Synthesis and structure of novel benzisothiazole-tetrazolyl derivatives for potential application as nitrogen ligands

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1. Introduction

Tetrazoles and benzisothiazoles have received much attention due to their important practical applications in major areas, such as medicine and agriculture.

In the last decade, a significant part of the research carried out in our laboratories has been directed to the investigation of structure-reactivity correlations in tetrazole- and benzisothiazole-based compounds, aiming at the development of new synthetic methodologies. For instance, ethers derived from tetrazole and benzisothiazole have important synthetic uses as intermediate compounds for reductive cleavage of the C–O bond, in phenols and alcohols. These ethers are easily obtained from reaction of the corresponding hydroxylic compound with commercially available 5-chloro-1-phenyl-(1H)-tetrazole or with 3-chloro-1,2-benzisothiazole 1,1-dioxide. The electron-withdrawing tetrazolyl or benzisothiazolyl system, together with oxygen from the original alcohol, represents an efficient nucleofuge in heterogeneous transformations. BNCC-0130381; No. of Pages 5

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co-exist simultaneously as ionic and coordinated species in the same structure. As a ligand, it can be engaged in N, O(=C=O) or O(SO₂) coordination, but can also act as a bidentate amido-like bridging agent [21–23]. The saccharinate anion interacts with metal centres in various ways, generating relatively strong interactions in crystalline environments, mostly through hydrogen bonding.

Although several tetrazole derivatives and saccharinate anion have demonstrated the ability to bind cations of transition metals individually, they have not been investigated together as ligands. Taking advantage of our experience concerning the synthesis and reactivity of tetrazole- and benzothiazole-based compounds, we have devised synthetic routes to benzisothiazole-tetrazolyl derivatives with the final aim of investigating their application as nitrogen ligands for coordination with transition metals. Accordingly, it was decided to synthesize novel potential benzisothiazole-tetrazolyl ligands for coordination with transition metals. Taking advantage of our experience concerning the synthesis and reactivity of various metal complexes with the final aim of investigating their application as nitrogen ligands for coordination with transition metals, we report on the synthesis and characterization of three new benzisothiazole-tetrazolyl derivatives, and their complexation with transition metals.

2. Experimental

2.1. Computational details

Quantum chemical calculations for the derivatives 4a and 6 were performed with the Gaussian 03 program package [24] at the DFT level of theory, using the 6-31G(d,p) basis set and the three-parameter density functional, abbreviated as B3LYP, which includes Becke's gradient exchange correction [25] and the Lee, Yang, Parr correlation functional [26]. No symmetry restrictions were imposed on the initial structures.

2.2. Synthesis

2.2.1. 3-Chloro-1,2-benzisothiazole 1,1-dioxide (2)

The experimental procedure used has been reported previously [27]. From saccharin (10.2 g; 56 mmol), and phosphorus pentachloride (14.0 g; 66 mmol) heated at 180 °C. Colourless needles from trichloromethane (7.00 g; 63% yield), mp 143–145 °C (lit. 143–145 °C [27]). IR νₘₐₓ (cm⁻¹): 1724, 1654, 1603 (C=C), 1346 (SO₂), 775 (Ar–H) and 692 (C=O); ¹H NMR (CDCl₃): δ 7.85 (4H, m, Ar–H). Found: C, 41.5%; H, 2.0%; N, 6.9%; Calcd for C₇H₄NO₂SCl: C, 41.7%; H, 2.0%; N, 7.0%. MS (EI), m/z 201 [M⁺].

2.2.2. 1-(1H-Tetrazol-5-yl)ethanol (3a)

Sodium azide (1.43 g; 22 mmol), zinc bromide (4.50 g; 20 mmol), 2-hydroxy-propanenitrile (1.45 mL; 20 mmol) and water (50 mL) were mixed in a 250-mL round-bottomed flask and the mixture was stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide (14.0 g; 66 mmol) heated at 180 °C under a nitrogen atmosphere, until no solid was present and the aqueous layer attained a pH of 1. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic layers were evaporated, aqueous NaOH (0.25 M; 200 mL) was added to the residue, and the mixture stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid washed with aqueous NaOH (1 M; 20 mL). Hydrochloric acid (3N; 40 mL) was added to the filtrate with vigorous stirring causing the separation of oil. After the addition of a saturated solution of NaCl (brine), the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated to afford the final product as a colourless solid (2.5 g; 71% yield), mp 176–177 °C (lit. 178–179 °C [28]). From sodium azide (1.43 g; 22 mmol), zinc bromide (4.50 g; 20 mmol), 2-hydroxy-propanenitrile (1.45 mL; 20 mmol) and water (50 mL) were mixed in a 250-mL round-bottomed flask and the mixture was stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid washed with aqueous NaOH (1 M; 20 mL). Hydrochloric acid (3N; 40 mL) was added to the filtrate with vigorous stirring causing the separation of oil. After the addition of a saturated solution of NaCl (brine), the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated to afford the final product as a white amorphous powder (1.70 g; 75% yield). IR νₘₐₓ (cm⁻¹): 3390 (OH), 1696, 1624, 1243, 1123; ¹H NMR (CDCl₃): δ 7.55 (br, 1H), 7.22–7.35 (q, 1H), 7.35 (d, 3H); MS (EI), m/z 115 (33% [M+H]+, m/z 132 (100% [M+Na⁺]). Acc. Mass (Cl): Found, 115.1145; Calcd for C₃H₇N₄O, 115.1134.

