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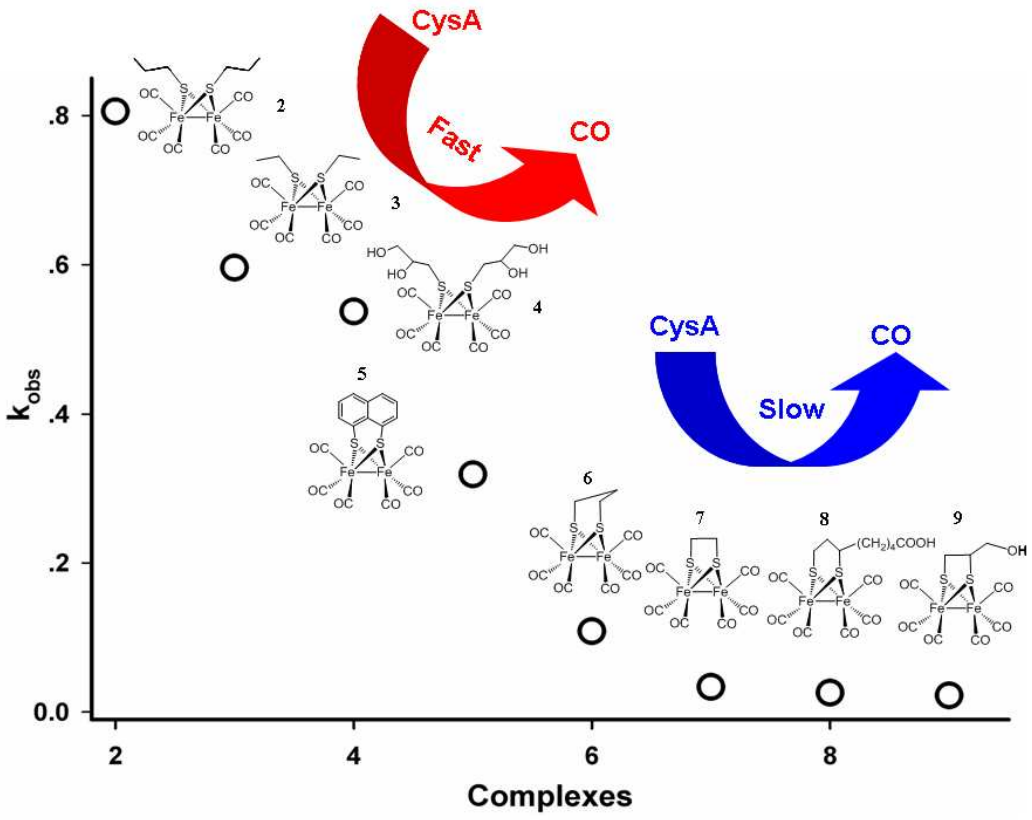
Graphic abstract



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ARTICLE TYPE

Diiron hexacarbonyl complexes as potential CO-RMs: their CO-releasing initiated by the substitution reaction with cysteamine and structural correlation to the bridging linkage

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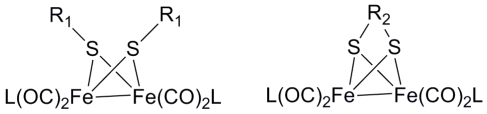
The CO-releasing behaviours of nine diiron carbonyl complexes (**1-9**) were examined *via* the substitution reaction of cysteamine (**CysA**), of which complex **4** was reported recently. These complexes fall into three categories, the diiron core bridged by two thiolates, a dithiolate and 1,8-naphthalene dithiolate. Our results reveal that the CO-releasing rates of these complexes are highly dependant on their structures. Complexes (**2-4**) bearing two monothiolates as their bridging linkage ("open" form) are more vulnerable to decomposition upon nucleophilic substitution reactions compared with complexes (**6-9**) which possess a dithiolate as their bridging linkage. When the bridging linkage is lack of electron-donating group (complex **1**), the metal centre is less negatively charged as revealed by DFT calculation, and thus it exhibits fast substitution reaction with **CysA** to release CO. A linkage with conjugating nature (**5**) shows similar effect since electron density on the metal centre decreases due to electron-density diverting from the metal centre into the naphthalene moiety. Kinetic analysis suggests that the CO-releasing at the first stage of these complexes is first-order reaction.

