Spectral Assignments and Reference Data

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Complete assignments of NMR data of salens and their cobalt (III) complexes

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Salens, derived from 1,2-ethylenediamine and salicylaldehydes, have been widely used as ligands for metal complexes which have been showing enormous potential in chemical properties of asymmetric catalysts as well as biological properties such as anticancer agents. Almost all of the salen–metal complexes with their corresponding metal (II)-complexes show the evidences of chelation of two oxygens in salens. However, several metal (II) complexes, especially cobalt (II) complexes, could not show NMR spectra due to their paramagnetism. Recently, it has been reported that one of the cobalt (III) complexes was used for NMR spectroscopy to evaluate its stereoselectivity as a catalyst. Even though many salen ligands are known, their NMR data are not assigned completely. It was possible that modification in northern part of salen with 2-hydroxyphenyl group afforded another oxygen chelation site in salen ligand. Here we report that synthesis and full NMR assignment of new salen ligands, which form *meso* 1,2-bis(2-hydroxyphenyl)ethylenediamine) and their cobalt (III) complexes. The assignments of ^{1}H and ^{13}C NMR data obtained in this experiment can help us to predict the NMR data of other salen ligands. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 2D NMR; salen; cobalt(III) complex

Introduction

Salen is a chelating ligand that bridges a metal ion with two nitrogen and two oxygen atoms. It resembles a heme group, which functions to facilitate oxygen transport. Unlike a heme group, however, salen can be easily derived from ethylene diamine and salicylic aldehyde, and it acts as a catalyst.[1] Salen–metal complex catalyzes epoxidation, epoxide ring opening, Diels-Alder reaction, and so on.[2] Furthermore, a cobalt–salen complex can prevent cells from undergoing proliferation because of its damage on DNA. As a result, it can act as an antitumor agent. Especially, it shows activities against breast cancer and prostate cancer. It is known that the substituents of methoxyl or hydroxyl groups on 1,2-diarylethane moiety can increase the selectivity for tumor cell lines.[3] In order to obtain novel cobalt(III)–salen complex, we synthesized four complexes with 1,2-diarylethane moiety, which contains hydroxyl groups on A-ring and C-ring as shown in Fig. 1. The derivatives containing three different substituents on B-ring and D-ring were prepared. Because salen ligands without cobalt(III) have a mirror plane symmetry, they show severe overlapped ^{1}H NMR data. In cobalt(III)–salen complexes, the mirror plane symmetry is broken so that severe overlapping of their ^{1}H NMR data can be distinguished. Until now, X-ray crystallographic structures of cobalt–salen complexes and their partial NMR data have been reported, but there is no complete assignment.[4] In this paper, we report the complete NMR data of eight novel salen compounds with or without cobalt(III).

Results and Discussion

According to the ^{13}C NMR spectral analysis, the spectrum of compound **1** showed 14 peaks. As compounds **1**–**4** were synthesized on meso form, they had to possess reflection symmetry. In addition, ten methine carbons were observed in the DEPT spectrum. The most upfield shifted ^{13}C peak at 70.2 ppm should be C7, which was connected directly to the ^{1}H peak at 5.51 ppm in the HMQC spectrum. In addition, C7 was long-range coupled to the ^{1}H peaks at 7.30 and 8.35 ppm where the latter was the most downfield shifted ^{1}H peak of compound **1**. Therefore, the ^{1}H peak at 8.35 ppm was assigned to be H8, which was directly attached to the ^{13}C peak at 165.1 ppm. Furthermore, there are two possible protons that can be long-range coupled with C7, H2, and H5. As a result, the ^{1}H peak at 7.31 ppm can be assigned H2 or H5. These two protons could be distinguished in the data of H7–H4 TOCSY but not in the NMR data of compound **1**. Therefore, they were determined on the basis of the interpretation of the NMR data of compound **3**. According to the COSY spectrum of compound **3**, the order of four protons such as H2, H3, H4, and H5 was decided. In the TOCSY spectrum, ^{5}J correlation between H4 and H7 was observed. From the COSY and TOCSY spectra H2 and H5 were determined, which were 6.76 and 7.31 ppm respectively. The ^{13}C peak at 155.2 ppm was long-range coupled with H3, H5, and H7, so that it was assigned C1. Since one of the quaternary carbons, the peak at 126.2 ppm, showed a long-ranged coupling with H4, it was assigned C6. In the HMBC spectrum, H8 was long-range coupled to two ^{13}C peaks at 118.7 and 131.7 ppm. Because the former was quaternary carbon and the latter was methine carbon, which were determined to be C9 and C14, respectively. The ^{1}H peak at 7.25 ppm was directly attached to C14, so that it was H14.

