Structure and conformational properties of three-layered cyclophanes prepared by a one-pot synthesis

Akihiko Tsuge[a,b]*, Takahiro Okamoto[a] and Tetsuji Moriguch[a]

[a]*Department of Applied Chemistry, Kyushu Institute of Technology, Tobata-ku, Kitakyushu 804-8550, Japan*

[b]*Institute of Materials Chemistry and Engineering, Kyushu University, Higashi-ku, Fukuoka 812-8581, Japan*

The coupling reactions of substituted bis(bromomethyl)benzene components and tetra(mercaptomethyl)benzene derivatives have been carried out under heterogeneous dilute reaction conditions to afford the three-layered cyclophanes **3a**–**e** as three kinds of conformational isomers in moderate yields.

Keywords: cyclophanes, conformation, X-ray analysis

Due to its innovative properties, the novel π–π stacking system[1] is one of the most interesting developments in various fields such as supramolecular chemistry[2] and biochemistry.[3] The most characteristic feature in the field of supramolecular chemistry is that the components are held together reversibly by intermolecular forces in which π–π stacking interactions play an important role. Such interactions, as well as hydrogen bonding and electrostatic forces, work very effectively in complementary molecular systems in biology. Furthermore, in the field of semiconductor materials[4] enforced face-to-face π-stacking of aromatics in the solid state is important.[5] In this context maximising π-orbital overlap is a key point to achieve efficient charge transport properties of such solids.

Cyclophanes,[6] which are bridged aromatic molecules, have been expanding their roles in helping to understand weak, non-covalent interactions involving π-electrons. The small-sized cyclophanes, in which the aromatic components are fixed in close proximity to each other could be an especially good models for the study of weak interactions[7] such as π–π, CH–π or NH–π interactions. From these reasons, layered cyclophanes consisting of more than three aromatic rings deserve intensive research.

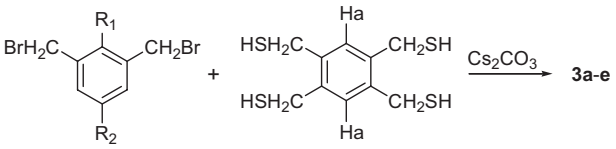
Although pioneering and extensive work concerning multi-layered cyclophanes has been carried out by Staab and Zaph[8] and Misumi,[9] their interests have mainly focused on the synthesis and charge-transfer complexes of the cyclophanes. In most cases, they have adopted a stepwise synthetic method. Thus, the functional groups on the aromatic rings have been limited to simple ones such as the methyl group.

For example, a six-layered [2.2]paracyclophane[10] was prepared and exhibited interesting optical properties. More recently a "molecular ribbon"[11] made of nine layers of diaza[3.3] metacyclophanes has also been reported to form a nano-sized structure. These results suggest that multi-layered cyclophanes can be expected to give unique structures based on the π-electron system. Functional groups which modify the electronic character on the aromatic rings could give some novel functions to the stacked π-electron system. To the best of our knowledge, however, multi-layered cyclophanes to which various functional groups are introduced have never been reported.

We have already reported[12] that the electronic nature of the substituents introduced into the aromatic components in cyclophanes has a great effect on their π-systems. We describe here the one-pot synthesis of three-layered cyclophanes having functional groups such as a methoxy and a nitro group on the aromatic components and also discuss their structural and conformational properties.

Results and discussion

At first, a conventional high-dilution coupling method of dibromide **1** and tetra(mercapotomethyl)benzenes **2** was adopted to prepare the desired cyclic compounds. However, a complex mixture was obtained after repeated trials. Thus, the reaction was then carried out under heterogeneous dilute conditions[13] at room temperature instead. A solution of **1** and **2** in a mixture of ethanol and benzene was stirred for 5 days at room temperature to give a separable mixture of the desired three-layered cyclophanes (Scheme 1). All isolated compounds were identified by ^{1}H NMR, mass spectrometry and elemental analysis.