Introduction

Contrary to its notorious poisoning nature, the physiological roles of carbon monoxide (CO) are less well-known. As we breathe out CO_2 continuously, we produce also CO which results from the degradation of heme [1, 2]. It is believed that this small diatomic molecule may be a messenger molecule like NO [3], CO shows also following biological effects: [3, 4], for example, anti-inflammatory, anti-apoptotic, anti-proliferative, anti-hypoxia, anti-bacteria [5], vasodilatation, protection tissues from reperfusion injury in operation, suppression of transplanted organ rejection [6], as well as the proliferation of smooth vascular muscle cells. Therefore, CO has great potentials in medical applications. To exploit the potentials, it is essential to deliver CO both safely and precisely. Traditional methods of CO-intake are *via* respiratory ingestion [7, 8] or metabolising pro-drugs (for example, dichloromethane) [9]. Obviously, the potential poisoning by directly applying CO and unnecessary side-effects caused by the metabolising of pro-drugs are the fatal shortcomings of the approaches, which become the hurdle of exploiting the medical application of CO. More appropriate means of delivering CO is necessary to bypass these hurdles. A decade ago, the concept of CO-releasing molecules (CO-RMs) was proposed [7]. CO-RMs are usually transition metal-carbonyl complexes. The CO molecules bound to a metal centre could be released under various initiations, for example, substitution reaction, redox reaction, irradiation, enzymatic degradation, or any combination of these approaches. Since transitional metal-carbonyl complexes are a large category of complexes in organometallic chemistry, and novel metal carbonyl complexes emerge continuously, they could be a category of promising pharmaceuticals as CO-RMs in the future [10-18]. Therefore, a wide spectrum of options is offered by this type of metal complexes in exploring them as potential CO-RMs. Indeed, in the past decade, many metallocarbonyl complexes have been developed as potential candidates for CO-releasing [19-21].



R_1, R_2 = organic moiety, L = CO or non-CO ligand

Scheme 1 The "open" form (left) and "close" form (right) of diiron carbonyl complexes.

Among the metal carbonyl complexes applicable as potential CO-RMs, iron carbonyl complexes are particularly favoured owing to the fact that iron is one of the essential elements for many life forms. This suggests that the metal residue after CO-releasing can more easily be handled and causes less detrimental effect compared with other transition metals. But compared with the reported CO-RMs, iron carbonyl complexes are under-developed [22-38]. Of the various types of iron-carbanyl complexes, diiron carbonyl complexes are of particular interest due to their biological relevance. These complexes are of the core of "$Fe_2(CO)_x$" (x = 4-6), in which the two iron atoms are bridged by two thiolates or a dithiolate, Scheme 1. Their synthetic chemistry

has been considerably stimulated over the past decade due to their resemblance to the diiron subunit of [FeFe]-hydrogenase [39]. And the number of complexes of this type as the mimics of the diiron subunit of the enzyme has significantly increased in the last decade [40]. In addition to the possibility that iron may be biologically less detrimental, the high CO-capacity (six-CO per molecule) makes also these complexes extremely attractive as potential CO-RMs.

Recently, we reported a water-soluble diiron complex (**4**) which releases CO *via* nucleophilic substitution by **CysA** [41]. The simplicity in both structure and composition suggests that both thermodynamic and kinetic stabilities of these diiron carbonyl complexes would masterly controlled by the non-CO ligands, or the bridging thiolates. As pointed out earlier, the bridging linkage can be either a monothiolate ("open" form) or a dithiolate ("close" form), Scheme 1. But how the bridging ligands correlate to the stability and hence the CO-releasing rate is an important issue in exploring these diiron carbonyl complexes as potential CO-RMs. Herein, we report our investigation into nine diiron carbonyl complexes, in an attempt to establish correlation between the CO-releasing rate and the structure of these complexes, $[Fe_2(\mu\text{-}S)_2(CO)_6]$ (**1**), $[Fe_2\{\mu\text{-}SCH_2CH_2CH_3\}_2(CO)_6]$ (**2**), $[Fe_2\{\mu\text{-}SCH_2CH_3\}_2(CO)_6]$ (**3**), $[Fe_2\{\mu\text{-}SCH_2CH(OH)CH_2(OH)\}_2(CO)_6]$ (**4**), $[Fe_2\{(\mu\text{-}S)_2C_{10}H_6\}(CO)_6]$ (**5**), $[Fe_2\{(\mu\text{-}SCH_2)_2CH_2\}(CO)_6]$ (**6**), $[Fe_2\{(\mu\text{-}SCH_2)\}_2(CO)_6]$ (**7**), $[Fe_2\{(\mu\text{-}SC_2H_4)(\mu\text{-}SCH)(CH_2)_4COOH\}(CO)_6]$ (**8**), $[Fe_2\{(\mu\text{-}SCH_2)(\mu\text{-}SCH)CH_2OH\}(CO)_6]$ (**9**). Our results indicate that the CO-releasing rates of these complexes are highly dependant on their bridging linkages. The complexes of the "open" form could be 30 times faster to release CO than those of the "close" form. All these complexes can release CO under the initiation of substitution reaction by cysteamine (**CysA**).

