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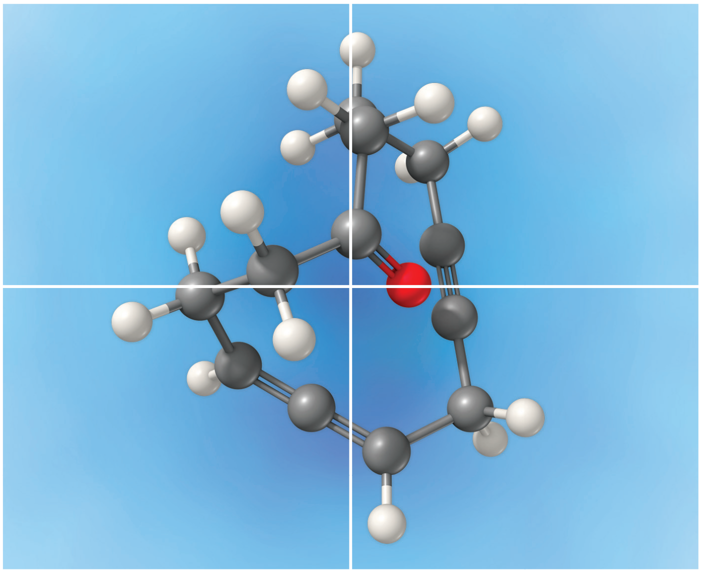

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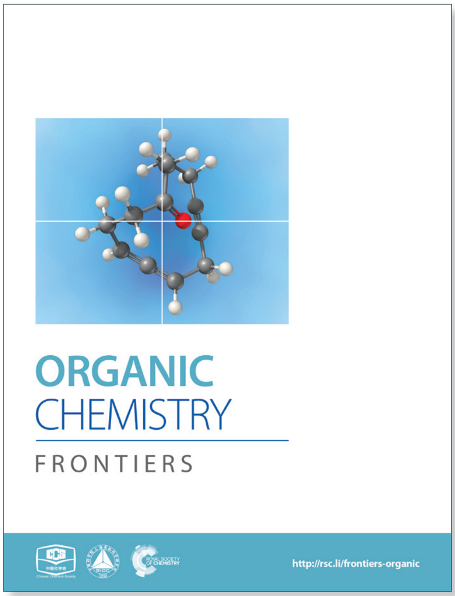

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RESEARCH ARTICLE

A thermally stable pH-responsive "supramolecular buckle" based on the encapsulation of 4-(4-aminophenyl)-N-methylpyridinium by cucurbit[8]uril

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Supramolecular building blocks that can respond to external stimuli are the basis for the fabrications of responsive materials. However, those that can be used in aqueous media and at elevated temperatures are extremely limited. In this work, a cucurbit[8]uril(CB[8])-based host-guest system has been developed. It exhibits excellent response to the change of pH through forming thermally stable 1:2 host-guest complex under neutral condition and transforming into 1:1 complex by releasing one guest molecule in the presence of acid. This transformation makes this system serve as a useful "supramolecular buckle", which can fasten and unfasten two components. These features endows it with great potentials in fabricating pH-responsive materials in aqueous media over a wide temperature range.

Introduction

Stimuli-responsive materials (also known as smart materials) have attracted widespread interest in materials science and technology for their conspicuous performance in energy transfer,[1] drug delivery,[2] data storage,[3] and heterogeneous separation.[4] These smart materials can response to external stimuli such as temperature,[5] light,[6] pH,[7] reduction/oxidation,[8] solvent,[9] and even specific species[10]. The key to fabricate stimuli-responsive materials is the use of stimuli-responsive building blocks on which other functional units can be feasibly incorporated. In this context, to develop novel building blocks that can exhibit excellent response to specific stimulus has recently became a topic of great interest. Among those supramolecular materials, it should be noted that most of them are thermally sensitive because their formations are driven by noncovalent interactions which are usually very weak. In order to fabricate smart materials that can work at elevated temperature, thermally stable building blocks must be employed. However, such building blocks are extremely limited.

