Template Reactions of 1,4-Bis(α-carboxybenzylidenehydrazino)phthalazine with Cobalt(II), Nickel(II), and Chromium(III)

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1,4-Bis(α-carboxybenzylidenehydrazino)phthalazine (**1**) has been prepared from 1,4-dihydrazinophthalazine and the methyl ester of phenylglyoxylic acid. The reaction of (**1**) with cobalt(II) and nickel(II) gives isostructural macrocyclic complexes [(**2a**) and (**2b**)] as a result of the template effect of these metal ions. In the case of the chromium(III) ion, a similar template reaction has not been observed, which is proposed to be due to the six-co-ordinate environment adopted by the Cr^{III} ion. Mass, i.r., n.m.r., and u.v.–visible data of the novel compounds are presented.

The template synthesis of macrocyclic ligands is one of the best examples of metal ions affecting the steric course of a reaction. Unsaturated polyazamacrocycles, and their metal complexes, have received special attention since they are considered as useful models for biological macrocyclic systems. Consequently, metal template cyclization reactions of 1,2-dihydrazones have been extensively studied for this purpose.[1,2]

The synthesis and complex formation of *vic*-dioximes and Schiff bases containing crown ether moieties have been reported previously.[3,4] The template effect of Co^{II} ions on the synthesis of azoquinoxalines from 2-(1*H*)-quinoxalinone oximes has also been investigated.[5]

1,4-Dihydrazinophthalazine, and its hydrazones with various aldehydes and ketones, have been tested systematically for their anti-bacterial and anti-tumour activity,[6] but there has been no report on their complexes with transition-metal ions. The steric hindrance arising from the *para* position of the hydrazine groups might explain the lack of such complexes. In addition to two hydrazone groups and two aza groups on the phthalazine ring, additional donor sites can be provided by choosing suitable aldehydes or ketones for the hydrazone formation. In the present study, carboxylic acid groups have been introduced into this new ligand *via* phenylglyoxylic acid, as the ketone for hydrazone synthesis. The reactions of the novel ligand with Cr^{III}, Co^{II}, and Ni^{II} are also investigated.

Results and Discussion

The condensation reaction of 1,4-dihydrazinophthalazine with the ketone group of phenylglyoxylic acid was performed using the methyl ester of the carboxylic acid. After hydrolysis, 1,4-bis(α-carboxybenzylidenehydrazino)phthalazine (**1**) was obtained as pale yellow crystals.

The i.r. spectrum of (**1**) was consistent with the structure given in Figure 1. The presence of hydrogen bonding was indicated by a broad absorption around 2 600 cm^{-1}. The absorptions of the NH, C=O, and C=N stretches were at 3 450, 1 750, and 1 565 cm^{-1}. The ^1H n.m.r. spectrum of (**1**) showed four deuterium exchangeable protons between 13.73 and 10.24 p.p.m.; this phenomenon also confirmed partial intra-molecular hydrogen bonding. In the mass spectrum, the molecular ion peak was observed at *m*/*z* 454 as expected. The weak $M + 1$ (*m*/*z* 455) and $M + 2$ (*m*/*z* 456) peaks were more intense than those calculated for isotopic abundance; this is due to the abstraction of protons from the neutral molecules by the molecular ion and frequently occurs in compounds containing heteroatoms.[7,8]

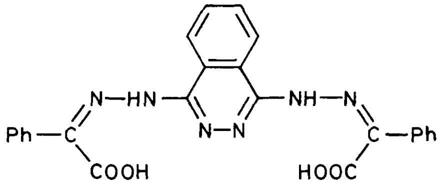

Figure 1. 1,4-Bis(α-carboxybenzylidenehydrazino)phthalazine (**1**)

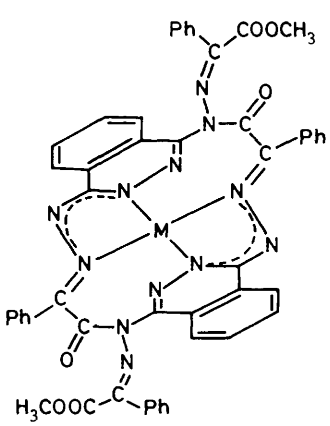

Figure 2. Reaction of product of Co^{II} and Ni^{II} with (**1**) [M = Co (**2a**) or Ni (**2b**)]