1a-e **2**

a: R_1= H, R_2= H
b: R_1= H, R_2= OCH_3
c: R_1= OCH_3, R_2= H
d: R_1= CH_3, R_2= $C(CH_3)_3$
e: R_1= NO_2, R_2= H

Scheme 1

The structural and conformational features of **3a**–**e** in the solution and in the solid state were determined by ^{1}H NMR spectroscopy and X-ray structural analysis. The ^{1}H NMR data are summarised in Table 1.

For **3a**, two major isomers **3a**–**1** and **3a**–**2** were obtained in 26% and 21% yields, respectively. **3a**–**1** shows one singlet and a set of doublets for the bridge protons and shielded signals for aromatic proton (R_1). On the other hand two singlets were observed for the bridge protons in **3a**–**2**. A slightly broadened peak was observed for the bridge protons of both **3a**–**1** and **3a**–**2** when lowering the temperature to –50°C, indicating that they are comformationally flexible structures. The upfield shift of the proton (R_1) in **3a**–**1** indicates that this proton should be located in the shielded area of the central aromatic ring. Taking into account the conformations that satisfy these NMR assignments, two possible isomers can be considered. They are the *anti-meta–meta* and the *meta–para* structures shown in Scheme 2. By means of the X-ray analysis shown in Fig. 1, **3a**–**1**[14] can be assigned the structure which contains a *meta–para*-linked benzene ring.

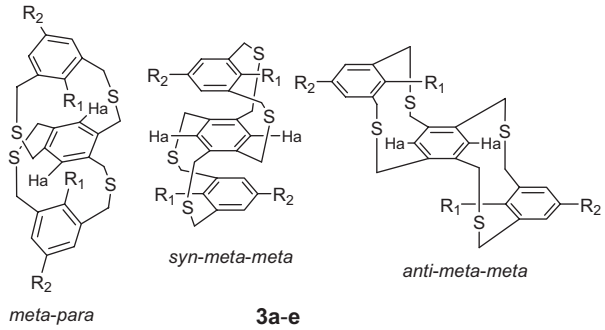
This conformation is consistent with the signal of the proton (R_1) which plunges into the π-cloud of the central aromatic ring as indicated by the ^{1}H NMR spectrum. This *meta-para* conformation is the first example in such a three-layered cyclophane ever synthesised. Although no suitable single crystal of **3a**–**2** could be obtained, the structural assignments could be made on the basis of its ^{1}H NMR signals. No upfield signal of the proton (R_1) strongly suggests the *syn* structure. Considering that the *meta* conformation is confirmed for the cyclophane **3c**–**2** as described later, it can be concluded that **3a**–**2** is the *syn-meta–meta* conformer.

* Correspondent. E-mail:tsuge@che.kyutech.ac.jp

Table 1 Chemical shifts[a] and structure of cyclophanes

Compound	Bridge proton	Ha	R1	Structure
		δ		
3a-1	3.88(s) 3.43(d) 4.11(d)	6.35	5.85	*meta–para*
3a-2	3.21(s) 3.66(s)	6.62	8.19	*syn-meta–meta*
3b-1	3.35(s) 3.44(d) 4.12(d)	6.35	5.24	*meta–para*
3b-2	3.67(s) 3.79(s)	6.09	6.49	*syn-meta–meta*
3c-1	3.49(d) 3.67(d) 3.82(d) 3.98(d)	5.82	2.94	*anti-meta–meta*
3c-2	3.40(d) 3.57(d) 4.11(d) 4.23(d)	6.58	3.66	*syn-meta–meta*
3d-1	3.31(d) 3.75(d) 3.81(d) 3.83(d)	4.82	1.06	*anti-meta–meta*
3d-2	3.31(d) 3.69(d) 3.77(d) 3.92(d)	5.77	2.01	*syn-meta–meta*
3e-1	3.54(d) 3.60(d) 3.95(d) 4.02(d)	5.82	–	*anti-meta–meta*
3e-2	3.52(d) 3.98(d) 3.93(d) 4.04(d)	6.84	–	*syn-meta–meta*

[a]In $CDCl_3$ at 27°C



3a-e

Scheme 2

Two isomers (**3b–1** and **3b–2**) for **3b** were also isolated in 22% and 17% yields, respectively. As indicated by the X-ray analysis shown in Fig. 1, the isomer having a *meta-para*-linked benzene ring is confirmed for **3b–1**.[16] **3b–1** exhibits the pattern of the ^{1}H NMR signals similar to that in **3a–1**. On the other hand two singlets are seen for the bridge protons in **3b–2** as well as **3a–2**. These results strongly suggest that inversion of the ring must occur in **3a–2** and **3b–2**. The Ha proton appears in the deshielded region. Thus, the conformation of **3b–2** can be assigned as the *syn-meta–meta* conformation as shown in Scheme 2.