2.2.3. Phenyl(1H-tetrazol-5-yl)methanol (3b)

Preparation of this compound followed a modified version of a procedure reported previously [28]. From sodium azide (1.43 g; 22 mmol), zinc bromide (4.50 g; 20 mmol), 2-hydroxy-2-phenylacetone (2.66 g; 20 mmol) and water (60 mL). The reaction mixture was refluxed for 18 h with vigorous stirring. Extraction, as described above for derivative 3a, afforded the required product as a colourless solid (2.5 g; 71% yield), mp 176–177 °C (lit. [28] 178–179 °C). IR νₘₐₓ (cm⁻¹): 3445 (OH), 2589, 1699, 1434, 1251, 1040; ¹H NMR (CDCl₃): δ 7.47 (m, 2H), 7.35 (m, 2H), 7.30 (m, 1H), 6.81 (br, 1H), 6.15 (s, 1H); MS (EI), m/z 178 (91% [M+2H]+, m/z 194 (100% [M+Na⁺]).

2.2.4. 3-[1-(1H-Tetrazol-5-yl)ethoxy]-1,2-benzisothiazole 1,1-dioxide (4a)

A mixture of 1-(1H-tetrazol-5-yl)ethanol (0.20 g; 1.75 mmol), 3-chloro-1,2-benzisothiazole 1,1-dioxide (0.35 g; 1.75 mmol) and a suspension of potassium tert-butoxide (0.65 g; 5.25 mmol) in dry THF (50 mL) was stirred at 60 °C under a nitrogen atmosphere, until TLC analysis (DCM/toluene 3:1) indicated the absence of starting material (48 h). The excess of base was filtered off and then ethyl acetate (100 mL) was added to the reaction mixture. The crude was washed with diluted hydrochloric acid (1 M; 3 × 50 mL), brine (3 × 100 mL).
50 mL) and finally dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure and recrystallisation from a mixture of toluene/dichloromethane (3:2) afforded compound 4a as a amorphous pale yellow powder (0.28 g; 58% yield), mp 210–211 °C. IR υmax (cm−1): 3091, 2974, 1722, 1686, 1453, 1336 (SO2), 1177; 1H NMR (CDCl3): δ 8.05–8.08 (d, 1H), 7.91–7.95 (m, 2H), 7.86–7.90 (d, 1H), 5.26 (1H, d), 1.39–1.41 (d, 3H); MS (EI), m/z 279 [M]+; Acc. Mass (CI): Found = 280.1089, Calcd for C10H10N5O3S: 280.1022.

2.2.5. 3-[(2H-Tetrazol-5-yl)benzoyl]-1,2-benzothiazole 1,1-dioxide (4b)

The procedure adopted for the preparation of compound 4b was similar to that described above for compound 4a. From phenyl[1H-tetrazol-5-yl]methanol (0.28 g; 1.50 mmol), 3-chloro-1,2-benzothiazole 1,1-dioxide (0.30 g; 1.50 mmol) and a suspension of potassium tert-butoxide (0.55 g; 4.50 mmol) in dry THF (50 mL), stirred at 60 °C for 72 h. Compound 4b was obtained as a light yellow solid (0.26 g; 50% yield), mp 210–211 °C. IR υmax (cm−1): 3091, 2974, 1722, 1686, 1453, 1336 (SO2), 1177; 1H NMR (CDCl3): δ 8.05–8.08 (d, 1H), 8.08–8.13 (m, 2H), 8.05–8.08 (d, 1H), 7.89–7.93 (m, 2H), 7.55–7.63 (m, 2H), 7.46–7.51 (t, 1H), 6.13 (s, 1H); MS (EI), m/z 342 [M+H]+; Acc. Mass (CI): Found = 342.1910, Calcd for C15H11N2O3S: 342.2131.

