_2 \), 7.14-7.79 \( \text{ (m, } 6\text{H, } \text{Ar-H}) \), 15.15 \( \text{(s, 1H, NH)} \).  

MS: \( m/\text{z} (%) = 401 (\text{M}^+, 27), 360 (56), 255 (12), 227 (25), 105 (100) \).  

Anal. Calcd for C₂₃H₂₃N₅O₂ (401.46): C, 68.81; H, 5.77; N, 17.44. Found: C, 68.90; H, 5.70; N, 17.75.

(b) To a solution of 1 (5 mmol) in ethanolic solution of sodium ethoxide [prepared from Na (2.30 g, 10 mmol) and absolute EtOH (100 mL)] was added 1,3-dibromopropane (5 mmol). The reaction mixture was removed in vacuo and the remaining material was purified as in method (a) to give 2a.  

7,19-Diallyl-5,21-dihydro-11H-tribenzo[b,i,m][1,11,4,5,7,8]dioxatetraazacyclopentadecine-13-carbonitrile (2b)
Application of the general procedure (using 3a) gave deep red crystals of 2b. Yield: 30%; Rₖ = 0.89; mp 255-257°C.
IR: \( \nu = 2225 (\text{CN}), 1639 \text{ (C=C), 1261, 1065 (N=N)} \).  

1H NMR (CDCl₃): \( \delta = 3.60 \text{ (d, } 4\text{H, } J = 6.4 \text{ Hz, } \text{CH}₂\text{CH}₂\text{CH}═\text{CH}_2 \), 5.11-5.21 \( \text{ (m, } 8\text{H, CH}_2\text{CH}_2\text{OH, CH}═\text{CH}_2 \), 5.99-6.18 \( \text{ (m, } 2\text{H, } \text{CH}═\text{CH}_2 \), 7.16-7.74 \( \text{ (m, } 10\text{H, Ar-H}) \), 14.96 \( \text{(s, 1H, NH)} \).  

MS: \( m/\text{z} (%) = 464 (\text{M}^+, 12), 423 (14), 359 (13), 251 (25), 161 (22), 104 (100) \).  

Macrocyclic Formazans 2c,d

A solution of the appropriate diamine dihydrochloride 3a,b (1 mmol) in H2O (5 mL) and concd HCl (3 mL) was diazotized at −5°C with a solution of NaNO2 (0.23 g in 5 mL H2O) during 30 min. Stirring was continued for 1 h at −5°C, and the mixture was added dropwise with stirring to a solution containing phenylpyruvic acid [in H2O (10 mL) containing NaOH (1.2 g)] over 1 h. The reaction mixture was then kept in the freezer overnight. The solid that precipitated was collected and purified on preparative TLC using silica gel (60 F254 SL)–petroleum ether (40–60°C).

1,13-Diallyl-16,17-dihydro-5H,15H-7-phenyldibenzo-[b,i]-[1,11,4,5,7,8]dioxatetraazacyclotetradecine (2c)

Prepared from 3a.

Deep red crystals; yield: 10%; Rf = 0.58; mp 140–142°C.

IR: ν = 1640 (C=C), 1422, 1245, 1220 cm−1.

1H NMR (CDCl3): δ = 3.29 (quintet, 2H, J = 5 Hz, OCH2CH2), 5.16 (d, 1H, J = 5.2 Hz, CH=CH2), 7.19–7.24 (m, 7H, Ar-H). Anal. Calcd for C21H28Cl2N2O2 (411.37): C, 61.31; H, 6.86; N, 6.81; Cl, 19.10. Found: C, 61.18; H, 6.89; N, 6.75; Cl, 19.40.

1,2-Bis(2-aminophenoxy)ether Dihydrochlorides 3a,b; General Procedure

To a solution of 3a (10 mmol) in absolute EtOH (20 mL) was added allyl bromide (5 mmol). The reaction mixture was heated under reflux for 4 h, the solvent was removed in vacuo, and the remaining precipitate was collected, washed with H2O, and crystallized from EtOH as colorless crystals.

Yield: 70%; mp 184-186°C.

N-(2-Allyloxyphenyl)phthalimide (9)

A solution of 8a (5 mmol) in an ethanolic sodium ethoxide solution [prepared from Na (1.15 g, 5 mmol) and absolute EtOH (30 mL)] was added allyl bromide (5 mmol). The reaction mixture was heated under reflux for 4 h, the solvent was removed in vacuo, and the remaining precipitate was collected, washed with H2O, and crystallized from EtOH as colorless crystals.

Yield: 70%; mp 170–172°C.

N-(2-Allyloxyphenyl)phthalimide (10)

Compound 9 (5 mmol) was heated in an oil bath at 180–190°C for 2 h. The remaining materials upon cooling were triturated with EtOH, collected, and crystallized from EtOH to give 10 as colorless crystals.

Yield: 55%; mp 168–170°C.

6-Allyl-2-aminophenol Hydrochloride (11)

(a) To a solution of 10 (10 mmol) in EtOH (20 mL) was added hydrazine hydrate (15 mmol) and HCl (2 mL). The reaction mixture was heated under reflux for 30 min. The solid obtained was collected by filtration. The filtrate was concentrated by rotary evaporator (approx. 10 mL) and then kept in the freezer overnight. The solid obtained was collected and crystallized from EtOH as colorless crystals.

Yield: 70%; mp 215–217°C.
References

(4) (b) Chem. Abstr. 1984, 100, 158896.