Over the past decade, cucurbit[8]uril (CB[8]) has been demonstrated as a versatile host molecule which can encapsulate many kinds of guests to form binary or ternary host–guest complexes.[11] Very recently we showed that the dimerization of 4-aryl-N-methylpyridinium (AMP) derivatives could be greatly enhanced by encapsulating two AMP molecules in the cavity of one CB[8].[12] Although these host-guest systems have many advantages such as high binding constants, good thermal stability, and excellent bonding direction control which made them useful supramolecular building blocks, stimuli-response has not been realized for them yet. Motivated by developing novel pH-responsive building blocks on the basis of this type of system without forfeiting its advantages, in this work we designed a new host-guest system by using 4-(4-aminophenyl)-N-methylpyridinium (**1**) as guest for CB[8] (Scheme 1). It exhibits good pH-responsive characteristic while still keeps the above three advantages and can be used as "supramolecular buckle", as revealed by ^{1}H NMR, UV-vis, isothermal titration calorimetry (ITC), and crystallographic studies.

Results and discussion

^{1}H NMR titration experiments were preformed to investigate the aggregation between **1** and CB[8] under neutral condition (pH = 7) (Figure 1). The addition of CB[8] into a solution of **1** in D_2O resulted in growing up of a new set of signals in the range of 8.6 – 5.8 ppm, which was accompanied by the decreasing

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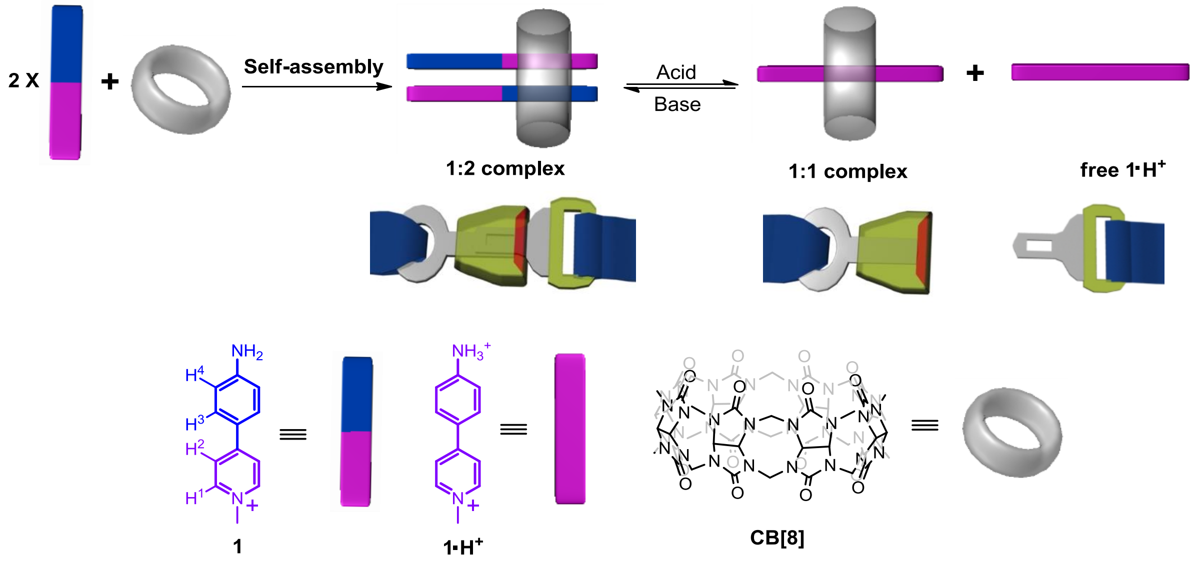
† Electronic Supplementary Information (ESI) available: Additional UV-vis spectra, Job's plots, ITC profile, ^{1}H and ^{13}C NMR spectra of 1. See DOI: 10.1039/x0xx00000x.



Scheme 1 The structure of compound **1** and cartoon representation of the “supramolecular buckle” on the basis of pH-controlled formation of 1:2 and 1:1 complexes. The 1:1 complex represents the frame of buckle and free **1**·H$^+$ represents the prong of buckle.