2.2.6. N-(1,1-dioxo-1,2-benzothiazol-3-yl)-amine-1H-tetrazole (6)

A mixture of commercial anhydrous 5-aminotetrazole (Sigma–Aldrich; 0.22 g; 2.56 mmol) and 3-chloro-1,2-benzothiazole 1,1-dioxide (0.53 g, 2.56 mmol) in dry THF (20 mL) was stirred at room temperature for 24 h under a nitrogen atmosphere. The solvent was then evaporated under reduced pressure and the remaining solid was washed with acetone, dried under vacuum at room temperature and recrystallised from a mixture of acetone/ethanol (1:1) to give the required product (0.10 g; 38% yield), mp 270–271 °C. IR υmax (cm−1): 3221 (NH), 3091, 1608, 1542, 1430, 1323 (SO2), 1177, 1037, 951; 1H NMR (DMSO): δ 8.67–8.70 (d, 1H), 8.08–8.13 (m, 2H), 8.05–8.08 (d, 1H), 7.89–7.93 (m, 2H), 7.55–7.63 (m, 2H), 7.46–7.51 (t, 1H), 6.13 (s, 1H); MS (EI), m/z 251 (17%) [M+H]+; Acc. Mass (CI): Found = 251.2109, Calcd for C15H11N2O3S: 251.2181.

2.3. Preparation of complexes

2.3.1. 3-[(2H-Tetrazol-5-yl)ethoxy]-1,2-benzothiazole 1,1-dioxide-Mn(II) complex (7)

A mixture of ligand 4a (0.10 g; 0.36 mmol) and manganese(II) acetate tetrahydrate (0.09 g; 0.36 mmol) in ethanol (10 mL) was stirred at room temperature for 24 h. Then the brown precipitate (resulting from degradation of ligand and manganese acetate complex) was filtered off and the remaining solution evaporated under reduced pressure, at room temperature, to afford the required product as a pale yellow solid (0.11 g; 68% yield). Acc. Mass (ES+): Found = 446.0053, Calcd for C12H12N2O2SNaMn: 445.9805.

2.3.2. N-(1,1-dioxo-1,2-benzothiazol-3-yl)-amine-1H-tetrazole-Mn(II) complex (8)

A mixture of ligand 6 (0.10 g; 0.40 mmol) and manganese(II) acetate tetrahydrate (0.1 g; 0.40 mmol) in ethanol (10 mL) was stirred at room temperature for 24 h. Then, the pale precipitate (resulting from degradation of ligand and manganese acetate complex) was filtered off and the remaining solution evaporated under reduced pressure (RT). The required product was obtained as a colourless solid (0.107 g; 62% yield). Acc. Mass (ES+): Found = 446.0013, Calcd for C12H12N2O2SNaMn: 445.9805.

3. Results and discussion

The synthetic methodologies adopted to produce the benzothiazole-tetrazoly derivatives are presented in Schemes 1 and 2. The synthesis of the hydroxyalkyl-tetrazoles 3a and 3b was performed in water, following a methodology similar to that developed by Demko and Sharpless [28,29].

Compounds 4a and 4b were prepared by reaction of the corresponding hydroxyalkyl-tetrazole (3a and 3b) with pseudo-saccharyl chloride, in the presence of base. The reaction yields achieved for the synthesis of these two derivatives are similar to those obtained for a large range of nucleophilic substitution reactions with pseudo-saccharyl chloride, involving different alcohols [3,4,10].

The procedure adopted for the synthesis of derivative 6 involves reaction of 5-aminotetrazole with saccharyl chloride in dry THF. The required 5-saccharylamino-1H-tetrazole 6 was obtained in a good yield (78%).

In order to obtain some relevant structural data on the synthesized molecules (4a-b, 7 and 8), DFT(B3LYP)/6-31G(d,p) calculations were carried out for derivatives 4a and 6. These derivatives have three and two internal rotational degrees of freedom respectively, which may result in the existence of different conformers. However, a complete conformational study of both compounds was not carried out during this work. The two conformers selected, presented in Fig. 1, are those that were predicted to possess the most suitable geometry for coordination of both tetrazole and benzothiazole nitrogen atoms with transition metals [16].

In both optimized structures of derivatives 4a and 6, the two heterocyclic

Fig. 1. B3LYP/6-31G(d,p) optimized structures of derivatives 4a and 6. Selected Mulliken atomic charges (a.u.) of nitrogen atoms are showed in parentheses. Colour atoms by charge with force symmetric charge range (red: atoms with positive partial charge; green: atoms with negative partial charge). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)
systems (tetrazole and benzisothiazole) have approximately planar geometries. However, only for derivative 6 these two moieties share the same plane. The angle between the tetrazole ring and the benzisothiazolyl system on derivative 4a was predicted by the calculations to be ca. 110°. Certainly, structural differences on the 1,2-benzisothiazolyltetrazoles, bearing an amino or ether linkage, will play a role in determining their coordination behaviour with transition metals. However, the rotational freedom of the tetrazolic moiety in relation to the benzisothiazolyl system allows us to expect that compounds 4a-b and 6 can adopt a conformation with the required orientation of the two ring units for formation of metal complexes.