The reaction of (**1**) with Co^{II} and Ni^{II} ions gave isostructural macrocyclic products [(**2a**) and (**2b**) respectively] as indicated by elemental analysis and spectral data. Since these reactions were carried out in methanol, one of the carboxylic acid groups was esterified and the free acid group of one molecule condensed with the NH group of the second molecule. This cyclization process is a typical example of a metal template reaction.[9] All attempts to synthesize a similar macrocyclic complex of Cr^{III} failed, the condensation reactions stopping short of macrocyclic ring formation.

The i.r. spectra of the Co^{II} and Ni^{II} complexes are very similar and support the structure proposed in Figure 2. A comparison of the spectra of the complexes with that of (**1**), reveals that the broad absorption of the COOH groups around 3 100 cm^{-1} and the stretching and bending vibrations of NH groups at 3 450 and 1 622 cm^{-1} are not present in the complexes. Esterification of one of the carboxylic acids was also shown by a new absorption at 2 940 cm^{-1} (ν_{C-H}) in the i.r. spectra of (**2a**) and (**2b**).

The cobalt(II) complex of (**1**) is paramagnetic, but the Ni^{II}

complex is diamagnetic, as expected for a planar d^8 metal ion. The ^{1}H n.m.r. spectrum of (**2b**) in CD_2Cl_2 indicates that all the deuterium exchangeable protons of (**1**) have vanished during formation of the complex. The methyl resonances of the ester group occur as a singlet at 2.7 p.p.m. The aromatic protons of the phthalazine ring exhibit a complicated spectrum of four bands in the range δ 6.5—10.7 p.p.m. This complication arises as a result of the anisotropic magnetic field created by the square-planar co-ordination environment of the metal ions.[1] The aromatic ring currents of the 1,4-disubstituted phthalazines are expected to be affected by the co-ordination of one of the N atoms of the phthalazine groups to the central metal ion.

In the electronic spectra of (**2a**) and (**2b**), well resolved *d–d* transitions could not be observed, but the intense charge-transfer bands, from *pπ* orbitals of the donor atoms to *d* orbitals of the metals, appeared as intense absorptions at 405 and 428 nm, respectively.

The mass spectra of these complexes showed molecular ions at *m/z* 957 for (**2a**) and *m/z* 956 for (**2b**). There is strong evidence for the mononuclear structures of these compounds since ^{59}Co is the only isotope of this element, while ^{58}Ni is the most abundant isotope of nickel and ^{59}Ni does not exist. The fragmentation patterns of the complexes are very similar to those of (**1**) up to $m/z < 400$ and the metal-containing ions of (**2a**) and (**2b**) are found for $m/z > 449$. An important feature of the metal-containing ions of these two complexes is the similarity in fragmentation patterns, and with a difference in *m/z* of 1 for the molecular ions. A reasonable interpretation of this is that both complexes should have identical structures.

The reaction of (**1**) with $CrCl_3 \cdot 6H_2O$ in a mixture of methanol–benzene (1:2) afforded an organic compound instead of a complex as in the cases of Co^{II} and Ni^{II}. The elemental analysis of the product (**3**) corresponds to $C_{50}H_{38}N_{12}O_7$. In the i.r. spectrum, NH stretching vibrations of the hydrazone groups appear at 3 320 cm^{-1}. The partial esterification of the carboxylic acid is verified by the stretching vibration of the methyl group at 2 830 cm^{-1}. In the ^{1}H n.m.r. spectrum of (**3**), a signal at lower magnetic field (δ 13.08 p.p.m.) indicates that a free carboxylic acid group is also present in the molecule. Other deuterium exchangeable protons, at 9.11 p.p.m., belong to the NH groups. The ratio NH:COOH is 3:1 indicating that the carboxylic acids are partially esterified. The ^{13}C n.m.r. spectrum of (**3**) exhibits 16 signals corresponding to 16 carbon atoms of different electron density. The highest signal (δ 52.65 p.p.m.) is assigned to the methoxy carbon atoms in (**3**) (Figure 3).