In the coupling of **1c** and **2**, **3c–1** and **3c–2** were isolated in 38% and 12% yields, respectively. Both isomers show two sets of doublets for the bridge protons in their ^{1}H NMR spectra. No apparent changes in the ^{1}H NMR signal patterns of these isomers were observed over the temperature range of –50°C to 50°C, indicating that they exist as rigid structures in this temperature range. This rigid feature excludes the *ortho–meta* conformation since *ortho–meta* cyclophanes are known to show flexibility.[15] The significant upfield shift of the signals for the methoxy protons in **3c–1** seems closely related to a shielding effect of the central aromatic ring. The central aromatic protons (Ha) in **3c–1** are also somewhat shielded. From these results it can be concluded that **3c–1** assumes the *anti-meta–meta* structure. On the contrary the signals for the methoxy protons in **3c–2** appear in the normal region and the chemical shift of Ha is located in the somewhat shielded region compared with the corresponding proton in the tetra(mercaptomethyl)benzene derivative. This behaviour is also seen for **3a–2** and **3b–2**. As shown in Figure 2 the *syn-meta–meta*-conformation is confirmed for **3c–2**.[17] This assignment strongly supports the conclusion that **3a–2** and **3b–2** also assume the *syn-meta–meta* conformation as expected above.

The coupling using **1d** gave two isomers (**3d–1** (18%) and **3d–2** (16%)). These compounds exhibit two sets of doublets as the signals of the bridge protons, indicating that they adopt a rigid conformation. The upfield shifts of both methyl protons and central aromatic protons in **3d–1** imply that this conformer is also the *anti-meta–meta* conformer. Thus, **3d–1** and **3d–2** can be assigned as the *anti-meta–meta* conformer and the *syn-meta–meta* conformer, respectively.

In the synthesis of the cyclophane having the nitro group at the inner position, **3e–1** and **3e–2** were isolated in the yields

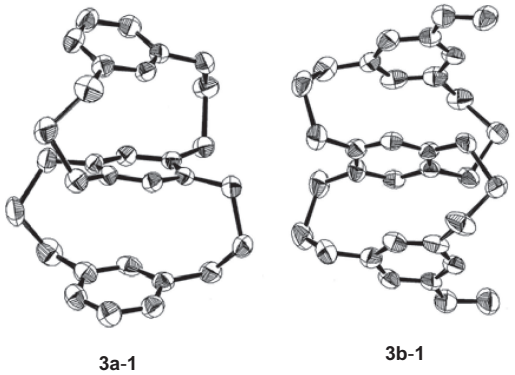


Fig. 1 X-ray structure of **3a-1** and **3b-1**.

Fig. 2 X-ray structure of **3c-2**.

of 8% and 10%, respectively. Considering the results of **3c** and **3d**, **3e–1** and **3e–2** can be assigned as the *anti-meta–meta*-conformer and the *syn-meta–meta*-conformer, respectively. From the results for **3c**–**3e** it can be seen that the substituent at the inner position (R_1) enforces a rigid conformation since the substituent hinders the rotation of the aromatic rings. This inner substituent also seems to prevent formation of the *meta–para* structure due to steric hindrance between the substituent and the central aromatic ring.

It has been found that three-layered cyclophanes can be obtained effectively by a one-pot synthesis under heterogeneous conditions. Three kinds of isomer were produced depending on the molecular structure of the aromatic components employed in the reaction. The three-layered cyclophane containing a *meta–para*-linked aromatic ring was successfully isolated and confirmed by the X-ray analysis for the first time. This unique conformer can be obtained when the aromatic component having the proton at its inner position is employed in the coupling reaction. On the contrary the aromatic component having a substituent at its inner position seems to induce the formation of the rigid *meta–meta* structure. These results suggest that the inner substituent has a significant influence on the conformation of the three-layered cyclophanes. It should be noted that these layered cyclophanes consisting of the stacked aromatic rings could be used as suitable models for the study of π-electron systems.