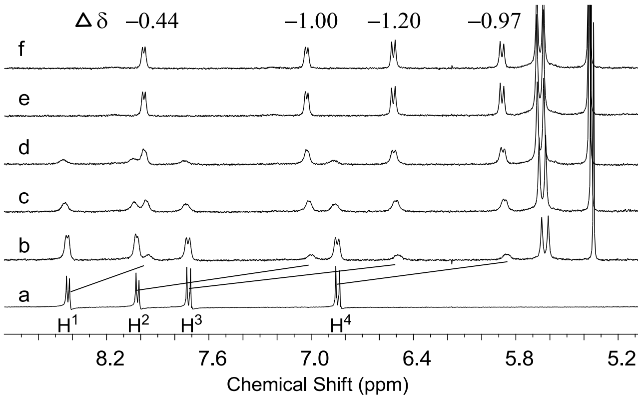


Fig. 1 Patial ^{1}H NMR spectra (500 MHz, 25 °C) of (a) **1** (2.0 mM), (b) **1** + CB[8] (0.15 equiv), (c) **1** + CB[8] (0.3 equiv), (d) **1** + CB[8] (0.45 equiv), (e) **1** + CB[8] (0.5 equiv), and (f) **1** + CB[8] (0.6 equiv) in D_2O (pD = 7).

intensities of the signals corresponding to free **1**. The new set of signals was rationally assigned to encapsulated **1** in the cavity of CB[8]. Compared with those of free **1**, the signals of encapsulated **1** shifted upfield (see Fig. 1 for the changes of chemical shifts), as a result of shielding effect of the stacked aromatic rings in the cavity of CB[8]. Furthermore, the signals of free **1** totally disappeared after 0.5 equiv of CB[8] was added and no further change was observed when an excess of CB[8] (0.6 equiv) was present, indicating a 1:2 binding stoichiometry for CB[8] and **1**. Their binding stoichiometry was further confirmed by a Job’s plot. It displayed the maximum change of UV-vis absorbance at 66.7% of **1** in a mixture of **1** and CB[8], clearly indicating that one CB[8] bound two molecules of **1** (Figure S1 in ESI). UV-vis study revealed that the maximum absorbance of **1** decreased by ca. 30% and the corresponding peak was red-shifted by 7 nm upon the addition of 0.5 equiv of CB[8] (Figure S1 in ESI), which also suggests stacking of **1** in the cavity of CB[8]. ITC was used to estimate the binding constant between **1** and CB[8] (Figure S2 in ESI). The ITC data were fitted using sequential binding model to give a binding constant of (4.13 ± 0.25) × 10^{11} M^{-2}. In addition, the thermal stability of the 1:2 complex of CB[8]–**1** was investigated by variable-temperature ^{1}H NMR experiment (Fig. 2). It was found that the complex exhibited high thermal stability. The signals of the complex CB[8]–**1** remained almost no change and no signals corresponding to free **1** or other components (e.g., 1:1 complex) were observed upon raising the temperature from 25 °C to 75 °C, suggesting the structure of the 1:2 host-guest complex was maintained over this temperature range.

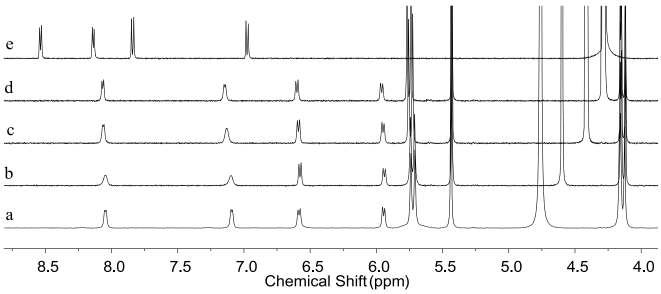


Fig. 2 Partial ^{1}H NMR spectra (500 MHz) of CB[8]–**1** at (a) 25 °C, (b) 40 °C, (c) 60 °C and (d) 75 °C, and (e) **1** at 75 °C in D_2O. The spectra were calibrated by the temperature dependence of HDO chemical shifts.[13]