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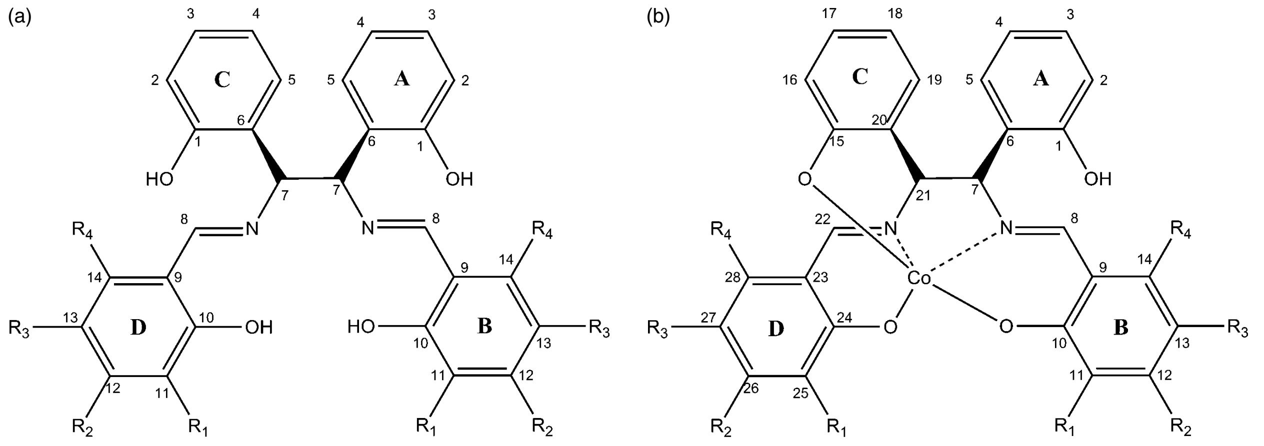
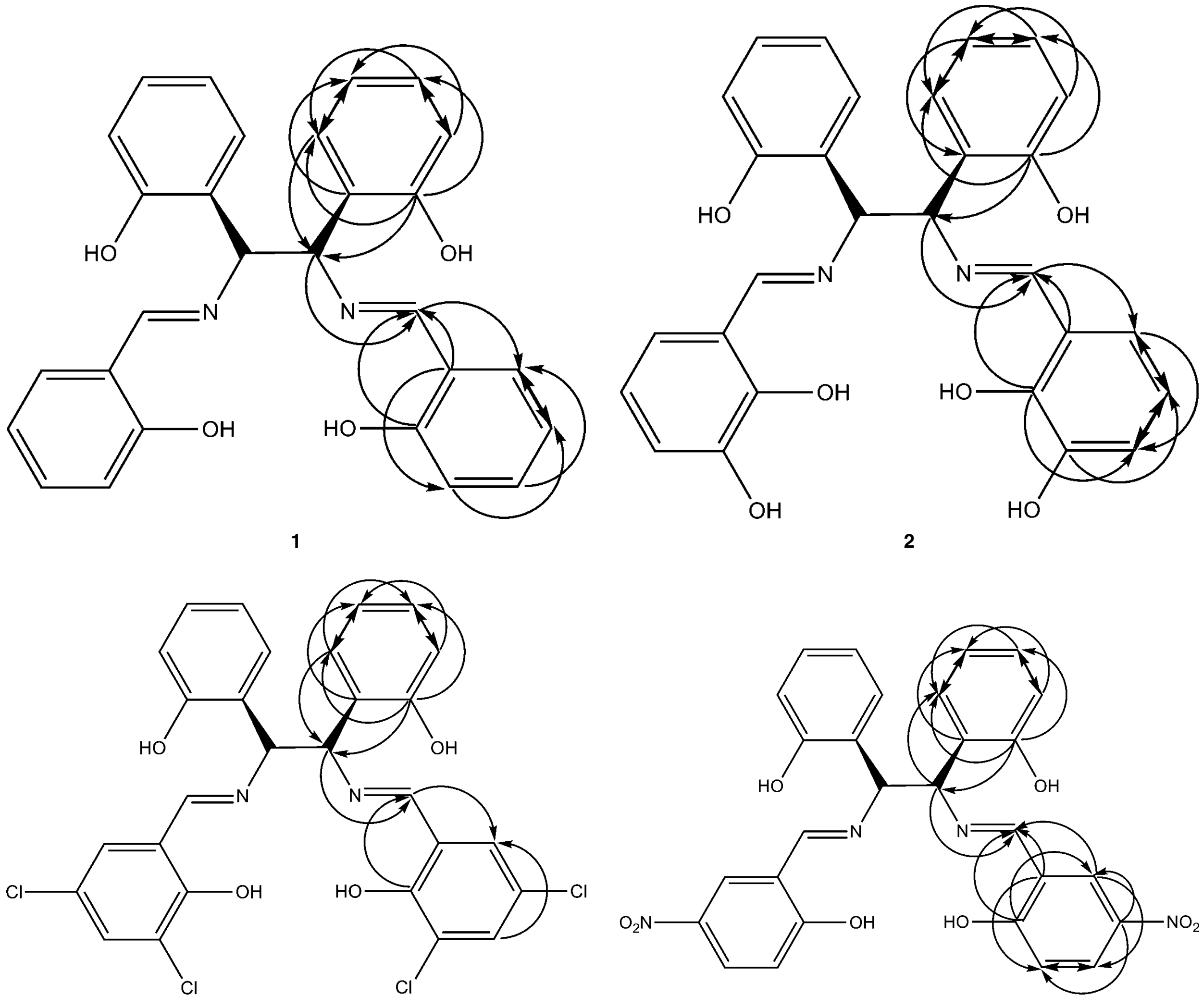