Experimental

Materials and instrumentations

Unless otherwise stated, all operations were carried out under Ar atmosphere using Schlenk technique. Reaction vessels were oven-dried at 150 ℃ and solvents were freshly distilled using appropriate drying agent prior to use. $Fe_3(CO)_{12}$ and 1,8-naphthalenedithiolate were synthesised following modified literature procedures [42]. Cysteamine, ethanethiol, propanethiol, 1-thioglycerol, 1,3-propanedithiol, dithioglycol, D, L-thioctic acid, 1,2-dithioglycerol were purchased from Aladdin used as received. Complexes **1-9** were synthesised by following the procedures described in the literatures with some modification when necessary [41, 43-49]. FTIR spectra in a solution were recorded on Agilent 640 using a CaF_2-cell with a spacer of 0.1 mm. NMR spectra were measured on Bruker Avance with tetramethylsilane as internal standard. Electrochemistry was performed in $[NBut_4][BF_4]$-CH_3CN Potentials were quoted against ferrocene couple. Detailed procedures for electrochemistry can be found elsewhere [50].

Theoretical investigations were performed to explore the correlations between the CO-releasing behaviours and the electronic properties of the complexes, The complexes **(1-9)** were fully optimized in gas phase without any symmetry constraints at the BP86/TZVP level of theory [51, 52], which has been proved to be suitable for investigating diiron hexacarbonyl complexes [53, 54]. Vibrational frequencies were calculated based on the optimised geometries and the absence of negative frequencies confirmed that the structures were local minimum–energy structures. The Charge population on the iron cores and the bridging linkages were estimated using natural population analysis (NPA). All DFT calculations were carried out using Gaussian 03 program [55].

Synthesis of complexes 1-9

Complex **1**: To a solution (125 mL) of $Fe(CO)_5$ (25 mL, 0.18 mol) in methanol was added a solution KOH (50%, 75 mL). The mixture was stirred vigorously for 30 min before being cooled to 0ºC *via* ice-bath. Then S_8 (33.0 g, 1.0 mol) was added within 5 min. The exothermic reaction changed to black. To the reaction was added water (100 mL) and petroleum ether (500 mL) before the addition of NH_4Cl (85.0 g, 1.6 mmol) in dropwise fashion. Then ice bath was removed after acidifying the above solution by dilute H_2SO_4. The reaction mixture was further stirred for 14 h at room temperature. After standing for 30 min, extraction and removal of the solvents (petroleum ether) was followed to produce a red solid, which was purified with column chromatography (petroleum ether) and then recrystallised in the solution of MeCN to produce a red solid (9.8 g, 28.0 mmol, 16%). IR (MeCN, ν / cm^{-1}): 2079, 2035, 1997.

Complex **2**: $Fe_3(CO)_{12}$ (2.19 g, 4.35 mmol) and ligand propanethiol (0.54 g, 8.70 mmol) in THF (20 mL) was heated at 70 ℃ for 2 h. The resulting reddish brown mixture was concentrated under reduced pressure and purified with column chromatography (eluent: ethyl acetate / petroleum ether = 1 : 4) to produce a red solid (1.2 g, 2.7 mmol, 63%) which was crystallised from DCM / hexanes at –4 ℃. IR (DMSO, ν / cm^{-1}): 2068, 2031, 1990. ^{1}H NMR (CD_2Cl_2): 2.39 (2H, s, $^{ae}CH_2$), 1.68 (2H, m, $^{ae}CH_2$), 1.02 (3H, t, J = 6.0 Hz, $^{ae}CH_3$), 2.06 (0.81H, s, $^{aa}CH_2$), 1.42 (0.82H, m, $^{aa}CH_2$), 0.9 (1.37H, s, $^{aa}CH_3$).

Complexes **3, 5-9** were analogously synthesised applying the procedure described above by using ligands, ethanethiol, 1-thioglycerol, 1,8-naphthalenedithiolate, 1,3-propanedithiol, dithioglycol, DL-thioctic acid and 1,2-dithioglycerol, respectively, except that the stoichiometric ratio of $Fe_3(CO)_{12}$ and dithiolate ligands is 1 : 1. Complex **3**: 1.1 g, 2.7 mmol, 61%. IR (DMSO, ν / cm^{-1}): 2068, 2031, 1990. ^{1}H NMR: 2.43 (2H, m, $^{ae}CH_2$), 2.12 (1.22H, m, $^{aa}CH_2$-H), 1.34 (3H, m, $^{ae}CH_3$), 1.09 (1.76H, t, J = 8.0 Hz, $^{aa}CH_3$). Complex **5**: 1.3 g, 2.7 mmol, 65%. IR (DMSO, ν / cm^{-1}): 2071, 2031, 1990. ^{1}H NMR: 8.24 (2H, d, J = 7.2 Hz, Nap*H*), 8.00 (2H, d, J = 7.6 Hz, Nap*H*), 7.40 (2H, t, J = 7.6 Hz, Nap*H*). Complex **6**: 1.1 g, 2.8 mmol, 65%. IR (DMSO, ν / cm^{-1}): 2071, 2031, 1990. ^{1}H NMR: 1.13 (4H, t, J = 6.0 Hz, CH_2), 1.79 (2H, m, CH_2). Complex **7**: 1.0 g, 2.6 mmol, 63%. IR (DMSO, ν / cm^{-1}): 2071, 2031, 1992. ^{1}H NMR: 2.37 (4H, s, CH_2). Complex **8**: 1.3 g, 2.6 mmol, 62%. IR (DMSO, ν / cm^{-1}): 2073, 2034, 1994. ^{1}H NMR: 2.58 (1H, d, C*H*), 2.39 (2H, m, CH_2), 2.09 (1H, m, CH_2), 1.79 (2H, m, CH_2), 1.64-1.44 (6H, m, CH_2), 1.23 (1H, m, CH_2). Complex **9**: 1.2 g, 2.9 mmol, 67%. IR (DMSO, ν / cm^{-1}): 2073, 2033, 1993. ^{1}H NMR: 3.62 (1H, m, CH_2-OH), 3.52 (1H, m, CH_2), 2.85 (1H, m, C*H*), 2.66 (1H, m, O*H*), 1.89 (2H, m, CH_2).