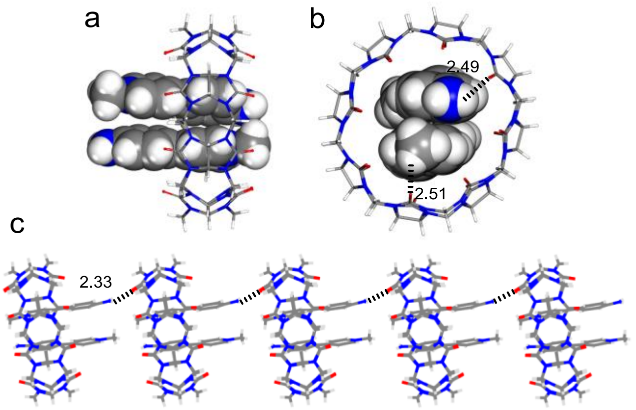


Fig. 3 Crystal structure (a) side view and (b) top view of the 1:2 complex formed from CB[8] and **1** under neutral condition, and (c) the linear arrangement of CB[8]–**1** complexes driven by the hydrogen-bonding between amino protons of **1** and carbonyl oxygen of the neighboring CB[8] in the crystal structure.

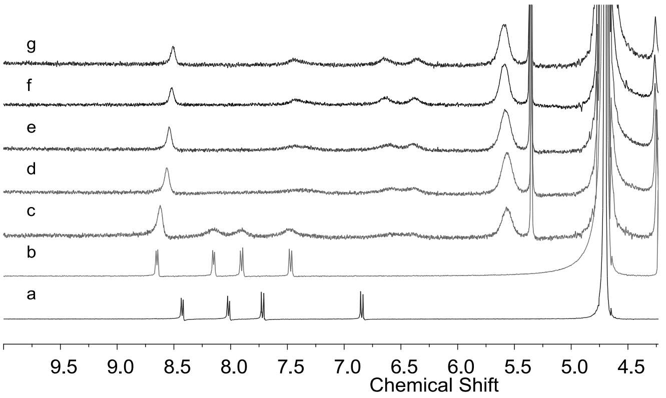


Fig. 4 Partial ^{1}H NMR spectra (500 MHz, 25 °C) of (a) **1** (2.0 mM), (b) **1**·H$^+$ (2.0 mM), (c) **1**·H$^+$ + CB[8] (0.3 equiv), (d) **1**·H$^+$ + CB[8] (0.6 equiv), (e) **1**·H$^+$ + CB[8] (0.9 equiv), (f) **1**·H$^+$ + CB[8] (1.0 equiv), and (g) **1**·H$^+$ + CB[8] (1.2 equiv) in D_2O at pD =1.

In order to figure out the arrangement of **1** in the cavity of CB[8], single crystals of complex CB[8]-**1** suitable for crystallographic analysis were grown by slow evaporation of an aqueous solution of CB[8] and **1** (1:2) at 25 °C.[14] From its crystal structure it can be clearly seen that two molecules of **1** are encapsulated in the cavity of one CB[8] molecule (Figure 3a). The two encapsulated molecules are antiparallel to each other and adopt a head-to-tail offset stacking with a mean distance of 3.62 Å, suggesting that aromatic stacking occurs between them. The aniline unit and the pyridinium segment of the encapsulated **1** slightly twist, with the dihedral angel between them being 15°. This 1:2 head-to-tail binding pattern is quite useful to link two components with excellent direction control, which has been well demonstrated by some recent works.[15] Interestingly, the crystal structure also reveals that CB[8] encapsulates **1** near one end of the guests, instead of at their midpoint. It is noticeably different from its analogs reported in previous work, in which CB[8] locates at the midpoint of the dimeric guests.[12] The position deviation of CB[8] is attributed to the formation of hydrogen bonds between the carbonyl oxygen atoms of CB[8] and protons of the NH_2 and the CH_3 of the encapsulated **1** (bonding distance being 2.49 and 2.51 Å, respectively) (Figure 3b). Furthermore, another stronger hydrogen bond (bonding distance being 2.33 Å) formed between the amino proton of **1** and carbonyl oxygen of the neighboring CB[8] was also observed, which should also make a contribution to the position deviation of compound **1** in the cavity of CB[8]. Such hydrogen-bonding leads to an infinite linearly extended arrangement of CB[8]–**1** complexes in solid state (Figure 3c). It should be noted that in solution state the position of CB[8] should not be fixed at one end of the guests. There should be fast movement of CB[8] alongside dimeric **1** molecules.