Experimental

Melting points were determined on a Yanaco Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Nippon Denshi JEOL JNM-400 spectrometer. Mass spectra were obtained on a Nippon Denshi JEOL DX-300 instrument at 75 eV using a direct-inlet system. Elemental analyses were carried out by Mr. Masatoshi Takeo on a Yanaco MT-3 spectrometer in the Centre for Instrumental Analysis. Column chromatography was performed on silica gel (Wako gel, C-300).

Typical procedure for coupling reaction

A solution of **1a** (1.32 g, 5.0 mmol), 2 (0.66 g, 2.5 mmol) and Cs_2CO_3 (3.26 g, 10.0 mmol) in a mixture of ethanol and benzene (1 : 1) (1 l) was stirred for 5 days at room temperature. The reaction mixture was concentrated and the residue was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, concentrated and chromatographed using 3 : 2 mixture of CH_2Cl_2 and hexane as an eluent to give **3a–1** (0.30 g, 26%) and **3a–2** (0.24 g, 21%). Both **3a–1** and **3a–2** were colourless prisms. **3a–1**; m.p. 232–234°C (chloroform-hexane); (Found: C, 66.7; H, 5.8. Calc. for $C_{26}H_{26}S_4$: C, 66.9; H, 5.6%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.38 (8H, s), 3.43 (4H, d, J = 13.6), 4.11 (4H, d, J = 13.6), 5.58 (2H, s), 6.35 (2H, s), 6.93 (4H, d, J = 6.8), 7.03 (2H, d, J = 6.8); m/z (EI) 466 (M^+). 3a–2; m.p. > 300°C (chloroform–hexane); (Found: C, 66.6; H, 5.8. Calc. for $C_{26}H_{26}S_4$: C, 66.9; H, 5.6%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.21 (8H, s), 3.66 (8H, s), 6.11 (2H, s), 6.62 (2H, d, J = 6.8), 6.98 (4H, d, J = 6.8), 8.19 (2H,s); m/z (EI) 466 (M^+).

Cyclophane **3b–1**: Colourless prisms; m.p. 258–261°C (chloroform–hexane); (Found: C, 63.7; H, 5.8. Calc. for $C_{28}H_{30}O_2S_4$: C, 63.8; H, 5.7%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.35 (8H, s), 3.44 (4H, d, J = 13.6), 3.72 (6H, s), 4.12 (4H, d, J = 13.6), 5.24 (2H, s), 6.35 (2H, s), 6.50 (4H, s); *m/z* (EI) 526 (M^+).

Cyclophane **3b–2**: Yellow prisms; m.p. >300°C (chloroform–hexane); (Found: C, 63.5; H, 5.8. Calc. for $C_{28}H_{30}O_2S_4$: C, 63.8; H, 5.7%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.64 (6H, s), 3.67 (8H, s), 3.79 (8H, s), 6.09 (2H, s), 6.48–6.51 (6H, m); *m/z* (EI) 526 (M^+).

Cyclophane **3c–1**: Colourless powder; m.p. 271–273°C (toluene); (Found: C, 63.4; H, 5.8. Calc. for $C_{28}H_{30}O_2S_4$: C, 63.8; H, 5.7%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.94 (6H, s), 3.49 (4H, d, J = 15.4), 3.67 (4H, d, J = 13.8), 3.82 (4H, d, J = 15.4), 3.98 (4H, d, J = 13.8), 5.82 (2H, s), 6.80 (2H, t, J = 9.3), 7.07 (4H, t, J = 9.3); *m/z* (EI) 526 (M^+).
Cyclophane **3c–2**: Colourless prisms; m.p. >300°C (chloroform–hexane); (Found: C, 63.7; H, 5.9. Calc. for $C_{28}H_{30}O_2S_4$: C, 63.8; H, 5.7%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.40 (4H, d, J = 14.3), 3.57 (4H, d, J = 15.0), 3.66 (6H, s), 4.11 (4H, d, J = 15.0), 4.23 (4H, d, J = 14.3), 6.46 (2H, d, J = 7.6), 6.58 (2H, s), 6.78 (4H, d, J = 7.6); *m/z* (EI) 526 (M^+).