Monitoring the CO-releasing

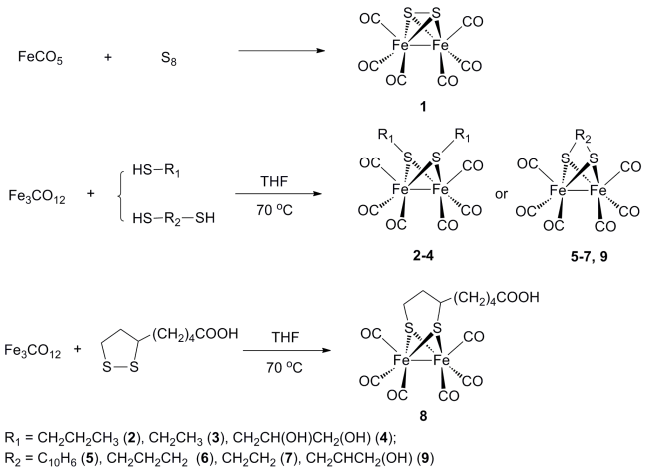
A typical protocol is as follows: to a solution of complex **1** (12

mg, 0.034 mmol) in DMSO (3 mL) was added an appropriate volume of an aqueous solution of **CysA** (5.2 mmol L^{-1}). The reaction was maintained at 37 ℃ and regularly monitored using infrared spectroscopy under inert atmosphere. The CO releasing monitoring for complexes **2-9** initiated by cysteamine were analogously performed.

Results and discussion

Synthesis and characterisation of complexes 1-9

All the complexes were synthesized using the procedures widely reported in literatures with some modification when necessary [41, 43-49]. Complex **1** was synthesised *via* the reaction of $Fe(CO)_5$ with S_8. Complexes **2-9** were synthesised *via* the reaction of $Fe_3(CO)_{12}$ with mercapto ligands or organic difulfide (**8**) (Scheme 2). Notably, in the synthesis of complex **8**, the reagent of $Fe_2(CO)_9$ in the literature were replaced by $Fe_3(CO)_{12}$, to react with D, L-thioctic acid. These complexes are stable in their solid state at room temperature and soluble in common organic solvents. Complex **4** is soluble in water as we reported recently [41]. These complexes fall into two categories by the nature of their bridging linkage, "open" form (**2-4**) and "close" form (**1**, **5-9**), Scheme 2.