In the next step, the binding behavior between protonated **1** (**1**·H$^+$) and CB[8] was investigated under acidic condition (pH = 1). After the pD of the solution of **1** in D_2O was adjusted to 1.0 by adding aqueous DCl, the signals of all the aromatic protons of **1** shifted downfield, indicating protonation of its amino group (Figure 4a-b). UV-vis study also revealed that a new absorbance peak at 279 nm appeared and the absorbance at 368 nm decreased upon the addition of HCl to the aqueous solution of **1** (Figure S3 in ESI). CB[8] was then added into this acidic solution to investigate the host-guest interaction between CB[8] and **1**·H$^+$. It was found that the signals of **1**·H$^+$ shifted upfield and broadened upon the addition of CB[8] (Figure 4c-g), suggesting that **1**·H$^+$ was encapsulated by CB[8] and there was a fast exchange between encapsulated **1**·H$^+$ and free **1**·H$^+$. Their binding stoichiometry was corroborated to be 1:1 by a Job's plot, which displayed the maximum change of UV-vis absorbance at 50 % of **1**·H$^+$ in a mixture of **1**·H$^+$ and CB[8] (Figure S3 in ESI). The binding behavior between **1**·H$^+$ and CB[8] was also investigated by UV-vis spectroscopy and it revealed that the addition of CB[8] resulted in a decrease of the absorbance of **1**·H$^+$ at 368 nm and a red shift of ca. 25 nm (Figure S3 in ESI). The fast exchange between encapsulated **1**·H$^+$ and free **1**·H$^+$ suggested that the binding strength between **1**·H$^+$ and CB[8] was not as strong as that of **1** and CB[8]. Unfortunately, although the binding constant of the latter could be obtained from ITC experiment, the same technique could not be applied to the system of **1**·H$^+$ and CB[8] to estimate their binding constant because of the corrosion of metallic sample pool of ITC instrument under acidic condition. Variable-temperature ^{1}H NMR experiment was also performed for complex CB[8]–**1**·H$^+$ (Figure S4 in ESI). Small shifts were observed for its signals with the increase of temperature. However, no free **1**·H$^+$ could be detected even the temperature reached 75 °C. This result indicates that complex CB[8]–**1**·H$^+$ also has good thermal stability but is not as stable as complex CB[8]–**1**. **1**·H$^+$ should be a good electron acceptor. We then examined the possibility for the complex CB[8]–**1**·H$^+$ to encapsulate one more guest. 2,6-dihydroxynaphthalene was selected because it is an excellent electron donor. Mixing CB[8], **1**, and 2,6-dihydroxynaphthalene in 1:1:1 ratio in acidic D_2O resulted in disappearance of the signals of **1** and 2,6-dihydroxynaphthalene and appearance of a new set of peaks (Figure S5 in ESI), indicating the formation of a ternary complex through the encapsulation of the donor (2,6-dihydroxynaphthalene) and acceptor (**1**·H^+) in by CB[8].

After the binding behavior between **1** and CB[8] and between **1**·H^+ and CB[8] was established, reversible transformation between them controlled by changing pH was then investigated. As shown in Figure 5, adding DCl (4.0 mol/L) into the solution of CB[8]–**1** in D_2O (pH = 7) leads to a transformation from 1:2 binding complex **1**-CB[8] to 1:1 binding complex CB[8]–**1**·H^+ (Fig. 5a-b). Upon the addition of aqueous K_2CO_3 (2.0 mol/L) into the above solution, the 1:1 binding complex disappeared and 1:2 binding complex CB[8]-**1** was regenerated (Fig 5c). Such transformation could be repeated several cycles and the two states were fully recovered in each cycle (Fig. 5a-e). This process could also be monitored by UV-vis spectroscopy. Alternately adding HCl and K_2CO_3 into the aqueous solution of 1:2 mixture of [CB[8] + **1**] resulted in alternating transformation between the spectrum of complex CB[8]-**1** and the spectrum of the acidic solution of [CB[8] + **1**] (Fig. 6). It should be noted that the absorption peaks of the latter were not exactly same as that of complex CB[8]–**1**·H^+ because of the co-existence of free **1**·H^+ in the same solution, which was released from the cavity of CB[8] when the binding stoichiometry changed from 1:2 (CB[8]–**1**) to 1:1 (CB[8]–**1**·H^+) under acidic condition. From the above results it can be found that transformation between 1:2 complex CB[8]–**1** and 1:1 complex CB[8]–**1**·H^+ can be well switched by changing pH of the system. We believe that this system could be used as a "supramolecular buckle" for which CB[8]–**1** corresponds to the state of "buckling up" while the mixture of CB[8]–**1**·H^+ and free **1**·H^+ corresponds to the state of "unbuckling" (Scheme 1, vide supra, there complex CB[8]–**1**·H^+ denoted as the frame of buckle and free **1**·H^+ denoted as the prong of buckle). Since the methyl group of 4-(4-aminophenyl)-N-methylpyridinium can be replaced by any other substituents, feasible construction of a variety of supramolecular building blocks carrying different functions can be expected from this scaffold. Considering its high thermal stability, this "supramolecular buckle" should be quite useful for the fabrication of pH responsive smart materials at elevated temperature. In this context, while these supramolecular building blocks can be fastened together by CB[8] to construct supramolecular materials under neutral condition, the resulting materials can be completely disaggregated by acids and reconstruction of the materials can be realized once neutral condition is recovered.