1: R1=R2=R3=R4=H
2: R1=OH, R2=R3=R4=H
3: R1=R3=Cl, R2=R4=H
4: R1=R2=R4=H, R3=NO_2

1: R1=R2=R3=R4=H
2: R1=OH, R2=R3=R4=H
3: R1=R3=Cl, R2=R4=H
4: R1=R2=R4=H, R3=NO_2

Figure 1. Structures and nomenclatures; (a) salens (**1**–**4**), (b) their cobalt (III) complexes (**5**–**8**).



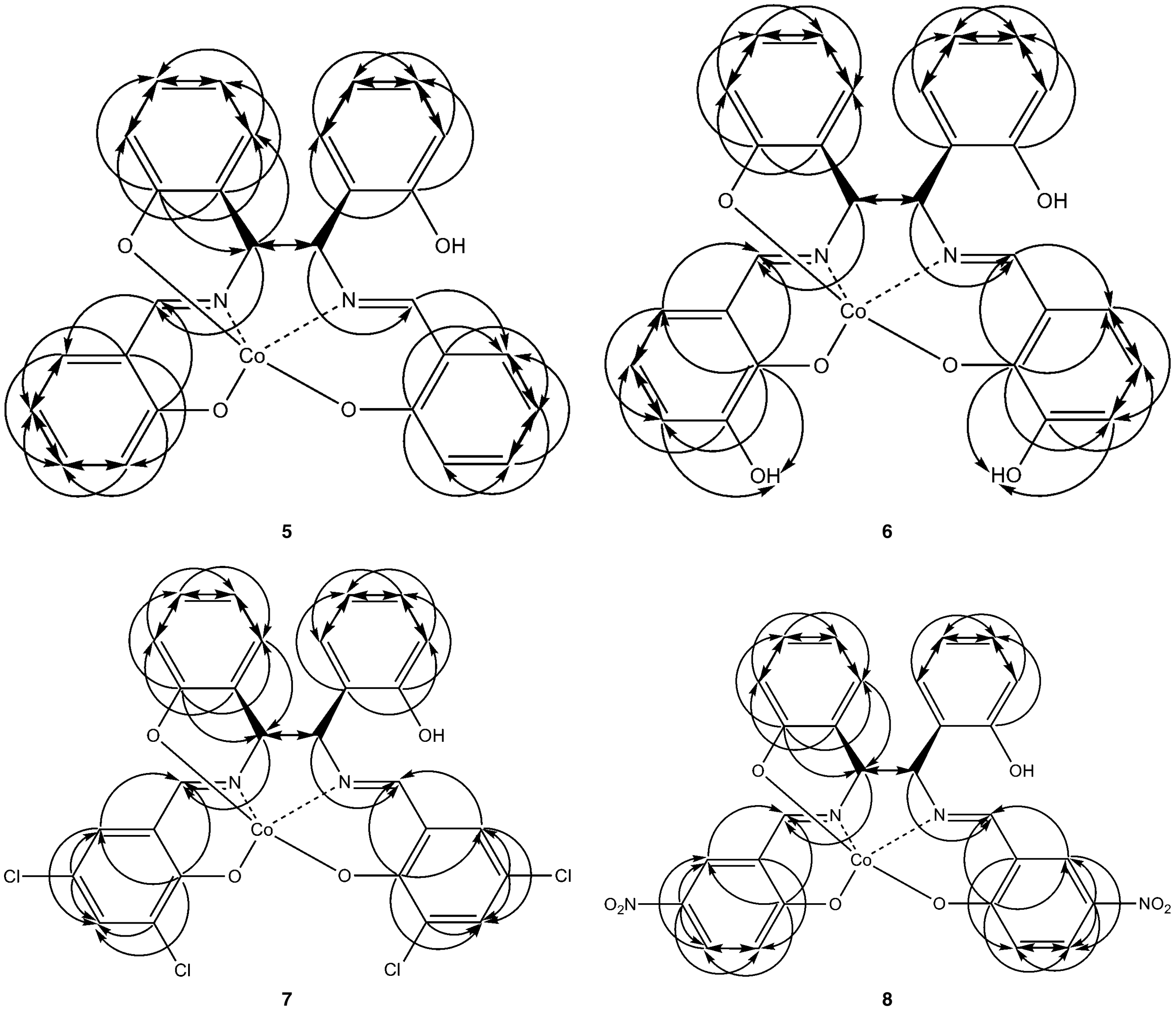
1

2

3

4

Figure 2. The connectivities observed from the interpretation of the COSY (↔) and HMBC (→) spectra of salen ligands (**1**–**4**) and cobalt (III)–salen complexes (**5**–**8**).



5 6 7 8

Figure 2. (*Continued*).

On the basis of the interpretation of the COSY and HMBC spectra, H11, H12, and H13 were determined. The undetermined ^{13}C peak at 160.4 ppm should be a hydroxylated carbon, C10. Furthermore, there were two hydroxyl protons observed at 9.60 and 13.36 ppm. When compound **1** was compared with compound **5**, the proton of 10-OH in compound **1** disappeared from compound **5**. As only the ^{1}H peak at 10.13 ppm was observed in compound **5**, the hydroxyl proton at 9.60 ppm in compound **1** was assigned 1-OH, and that at 13.36 ppm in compound **1** was 10-OH. Compounds **2**, **3**, and **4** contain 11-OH, 11-Cl/13-Cl, and 13-NO$_2$, respectively. On the basis of a comparison of the NMR data of compound **1** with those of other compounds, its NMR data could be analyzed completely. As a result, the assignments for the peaks are listed in Tables 1 and 2.