Scheme 2 Synthesis of complexes **1-9.**

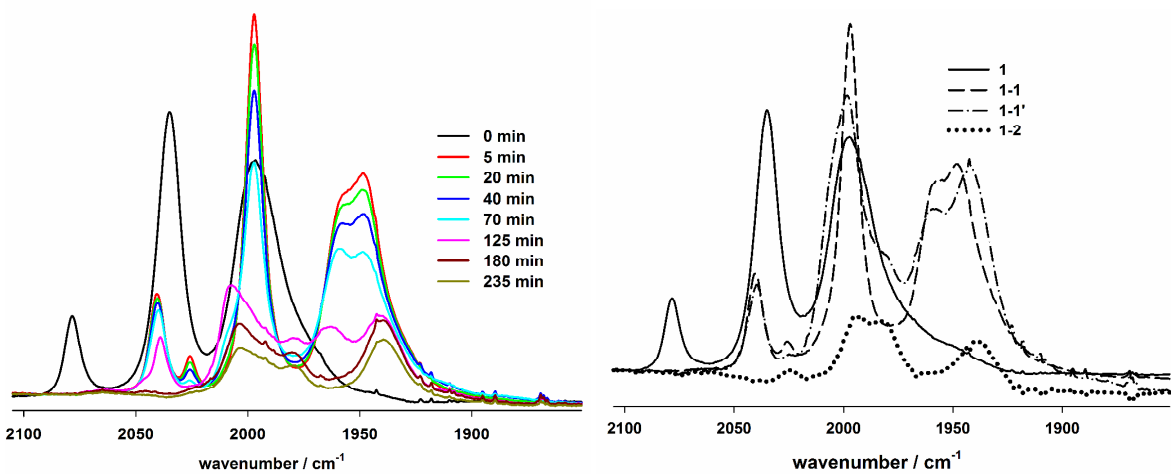


Fig. 1 Infrared spectral variation during the CO-releasing process of complex **1** ([**1**] = 0.011 mol L^{-1} and [**CysA**] = 0.066 mol L^{-1}) (left) and the intermediates in the reaction mixture (right), when the reaction proceeded for 0.5 min (**1-1**), 180 min (**1-1'**) and 235 min (**1-2**), respectively, in DMSO at 37 ℃.

CO-releasing mechanism

As we reported recently, complex **4** decomposes to release CO under the initiation of substitution reaction with **CysA** [41]. Since **CysA** ($HSCH_2CH_2NH_2$) is a bidentate ligand which could react with the diiron complexes with and without the thiol deprotonated to replace two bound-CO to form two diiron tetracarbonyl species in which the ligand bridges the diiron centre. The substituted diiron species undergo further oxidative decomposition to give a monoiron dicarbonyl species in which the iron adopts oxidation state Ⅱ as suggested by its distinct infrared spectral pattern (Scheme S1). Using the spectra of both the parent complex and the monoiron dicarbonyl species, we were able to "deconvolute" the spectral data by simple subtractions as described in our previous report [41]. All the spectral data were processed in this manner to acquire the spectrum of those intermediates during the reaction course. Figs. 1-4 and Figs. S1-4 show the spectral variations and their "deconvoluted" spectra. These spectral results suggest that most of the complexes decompose analogously to release CO

following the same pattern as complex **4**. But individual features are also obvious. Complex **1** exhibited the most distinct mechanism of decomposition as shown in Fig. 1. Unlike the other analogues, two sets of infrared absorption bands were observed, in which three absorption bands positioned approximately at 2500, 2000 and 1950 cm^{-1}, respectively, with two sharp bands at high frequency and one broad band at low frequency bands. This is the characteristic spectral profile for diiron pentacarbonyl complexes [45]. Therefore, we assign tentatively the two absorption bands to two diiron pentacarbonyl species (**1-1** and **1-1'**), respectively. This unusual behaviour can be attributed to the strong electrophilicity of its metal centre, which leads to its fast reaction with **CysA**. And **CysA** is a bidentate ligand in which both the thiol and the amine can attack the metal centre. Thus two types of diiron pentacarbonyl complexes are formed before further substitution reaction takes place. For complexes **2** and **3**, in addition to the species observed in the decomposition of complex **4**, a single peak at 1900 cm^{-1} is observed (**2-3** and **3-3**). By considering its low frequency, this absorption band is very likely associated with species containing Fe(0) [56]. Further scrutinising the spectra of reaction products of complex **4** [41], we could find that such an absorption band may be also presented (**4-3**, Fig. S2). It seems that such a band is only observable for "open" form complexes (**2-4**), in which the two thiolates hold the two iron atoms together. It is well known that dithiolate-bridged complexes (**5-9**) possess much stronger capability of retaining the integrity of the diiron core either upon substitution reaction or electrochemical reduction [57]. Due to this effect, the degradation of complexes **5-9** to release CO produces more simple and clean spectra, suggesting cleaner decomposition. In other words, the complexes of the "open" form undergo more complicated decomposition from which species of Fe(0) may generate.

To gain further insight of the decomposition, the final decomposition product(s) of complex **4** was examined. The complex was stirred with 6 equivalents of **CysA** under inert atmosphere at room temperature for 24 h to produce an oily and pale red liquid. Both NMR (Fig. S6) and ESI–MS data (Figs. S7-8) suggest a formula of $[Fe(\square)(SCH_2CH_2NH_2)_2]$. The neutrality of the product was supported by its development on TLC plate in organic solvents. In the MS spectra, fragments of m / z = 153 for $[M- {}^{-}SCH_2CH_2NH_2 + Na]^+$, 239 for $[M + CH_3OH]^+$ and 294 $[M + CH_3OH + Na]^+$ were observed, respectively.