Cyclophane **3d–1**: Colourless prisms; m.p. >300°C (toluene); (Found: C, 71.0; H, 7.6. Calc. for $C_{36}H_{46}S_4$: C, 71.2; H, 7.6%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.26 (18H, s), 1.60 (6H, s), 3.31 (4H, d, J = 14.8), 3.75 (4H, d, J = 13.6), 3.81 (4H, d, J = 14.8), 3.83 (4H, d, J = 13.6), 4.82 (2H, s), 7.12 (4H, s); *m/z* (EI) 606 (M^+).

Cyclophane **3d–2**: Colourless prisms; m.p. >300°C (chloroform–hexane); (Found: C, 70.6; H, 7.8. Calc. for $C_{36}H_{46}S_4$: C, 71.2; H, 7.6%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22 (18H, s), 2.01 (6H, s), 3.31 (4H, d, J = 14.9), 3.69 (4H, d, J = 14.9), 3.77 (4H, d, J = 13.6), 3.92 (4H, d, J = 13.6), 5.77 (2H, s), 7.10 (4H, s); *m/z* (EI) 606 (M^+).

Cyclophane **3e–1**: Yellow prisms; m.p. 288–290°C (chloroform–hexane); (Found: C, 56.0; H, 4.6. Calc. for $C_{26}H_{24}N_2O_4S_4$: C, 56.1; H, 4.4%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.54 (4H, d, J = 15.1), 3.60 (4H, d, J = 14.3), 1.22 (18H, s), 3.95 (4H, d, J = 14.3), 4.02 (4H, d, J = 15.1), 5.82 (2H, s), 7.10 (2H, t, J = 7.3), 7.22 (4H, d, J = 7.3); *m/z* (EI) 556 (M^+).

Cyclophane **3e–1**: Yellow prisms; m.p. >300°C (chloroform–hexane); (Found: C, 55.7; H, 4.6. Calc. for $C_{26}H_{24}N_2O_4S_4$: C, 56.1; H, 4.4%); δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.52 (4H, d, J = 14.6), 3.89 (4H, d, J = 15.7), 3.93 (4H, d, J = 15.7), 4.04 (4H, d, J = 14.6), 6.65 (2H, t, J = 7.3), 6.84 (2H, s), 6.88 (4H, d, J = 7.1); *m/z* (EI) 556 (M^+).

Received 23 May 2007; accepted 5 July 2007
Paper 07/4654 doi: 10.3184/030823407X228786