Unlike compounds **1**–**4**, compounds **5**–**8** are unsymmetry, so that 28 ^{13}C peaks and 20 ^{1}H peaks should be unambiguously assigned. Because the hydroxyl group of C-ring is connected to cobalt (III), it can be considered that the chemical shifts of C-ring are changed much more readily than those of A-ring. The most upfield shifted ^{13}C peak at 69.2 ppm could be assigned to C7 which was directly connected to the ^{1}H peak at 6.21 ppm (H7) in HMQC. That was a cross peak between two protons at 6.21 and 4.88 ppm in the COSY spectrum, and the ^{13}C peak at 75.3 ppm was attached to the latter proton at 4.88 ppm. Therefore, they were C21 and H21. The ^{1}H peaks and ^{13}C peaks of A-ring of compound **5** could be assigned based on a comparison of the chemical shifts with those determined in compound **1**. Consequently, six ^{13}C peaks at 156.2, 115.2, 129.1, 118.2, 129.4, and 117.2 ppm were C1, C2, C3, C4, C5, and C6, respectively. In addition, C21 was long-range coupled to two protons at 6.15 and 8.47 ppm. Because the former was doublet of doublet and the latter was singlet, the former was assigned H19, and the latter, H22. According to the spectral analyses of COSY, TOCSY, and HMBC (Fig. 2), the chemical shifts of C-ring could be determined. Since the ^{1}H peak at 7.38 ppm showed a long-ranged coupling with C22, it was assigned H28. Also, C28 determined by HMQC, 133.4 ppm, was long-range coupled to the ^{1}H peak at 7.26 ppm. Since the cross peaks around 7.26, 6.51, 7.16, and 7.38 ppm were observed in the COSY spectrum, they should belong to D-ring. On the basis of the interpretation of the COSY,

Table 1. The ^{1}H chemical shifts of salens (**1**–**4**) and their cobalt (III) complexes (**5**–**8**)

	d of ^{1}H (*J*, Hz)							
Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
2	6.76(m)	6.76(m)	6.83(m)	6.85(m)	7.01(d, 7.6)	7.00(d, 7.4)	7.02(d, 7.4)	7.03(d, 7.4)
3	7.02(td, 1.5, 7.7)	7.03(td, 1.0, 7.7)	7.10(td, 1.8, 7.4)	7.13(td, 1.5, 7.3)	7.17(m)	7.17(td, 1.4, 7.4)	7.20(td, 1.6, 7.4)	7.21(m)
4	6.77(m)	6.78(m)	6.81(m)	6.81(m)	6.52(m)	6.53(t, 7.4)	6.55(m)	6.57(t, 7.4)
5	7.31(dd, 1.5, 7.7)	7.31(dd, 1.0, 7.7)	7.32(.dd, 1.8, 7.4)	7.31(dd, 1.5,7.3)	5.89(d, 7.6)	5.92(d, 7.4)	5.90(d, 7.4)	5.90(d, 5.9)
7	5.51(s)	5.52(s)	5.56(s)	5.60(s)	6.21(m)	6.22(m)	6.24(dd, 2.1, 4.9)	6.23(d, 1.6)
8	8.35(s)	8.30(s)	8.30(s)	8.50(s)	7.35(m)	7.34(d, 1.8)	7.50(d, 2.1)	7.72(d, 1.6)
11	6.80(m)	–	–	6.75(d, 9.5)	7.34(m)	–	–	7.45(d, 9.5)
12	7.27(m)	6.77(m)	7.55(d, 2.5)	8.06(dd, 2.9, 9.5)	7.33(m)	6.82(dd, 1.4, 7.4)	7.64(d, 2.7)	8.16(dd, 2.9, 9.5)
13	6.78(m)	6.57(t, 7.8)	–	–	6.43(ddd, 1.8, 6.1, 8.0)	6.32(t, 7.4)	–	–
14	7.28(m)	6.70(dd, 1.5, 7.8)	7.34(d, 2.5)	8.30(d, 2.9)	7.10(dd, 1.5, 8.0)	6.60(m)	7.41(d, 2.7)	8.49(d, 2.9)
16	–	–	–	–	6.41(dd, 1.0, 8.3)	6.41(m)	6.52(m)	6.51(dd, 1.5, 7.5)
17	–	–	–	–	6.61(ddd, 1.7, 7.3, 8.3)	6.62(m)	6.67(td, 1.6, 7.3)	6.67(td, 1.5, 7.5)
18	–	–	–	–	5.98(td, 1.0, 7.3)	6.01(td, 1.1, 7.2)	6.06(td, 1.1, 7.3)	6.08(td, 1.5, 7.5)
19	–	–	–	–	6.15(dd, 1.7, 7.3)	6.18(dd, 1.5, 7.2)	6.20(dd, 1.6, 7.3)	6.22(m)
21	–	–	–	–	4.88(d, 4.1)	4.90(d, 3.7)	4.93(d, 4.9)	4.97(d, 3.8)
22	–	–	–	–	8.47(s)	8.45(s)	8.56(s)	8.76(s)
25	–	–	–	–	7.16(m)	–	–	7.23(d, 9.5)
26	–	–	–	–	7.26(ddd, 1.8, 6.9, 8.5)	6.74(dd, 1.5, 7.7)	7.56(d, 2.7)	8.11(dd, 2.9, 9.5)
27	–	–	–	–	6.51(m)	6.39(t, 7.7)	–	–
28	–	–	–	–	7.38(m)	6.87(dd, 1.5, 7.7)	7.47(d, 2.7)	8.53(d, 2.9)
1-OH	9.6	9.61	10	10.19	10.13	10.14	10.17	10.21
10-OH	13.36	13.48	14.7	14.79	–	–	–	–
11-OH	–	8.89	–	–	–	9.12	–	–
25-OH	–	–	–	–	–	8.89	–	–