Partial negative charges on nitrogen atoms of 4a-b and 6 are also shown in Fig. 1. The relatively high values of these charges in two of the nitrogen atoms of the tetrazolyl ring and in the nitrogen atom of benzisothiazolyl system (see Fig. 1) suggest that these atoms bear the capacity for charge donation and, therefore, the ability to form coordination bonds with transition metals. Preliminary complexation reactions involving derivatives 4a and 6 as potential multidentate nitrogen ligands, with manganese(II) and iron(II) complexes are now discussed. Because of their potential interest of Fe(II) spin-crossover coordinating materials [15] the two derivatives were first tested as nitrogen ligands in reactions with an iron(II) complex. The procedure adopted in the synthesis involved vigorous stirring of 4a or 6 with the iron(II) perchlorate complex, Fe(ClO$_4$)$_2$·6H$_2$O, in equimolar amounts, at room temperature, in ethanol. However, product analysis indicated that no complex associating iron and derivatives 4a or 6 had been formed (Scheme 3).

Mass spectrometry confirmed the occurrence of degradation of ligands 4a and 6 during reaction, inferred by the presence of molecular ion peaks corresponding to isolated saccharin. Thus, in the reaction conditions used, both compounds are susceptible to nucleophilic attack on the sp$^2$ imino carbon of the benzisothiazolyl system, and the reaction might be accelerated in the presence of perchlorate salts, if the mechanism operating is sensitive to the solvent ionizing power [30]. Degradation of the two potential ligands possibly induced by the oxidative nature of the perchlorate ligand, can explain the failure on coordination of iron(II) with the benzisothiazole-tetrazolyl derivatives. Analysis of the literature also revealed that coordination of ditetrazole ligands with Fe(II) is not always feasible, depending largely on the structure of the bridge connecting the two heterocycles [31]. In our case, one tetrazolyl ring is replaced by a benzoisothiazolyl structure, but the difficulties appear to be the same.

Derivatives 4a and 6 were stirred with the manganese(II) acetate tetrahydrate complex, Mn(CH$_3$COO)$_2$·4H$_2$O, in ethanol. The experimental procedure adopted in these reactions was identical to that used in the attempted preparation of the iron(II) complexes (see Scheme 4). However, in this case, after solvent evaporation, an amorphous pale yellow powder was obtained from complexation of derivative 4a with Mn(II), and a white powder from complexation of derivative 6 with the same metal cation. Product analysis attested the presence of coordination complexes between manganese and both derivatives. Structures 7 and 8, represented in Scheme 4, were proposed for the final products.

Mass spectra of compound 8 were obtained using electrospray as the ionization technique. Interestingly, in the positive mode, using methanol as solvent, peaks corresponding to molecular ions of 336, 368 and 400 were found. These peaks clearly indicate the formation of complexes involving ligand 6 with Mn plus one methoxide (m/z: 336), ligand 6 with Mn plus methoxide and one molecule of methanol (m/z: 368) and ligand 6 with Mn plus methoxide and two molecules of methanol (m/z: 400). Thus, derivative 6 is complexed with Mn and methanol molecules replaced the acetate groups present in the starting manganese(II) acetate (8). A comparable result was obtained when ethanol + 0.1% of formic acid was used as solvent, with substitution of acetate groups by ethoxide groups.

In summary, the synthesis and structural analysis of three novel benzisothiazole-tetrazolyl derivatives (4a-b and 6) from pseudo-saccharyl chloride 2 and tetrazoles 3a-b and 5 were achieved. Complexation of compounds 4a and 6 with manganese(II) acetate tetrahydrate complex, Mn(CH$_3$COO)$_2$·4H$_2$O, lead to formation of two new benzisothiazole-tetrazolyl manganese complexes 7 and 8.
At this stage, original strategies aiming at the coordination of transition metals (for instance: Ni, Co, Cu, Pd), with the three potential benzisothiazole-tetrazolyl nitrogen ligands synthesized, 4a-4b and 6, are in progress. A subsequent investigation of catalytic applications of the resulting complexes (such as compounds 7 and 8) was already devised and is the next step for this research.

4. Conclusions

Synthetic methodologies for the preparation of novel benzisothiazole-tetrazolyl derivatives, differing on the spacer-group used for linkage of the two heterocycles, were devised. Structural characterization of intermediate compounds through molecular orbital calculations (DFT(B3LYP)/6-31G(d,p)) was used to correlate structural features with differences in reactivity. The application of these compounds as nitrogen ligands for coordination with transition metals was also explored, leading to the easy preparation of 3-[1-(2-1H-tetrazol-5-yl)ethoxy]-1,2-benzisothiazole 1,1-dioxide-Mn(II) and N-(1,1-dioxo-1,2-benzisothiazol-3-yl)-amino-1H-tetrazole-Mn(II) complexes.

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