In contrast to the complexes, the molecular ion peak for (**3**) could not be observed in the mass spectrum. The reason might be the bulky substituents on the chain structure. The biggest ion observed is at *m/z* 450 and the rest of the fragmentation pattern is similar to those of (**1**), (**2a**), and (**2b**).

In order to verify whether the role of the Cr^{3+} ion in this reaction was a true template effect or a transient template effect, where the only function of the metal ion was to provide protons,[10] the condensation of (**1**) was carried out in the presence of H$^+$ ions alone, but no dimerization or macrocyclization was observed. In fact, one should not expect any influence of protons on the formation of hydrazides from carboxylic acids and hydrazines similar to the condensation of aldehydes or ketones with hydrazines. Consequently, the reaction of (**1**) with Cr^{3+} can be taken as a true template reaction. Another interesting feature of compound (**3**) was that it could not be converted into a macrocyclic complex [*e.g.* (**2a**) or (**2b**)] by reacting with Co^{2+} or Ni^{2+} ions.

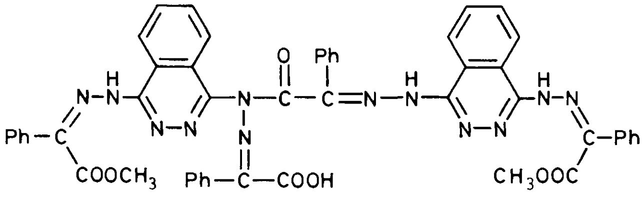

Figure 3. Product of the reactions of Cr^{III} with (**1**), compound (**3**)

The conversion of (**1**) into a macrocyclic complex in the case of Co^{II} and Ni^{II} ions, and an acyclic organic compound in the case of Cr^{III} can be explained on the basis of the complexation properties and ionic radii of the metal ions. While Co^{II} and Ni^{II} ions are capable of forming four-co-ordinate square-planar complexes, Cr^{III} shows a tendency to form six-co-ordinated compounds. Consequently, Co^{II} and Ni^{II} ions organise and orientate two molecules of (**1**) such that the required macrocycle is formed by condensation of two carboxylic acid groups with the NH groups of the hydrazone moieties. Steric features hinder similar orientations with six-co-ordinated Cr^{III} ions, so the reaction stops at the dimerization stage and the main product is an organic compound.

Experimental

Infrared spectra were obtained on a Perkin-Elmer 598 spectrophotometer in KBr pellets. The ^{1}H and ^{13}C n.m.r. spectra were recorded on a Bruker AC-200 Fourier-transform n.m.r. spectrometer. Mass spectra were measured on a Varian Mat 711 spectrometer. U.v.–visible spectra were obtained on a Varian DMS-90 spectrophotometer. 1,4-Dihydrazinophthalazine was prepared according to published methods.[11]

1,4-*Bis(α-carboxybenzylidenehydrazino)phthalazine* (**1**).—To a solution of 1,4-dihydrazinophthalazine (19.0 g, 0.1 mol) in hot water (300 cm^3) was gradually added a solution of the methyl ester of phenylglyoxylic acid (33.0 g, 0.2 mol) in methanol (200 cm^3). When the mixture was refluxed under an N_2 atmosphere an oily product formed after 15 min and became an orange precipitate after 2 h. The product was filtered off, washed with ethanol and then with diethyl ether, and dried. Yield: 35.0 g (90%); m.p. 165—167 °C.