Table 2. The ^{13}C chemical shifts of salens (**1**–**4**) and their cobalt (III) complexes (**5**–**8**)

	d of 13C							
Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	155.2	155.1	154.8	155.1	156.2	156.3	156.4	156.1
2	115.3	115.3	115.3	115.7	115.2	115.3	115.4	115.2
3	128.2	128.3	128.7	129.5	129.1	129.3	129.5	129.4
4	119.0	117.7	118.9	119.3	118.2	118.2	118.5	118.4
5	128.7	128.8	128.9	129.4	129.4	129.5	129.5	129.3
6	126.2	125.9	123.9	123.2	117.2	118.1	117.2	117.1
7	70.2	69.6	68.9	68.3	69.2	69.1	69.9	70.0
8	165.1	165.4	164.3	165.5	165.3	164.8	165.6	166.4
9	118.7	118.2	117.8	115.4	117.5	116.0	118.9	125.1
10	160.4	150.9	159.3	172.4	166.0	154.5	159.3	171.3
11	118.4	145.7	122.6	120.5	122.1	149.9	126.7	122.4
12	132.3	119.0	132.1	128.7	134.2	114.6	133.1	128.6
13	116.4	117.6	117.9	136.2	113.1	113.3	115.6	134.7
14	131.7	121.9	129.8	130.4	134.7	123.8	132.6	133.2
15	–	–	–	–	161.4	161.3	160.9	160.5
16	–	–	–	–	119.5	119.6	119.8	119.6
17	–	–	–	–	127.9	127.9	128.4	128.3
18	–	–	–	–	111.7	111.9	112.6	112.7
19	–	–	–	–	128.6	128.7	128.8	128.7
20	–	–	–	–	120.9	121.0	120.4	120.2
21	–	–	–	–	75.3	75.4	75.7	75.6
22	–	–	–	–	163.8	164.2	164.5	165.0
23	–	–	–	–	119.8	118.6	121.1	118.9
24	–	–	–	–	166.4	154.9	159.7	171.9
25	–	–	–	–	121.9	150.1	126.6	122.2
26	–	–	–	–	133.5	114.1	132.6	128.1
27	–	–	–	–	113.2	113.5	115.5	134.6
28	–	–	–	–	133.4	122.6	131.3	131.7

HMQC, and HMBC spectra, they were assigned H26, H27, H25, and H28, respectively. The connectivities obtained from the COSY and HMBC spectra are shown using arrows in Fig. 2. In addition, the ^{13}C peak at 119.8 ppm showing two long-ranged couplings with H25 and H27 should be C23. Moreover, another ^{13}C peak at 166.4 ppm showing two long-ranged couplings with H22 and H26 should be assigned C24. Because the ^{1}H peak at 7.35 ppm was long-range coupled to C7, it could be either H5 or H8. In addition, the ^{1}H at 7.35 was attached to ^{13}C peak at 165.3 ppm in HMQC, thus the proton peak should be H8. Like D-ring, with the help of the interpretation of the COSY, HMQC, and HMBC spectra, H11/C11, H12/C12, H13/C13, and H14/C14 could be determined. The connectivities obtained from the COSY and HMBC spectra are shown using arrows in Fig. 2. Thus far, only two ^{13}C peaks at 166.0 and 117.5 ppm have not been assigned yet. However, since C10 was a hydroxylated carbon, the former should be assigned C10. The complete assignments of the ^{1}H and ^{13}C NMR data of compounds are listed in Tables 1 and 2, respectively.