References

1 C.A. Hunter and J.K.M. Sanders, *J. Am. Chem. Soc.*, 1990, **112**, 5525.
2 For example, see: F. Vögtle, *Supramolecular Chemistry*; Wiley, Chichester, 1989; J.-M. Lehn, *Pure Appl. Chem.*, 1994, **66**, 1961; J.-M. Lehn, *Supramolecular Chemistry*, VCH: Weinheim, 1995; J.W. Steed and J.F. Atwood, *Supramolecular Chemistry*, Wiley: Chichester, 2000.
3 C.R. Calladine and H.R. Drew, *Understanding DNA*, Academic Press, New York, 1998.
4 M. Bendikove, F. Wull, and D.F. Perepichka, *Chem. Rev*., 2004, **104**, 4891; A. Facchetti, M.-H. Yoon, C.L. Stern, G.R. Hutchison, M.A. Ratner and T.J. Marks, *J. Am. Chem. Soc.*, 2004, **126**, 13480; M. Halik, H. Klauk, U. Zschieschang, G. Schmid, S. Ponomarenko, S. Kirchmeyer and W. Weber, *Adv. Mater*., 2003, **15**, 917.
5 H. Moon, R. Zeis, E.-J. Borkent, C. Besnard, A.J. Lovinger, T. Siegrist, C. Kloc and Z. Bao, *J. Am. Chem. Soc.*, 2004, **126**, 15322; H. Meng, M. Bendikov, G. Mitchell, R. Holgeson, F. Wudl, Z. Bao, T. Siegrist, C. Kloc and C.-H. Chen, *Adv. Mater*., 2003, **15**, 1090.
6 F. Vögtle, *Cyclophane Chemistry*, Wiley, Chichester, 1989; F. Diederich, *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991.
7 J.M. Ma and D. Dougherty, *Chem. Rev*., 1997, **97**, 1303; M. Nishino, M. Hirota and Y. Umezawa, *The CH/π interaction*, Wiley-VCH, New York, 1998.
8 H.A. Staab and U. Zaph, *Angew. Chem. Int. Ed. Engl*., 1978, **17**, 757.
9 S. Misumi, in *Cyclophanes*, ed. by P.M. Keehn, S.M. Rosenfeld, Academic Press, New York, 1983, Vol. 2, pp. 573.
10 M. Nakazaki, K. Yamamoto, S. Tanaka and H. Kametani, *J. Org. Chem*., 1977, **42**, 287.
11 S. Breidenbach, S. Ohren and F. Vögtle, *Chem. Eur. J.*, 1996, **2**, 832.
12 A. Tsuge, M. Otsuka, T. Moriguchi and K. Sakata, *Org. Biomol. Chem*., 2005, **3**, 3590; A. Tsuge, W. Iwasaki, T. Moriguchi and K. Sakata, *Chem. Lett*., 2004, **33**, 756; A. Tsuge, H. Nishimoto, T. Moriguchi and K. Sakata, *Chem. Lett*., 2003, **32**, 776; A. Tsuge, Y. Tanba, T. Moriguchi and K. Sakata, *Chem. Lett*., 2002, 384.
13 S. Breidenbach, S. Ohren, R.H. Irmer, S. Kotila, M. Nieger and F. Vögtle, *Liebigs Ann*., 1996, 2115.
14 *Crystal data* **3a–1**. $C_{26}H_{26}S_4$, M = 466.73, monoclinic, space group $P2_1/n$ (No. 14), a = 17.188(4) Å, b = 9.731(3) Å, c = 14.125(3) Å, β = 103.70(2)°, V = 2295.2(8) Å^3, Z = 4, D_{calcd} = 1.351 gcm^{-3}, Rigaku AFC7R diffractometer, R_1 = 0.046 (for 3619 reflections with $I > 3\sigma(I)$), wR_2 = 0.167 (for all data (4174 reflections)). CCDC reference No. 609648.
15 *Crystal data* **3b–1**. $C_{28}H_{30}O_2S_4$, M = 526.78, monoclinic, space group $P2_1/n$ (No. 14), a = 16.917(3) Å, b = 17.858(3) Å, c = 16.809(3) Å, β = 91.41(1)°, V = 5076(1) Å^3, Z = 8, D_{calcd} = 1.378 gcm^{-3}, Rigaku AFC7R diffractometer, R_1 = 0.084 (for 5107 reflections with $I > 3\sigma(I)$), wR_2 = 0.1249 (for all data (9216 reflections)). CCDC reference No. 609965.
16 R.H. Mitchell, in *Cyclophanes*, ed. by P.M. Keehn, S.M. Rosenfeld, Academic Press, New York, 1983, Vol. 2, pp. 240.
17 *Crystal data* **3c–2**. $C_{28}H_{30}O_2S_4$, M = 526.78, monoclinic, space group $P2_1/n$ (No. 14), a = 11.4375(9) Å, b = 11.315(1) Å, c = 9.9296(8) Å, β = 95.681(6)°, V = 1278.7(2) Å^3, Z = 2, D_{calcd} = 1.368 gcm^{-3}, Rigaku AFC7R diffractometer, R_1 = 0.047 (for 2200 reflections with $I > 3\sigma(I)$), wR_2 = 0.159 (for all data (2326 reflections)). CCDC reference No. 609826.

CCDC 609648, CCDC 609965 and CCDC 609826 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from cambridge Crystllographic Data Centre via 609648, CCDC 609965 and CCDC 609826.