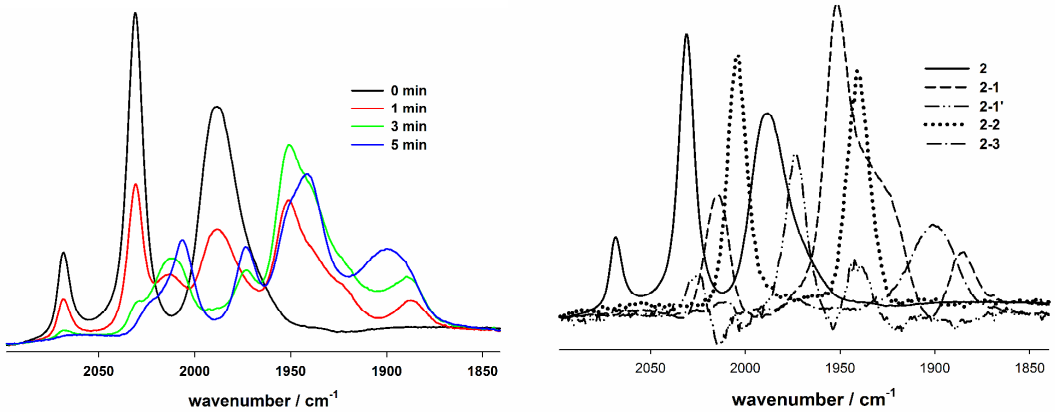


Fig. 2 Infrared spectral variation during the CO-releasing process of complex **2** ([**2**] = 0.011 mol L^{-1} and [**CysA**] = 0.066 mol L^{-1}) (left) and the intermediates in the reaction mixture (right), when the reaction proceeded from 1 min to 5 min in DMSO at 37 ℃.

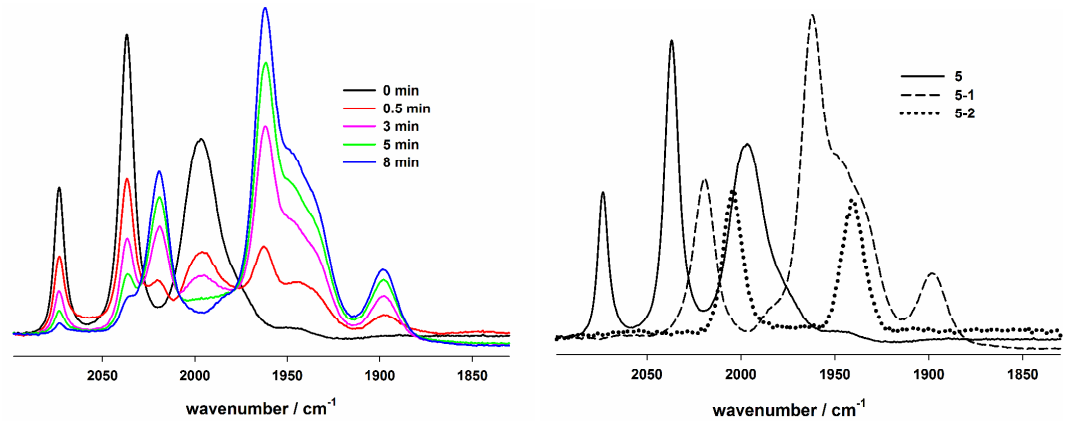


Fig. 3 Infrared spectral variation during the CO-releasing process of complex **5** ([**5**] = 0.011 mol L^{-1} and [**CysA**] = 0.066 mol L^{-1}) (left) and the intermediates in the reaction mixture (right), when the reaction proceeded for 15 min (**5-1**) and 320 min (**5-2**), respectively, in DMSO at 37 ℃.

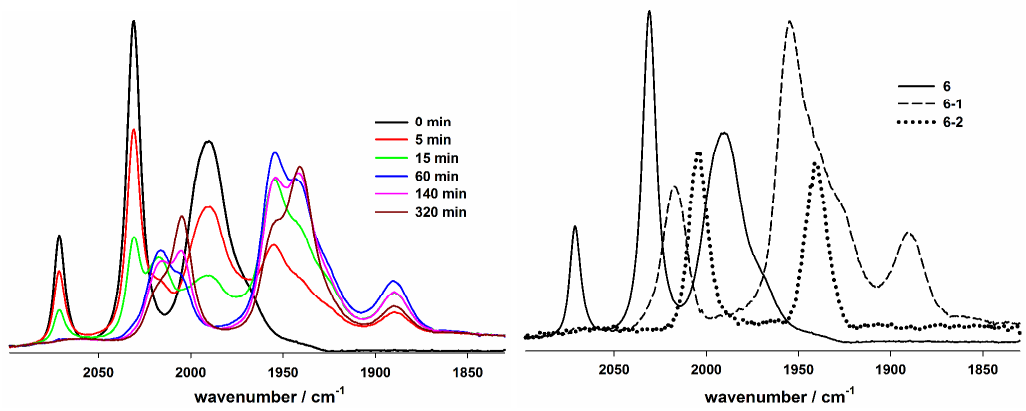


Fig. 4 Infrared spectral variation during the CO-releasing process of complex **6** ([**6**] = 0.011 mol L^{-1} and [**CysA**] = 0.066 mol L^{-1}) (left) and the intermediates in the reaction mixture (right), when the reaction proceeded for 260 min (**6-1**) and 320 min (**6-2**), respectively, in DMSO at 37 ℃.