Like compounds **2**–**4**, compounds **6**, **7**, and **8** contained more substituents such as 11-OH/25-OH, 11-Cl/13-Cl/25-Cl/27-Cl, and 13-NO_2/27-NO_2, respectively, so that their NMR data could be used to assign those functional groups based on a comparison of the NMR data of those compounds with literature data of closely related to the corresponding compounds. They are listed in Tables 1 and 2.

In salen ligands (**2**–**4**), the substitutions on B- and D-rings do not affect the ^{1}H and ^{13}C chemical shifts of A- or C-rings. The substitution of hydroxyl group in salen ligand **2** causes about 10 ppm upfield shift of the ^{13}C chemical shifts at *ortho* and *para* positions, but the chlorinated substitution in salen ligand **3** causes only 1 ppm upfield shift. In the case of nitro group, *ortho* position is upfield shifted and *para* position is downfield shifted. In cobalt (III)–salen complexes (**5**–**8**), cobalt (III) is bound to two nitrogens and two oxygens and causes changes in the ^{13}C chemical shifts. Moreover, C6 in A-ring is placed at the β-position from nitrogen. Unlike other β-positioned carbons, the ^{13}C chemical shift of C6 involves an upfield shift of around 10 ppm. While C6 is connected to nitrogen atoms through two single bonds, other β-positioned carbons are connected to nitrogen or oxygen that is bound to cobalt (III) through a conjugated double bond. Furthermore, the substituents on B- and D-rings of cobalt (III)–salen complexes (**6**–**8**) result in the same pattern as the salen ligands (**2**–**4**). The assignments of ^{1}H and ^{13}C NMR data obtained in this experiment can help us to predict the NMR data of other salen ligands.

Experimental

Synthesis

Meso 1,2-bis(2-hydroxyphenyl)ethylenediamine was prepared according to literature method[5] and used for synthesis of salen ligands (**1**–**4**) with the following general synthetic procedure.[6] Briefly, substituted salicylic aldehydes (3 mmol, 2 eq.) was added to a suspension of diamine (1.5 mmol, 1 eq.) in acetonitrile solution and stirred at room temperature to give a clear solution. After 2 h, the reaction mixture gave yellow precipitation, which was filtered off and dried to furnish corresponding salen ligands (**1**–**4**) in 86–92% yield. Then, the salen ligand was suspended in ethanol solvent and equal equivalent of $Co(OAc)_2$ was added to the suspension. After 3 h reflux, the reaction mixture was cooled down and solvent was evaporated under reduced pressure. The residue was washed with chloroform twice and filtered to give the resultant brown to black solid of cobalt complex (**5**– **8**).

NMR Spectra

All NMR experiments were performed on a Bruker Avance 400 spectrometer system (9.4 T, Karlsruhe, Germany) at 298 K. The samples were dissolved in 500 µl DMSO-d_6 and transferred into 5 mm NMR tubes. They were prepared to be approximately 50 mM. For the ^{1}H NMR and ^{13}C NMR analyses, 16 and 1024 transients were acquired with 1 and 3 s relaxation delay using 32 and 64 K data points, respectively. Their 90° pulses were 10.2 µs and 10.3 µs with spectral widths of 6000 and 23 809 Hz, respectively. All two-dimensional spectra except NOESY were acquired with 2048 data points for t_2 and 256 for t_1 increments using magnitude mode. The NOESY spectra were collected using time proportional phase increments at the mixing time of 1 s, whereas the long-ranged coupling time for HMBC was 70 ms. Prior to Fourier transformation, zero filling of 2 K and sine squared bell window function were applied using XWIN-NMR (Bruker).[7]

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