In order to hydrolyse the methyl ester, the product was refluxed in aqueous 10% NaOH solution for 2 h. After cooling to room temperature the mixture was neutralized with HCl up to pH 4—4.5 and a pale yellow compound was precipitated. This was filtered off, washed with water and then with ethanol and diethyl ether. Recrystallization in methanol-benzene (1:2) gave pale yellow crystals. Yields: 25.0 g (55%); m.p. 184 °C (decomp.). T.l.c. on silica plates with methanol–benzene (1:2) as eluant showed a single spot (R_f = 0.515). This compound was soluble in dimethylformamide (dmf) and slightly soluble in methanol and chloroform (Found: C, 63.25; H, 3.60; N, 18.20. $C_{24}H_{18}N_6O_4$ requires C, 63.45; H, 4.00; N, 18.50%); $\lambda_{max.}$(methanol) 222 (84 000), 229 (93 500), 253 (37 250), 283 (19 000), 297 (13 000), 325 (1 750), and 382 nm (ε 217 dm^3 mol^{-1} cm^{-1}); ^{1}H n.m.r. [$(CD_3)_2SO$], δ 13.73 (1 H, s), 12.85 (1 H, s), 12.52 (1 H, s), 10.24 (1 H, s) (these four signals disappear on deuterium exchange), and 9.3—7.0 p.p.m. (14 H, m); *m/z* 454 (M^+, 6%); $\nu_{max.}$ 3 450, 3 300 (NH), 3 070 (NH), 3 070 ($CH_{aromatic}$), 1 750, 1 710 (C=O), 1 622 (NH), 1 565 (C=N), 1 430 (OH), 1 317, 1 270 (C–O), 950, 765, and 698 cm^{-1}.

Reaction of (**1**) *with Cobalt*(II) *Nitrate*.—Compound (**1**) (0.454 g, 1 mmol) was dissolved in methanol–benzene (150 cm^3, 1:2) by refluxing. $Co(NO_3)_2 \cdot 6H_2O$ (0.58 g, 2 mmol) was dissolved in methanol (50 cm^3) and added to the refluxing solution. After refluxing for 48 h, the colour of the clear solution became dark red. The mixture was evaporated to dryness under reduced pressure. T.l.c. on silica plates with methanol–benzene (1:2) as eluant showed the main product (R_f = 0.72) and the impurities. Column chromatography on silica (Mac-Loney and Nagel) with methanol–benzene (1:2) as eluant separated the front running band, which was collected, evaporated to dryness, and crystallized from methanol–benzene (1:2) as dark brown needles, (**2a**). Yield 0.115 g (24%), m.p. 316 °C (decomp.). This compound was also soluble in dichloromethane and chloroform and slightly soluble in dioxane (Found: C, 62.95; H, 3.60; Co, 5.80; N, 17.80. $C_{50}H_{34}CoN_{12}O_6$ requires C, 62.70; H, 3.60; Co, 6.15; N, 17.55%); $\lambda_{max.}$($CHCl_3$) 245 (3 830), 255 (1 710), 296 (15 700), 335 (1 150), and 405 nm (ε 1 290 dm^3 mol^{-1} cm^{-1}); *m/z* 957 (M^+ 5.39%); $\nu_{max.}$ 3 060, 2 940, 1 745, 1 600, 1 510, 1 440, 1 390, 1 220, 1 120, 1 050, 1 020, 770, 690, and 670 cm^{-1}.

Reaction of (**1**) *with Nickel*(II) *Nitrate.*—This reaction was carried out as above using $Ni(NO_3)_2 \cdot 6H_2O$ in place of $Co(NO_3)_2 \cdot 6H_2O$ and a pale brown crystalline product, (**2b**), was obtained. Yield: 0.086 g (18%); m.p. 325 °C (decomp.). This compound was also soluble in dichloromethane and chloroform, and slightly soluble in dioxane (Found: C, 62.85; H, 3.55; N, 17.80; Ni, 5.80. $C_{50}H_{34}N_{12}NiO_6$ requires C, 62.70; H, 3.60; N, 17.55; Ni, 6.15%); $\lambda_{max.}$($CHCl_3$) 245 (11 300), 255 (9 950), 300 (24 500), 335 (4 400), and 428 nm (ε 1 520 dm^3 mol^{-1} cm^{-1}); ^{1}H n.m.r. (CD_2Cl_2), δ 10.7—6.5 (28 H, m), and 2.7 p.p.m. (6 H, s); *m/z* 956 (M^+, 0.45%); $\nu_{max.}$ 3 050, 2 940, 1 730, 1 595, 1 500, 1 440, 1 390, 1 230, 1 110, 1 045, 1 020, 770, 695, and 670 cm^{-1}.