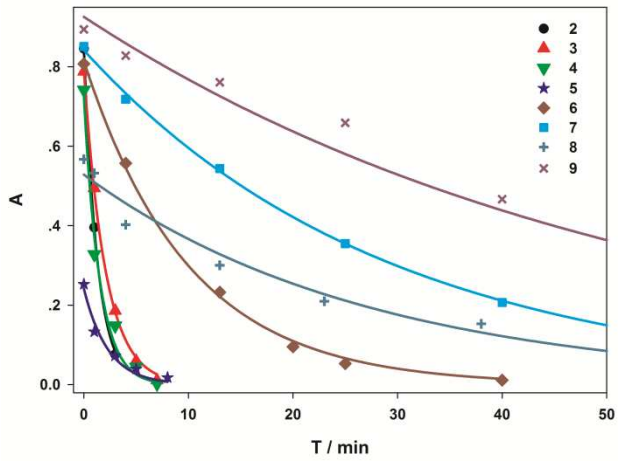


Fig. 5 Variation in concentrations of complexes **2-9** during the reaction course ([**CysA**] = 0.066 mol L^{-1}, [**2-9**] = 0.011 mol L^{-1}). Please note that the absorbance used for the kinetic analysis was taken at 2031 cm^{-1}.

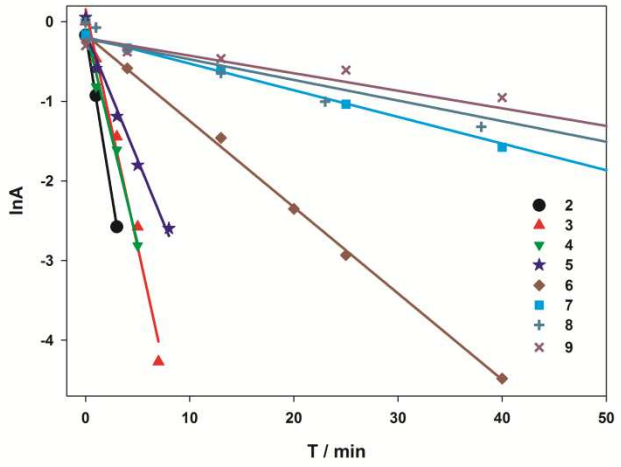


Fig. 6 Plot of the first-order reaction for the loss of their first CO of complexes **2-9** ([**CysA**] = 0.069 mol L^{-1}, [**2-9**] = 0.011 mol L^{-1}) with the data (Fig. 5).

CO-releasing kinetics of the first stage of CO-releasing

In our recent report [41], it has been revealed that the kinetics of the reaction of losing its first CO of complex **4** is first-order reaction. Despite of the variation in the bridging linkage, the rest of the complexes release their first CO following the same kinetics, Figs. 5 and 6. In earlier discussion, we mentioned that the nature of the bridging linkage affects their decomposition. The "close" form complexes give cleaner products than the "open" form. In the kinetic analysis, the latter exhibited much faster CO-releasing rate, and the pseudo first-order rate constant k_{obs} could be 40-fold larger.

As shown in Table 1 and Fig. 7, those k_{obs} values fall into two distinct groups, if complex **5** is not temporarily considered. One is of larger k_{obs} ("open" form complexes) and the other smaller ones ("close" form complexes). Complex **5** deviates from the group of the "close" form at the borderline. Although its k_{obs} is smaller than those of the "open" form complexes by about 50%, it is much larger than those of "close" form by about 10-fold. We attribute this deviation to its structural nature. The conjugating system of the naphthalene ring in complex **5** is certainly beneficial to divert the electron density from the diiron centre, which enhances its eletrophilicity. Therefore, the nucleophilic substitution reaction of complex **5** proceeds faster than the other complexes in the same group ("close" form). Its stronger electrophilicity is supported by its more positive reduction potential by about 150 mV compared with those of the other "close" form complexes, Table 1.

Table 1 Kinetic analysis of the substitution reaction of complexes **1-9** by **CysA** in DMSO at 37 ℃ ([complexes **1-9**] / [**CysA**] = 1 : 6) and their reduction potentials.

Complexes	$t_{1/2}$ (min)	K_{obs}	E_{Red} (V)
[a]**1**	–	–	–0.561
2	0.86	0.806	–1.145
3	1.16	0.596	–1.071
4	1.29	0.537	–1.162
5	2.17	0.319	–1.010
6	6.40	0.108	–1.126
7	20.69	0.034	–1.180
8	26.76	0.026	–1.140
9	31.36	0.022	–1.176

[a] The first stage of the reaction of complex **1** initiated by **CysA** is too fast (less than millisecond) to estimate its kinetic data.

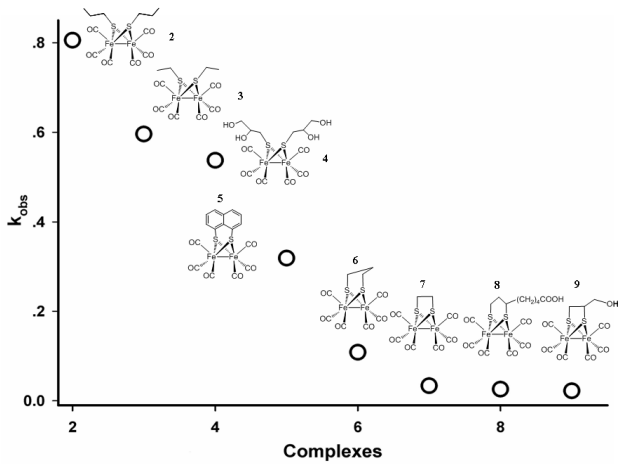


Fig. 7 Schematic presentation of the structural correlation between the CO-releasing rate of the complexes and their bridging linkage.

CO-releasing behaviours and the electronic properties of the metal centre

All diiron hexacarbonyl complexes are electroactive and show a two-electron process with an ECE mechanism [58-60]. It has been well recognized that the more acidic the diiron core, the less negative its reduction potential. Among the nine complexes (**1-9**), complex **1** possesses the least negative potential since its bridging linkage is only a disulfide with no any organic moiety attached. An organic group may enrich the electron density of the diiron core. Since strong acidity or electrophilicity of the metal core can certainly promote the **CysA** substitution reaction to release CO. Therefore, complex **1** is expected to have fast CO-releasing rate at the first stage. This is, indeed, what was experimentally observed. The correlation is further supported by the CO-releasing behaviour of complex **5**. As discussed earlier, it belongs to the group of "close" form (**5-9**). But its k_{obs} for the first CO-releasing could be 10-folder faster due to the conjugating effect offered by the naphthalene skeleton, which diverts the electron density away from the metal centre and therefore, increase its acidity. This is in agreement with the observation that its reduction potential is about 150 mV less negative compared with the others. For the other complexes in both groups (**2-4** and **5-9**), no straightforward correlation between CO-releasing rate and the reduction potential can be observed. This suggests that the electrochemical parameter is not the only factor exerting effect on the substitution reaction and structural factor needs to be also considered.

To gain insight into the correlation between the CO-releasing behaviours and the electronic properties of the complexes, natural population analysis (NPA) were performed using BP86/TZVP method, and the NPA charges on the metal cores were tabulated in Table S1. Among the calculated parameters, the partial charges correlate well with the value of k_{obs}. The less the charge, the larger the value of k_{obs} or faster the CO-releasing, Fig. 8. This correlation is in agreement with the nature of CO-releasing since the CO-releasing is initiated by the nucleophilic substitution of CO with **CysA**. The less negatively charged the metal centre, the more easily the substitution occurs.

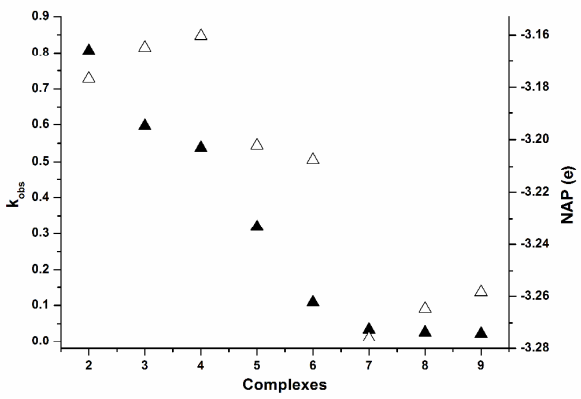


Fig. 8 Correlation between k_{obs} (▲) and NPA charges (△) of these complexes.

Conclusions

In summary, the CO-releasing behaviours of eight complexes plus complex **4**, which we reported recently, [41] were examined under the initiation of **CysA** substitution reaction. The pathways of their decomposition are essentially the same as that of complex **4**. Our investigation reveals that the decomposition of those diiron complexes *via* **CysA** substitution reaction is both structure and bridging linkage dependant. Complexes of following features would exhibit fast CO-releasing rate, ⅰ) that the diiron centre is bridged by two monothiolate, that is, the "open" form (**2-4**), and ⅱ) that the bridging linkage possesses the electron-withdrawing nature (**1** and **5**), and thus the reduction potential of the complex shifts positively. DFT calculations confirm that the structural correlation is associated with the electrophilicity of the diiron centre. The observation shown in this current work has general significance in exploring potential CO-RMs and would be particularly informative of both selecting candidates among existing complexes and synthesising novel diiron carbonyl complexes as potential CO-RMs.

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Notes and references

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