Reaction of (**1**) *with Chromium*(III) *Chloride.*—A solution of $CrCl_3 \cdot 6H_2O$ (1.85 g, 6 mmol) in methanol (120 cm^3) was added to a hot (60 °C) solution of (**1**) (1.36 g, 3 mmol) in a mixture of methanol–benzene (360 cm^3, 1:2). When the mixture was refluxed for 24 h, the colour changed from green to red. After reducing the volume to a half, the reaction mixture was left overnight and a pale brown crystalline product (**3**) was precipitated. This was filtered off, washed with methanol and then with diethyl ether, and dried. Yield: 0.5 g (36%); m.p. 220 °C (decomp.). T.l.c. on silica plates with methanol–benzene (1:2) as eluant showed a single spot (R_f = 0.716). This compound was soluble in dichloromethane and chloroform (Found: C, 65.20; H, 4.40; N, 18.60. $C_{50}H_{38}N_{12}O_7$ requires C, 65.35; H, 4.15; N, 18.30%); $\lambda_{max.}$($CHCl_3$) 243 (6 610), 303 (4 180), 318 (3 890), and 395 nm (ε 920 dm^3 mol^{-1} cm^{-1}); ^{1}H n.m.r. ($CDCl_3$), δ 13.08 (1 H, s), 9.11 (3 H, s) (these two singlets disappear on deuterium exchange), 8.54—7.62 (28 H, m), and 3.93 (6 H, s); ^{13}C n.m.r. ($CDCl_3$), δ 52.65, 119.80, 123.85, 126.60, 128.06, 128.65, 128.81, 129.62, 130.16, 133.61, 134.26, 137.23, 142.89, 148.12, 152.49, and 163.44 p.p.m.; *m/z* 450 (M^+ − 468, 10), 420 (7%); $\nu_{max.}$ 3 320 (NH), 3 050 ($CH_{aromatic}$), 2 830 ($CH_{aliphatic}$), 1 705 (C=O), 1 610 (C=N), 1 550, 1 510, 1 440, 1 320, 1 295, 1 230, 1 140, 1 060, 940, 800, 765, 700, 680, 660, and 540 cm^{-1}.

Acknowledgements

I would like to thank Professor Özer Bekâroğlu (İstanbul, Turkey) for valuable discussions. I am also indebted to Professor M. L. Ziegler (Heidelberg University, West Germany) for providing laboratory facilities.

References

1 S. Peng, G. C. Gordon, and V. L. Goedken, *Inorg. Chem.*, 1978, **17**, 119.
2 J. E. Baldwin, R. H. Holm, R. W. Harper, J. Huff, S. Koch, and T. J. Truex, *Inorg. Nucl. Chem. Lett.*, 1972, **8**, 393.
3 A. Gül, A. İ. Okur, A. Cihan, N. Tan, and Ö. Bekâroğlu, *J. Chem. Res.*, 1986, (*S*) 90; (*M*) 881.
4 A. Gül, A. İ. Okur, A. Cihan, N. Tan, and Ö. Bekâroğlu, *Synth. React. Inorg. Met.-Org. Chem.*, 1986, **16**, 871.
5 A. Gül, A. İ. Okur, S. Can, and Ö. Bekâroğlu, *Chem. Ber.*, 1986, **119**, 3870.
6 B. Prescott, G. Lones, and G. Caldes, *Antimicrob. Agents Chemother.*, 1968, 262.
7 F. W. Mclafferty, 'Interpretation of Mass Spectra,' W. A. Benjamin, Inc., London, 1973, p. 36.
8 A. Koçak and Ö. Bekâroğlu, *Helv. Chim. Acta*, 1984, **67**, 1503.
9 L. F. Lindoy, *Q. Rev. Chem. Soc.*, 1971, **25**, 379.
10 L-Y. Chung, E. C. Constable, M. S. Khan, J. Lewis, P. R. Raithby, and M. D. Vargas, *J. Chem. Soc., Chem. Commun.*, 1984, 1425.
11 E. Enders, in 'Methoden der Organischen chemie Strikstoff-Verbindungen I-Vol. X/2,' ed. R. Stroh, Georg Thieme Verlag, Stuttgart, 1967, p. 317.

Received 15*th September* 1987; *Paper* 7/1662