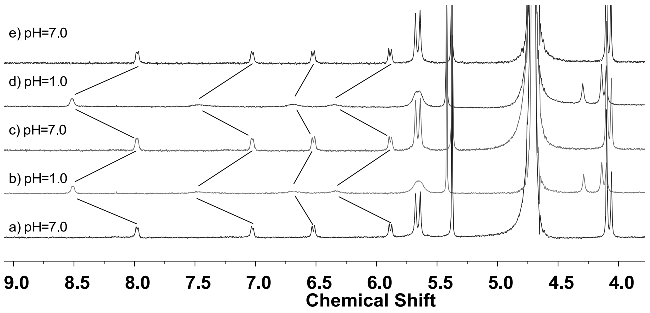


Fig. 5 Partial ^1H NMR (500 MHz) of the solution of 1:2 mixture of [**1** + CB[8]] responding to the change of pH at 25 °C. The concentration of **1** f was 2.0 mM.

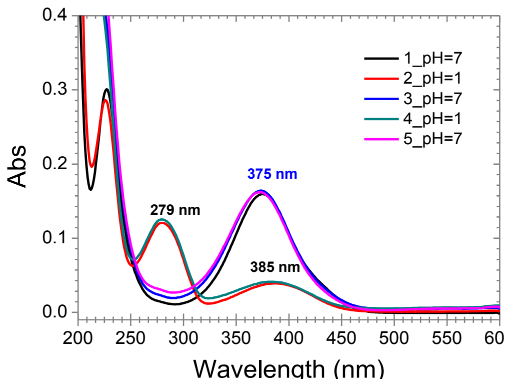


Fig. 6 UV-vis spectra of the solution of 1:2 mixture of [**1** + CB[8]] responding to the change of pH at 25 °C. The concentrations of **1** was 13.3 µM.

Conclusions

In summary, a "supramolecular buckle" has been developed on the basis of the host-guest interaction between CB[8] and 4-(4-aminophenyl)-N-methylpyridinium in aqueous media. The host and guest assemble into 1:2 complex under neutral condition and 1:1 complex under acidic condition. In this way, "buckling up" and "unbuckling" of the "supramolecular buckle" can be realized by adjusting pH through alternately adding acid and base. This "supramolecular buckle" exhibited extremely high binding strength and good thermal stability. It should have great potentials in the fabrications of pH-response supramolecular materials over a wide temperature range. Such potentials are currently under investigation in our laboratory.

Experimental

Synthesis of compound 1. A mixture of 4-(4-nitrophenyl)-N-methylpyridinium iodide[12] (50 mg, 0.2 mmol), 10% Pd/C (25 mg), and anhydrous methanol (20 ml) was stirred under a hydrogen atmosphere (1 atm) for 24h at ambient temperature. The reaction mixture was then filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure to give compound **1** as a yellow solid (41 mg, 91%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.68 (d, J = 6.9 Hz, 2H), 8.20 (d, J = 6.9 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.27 (s, 2H), 4.18 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.2, 154.0, 144.8, 130.3, 120.8, 119.2, 114.5, 46.6. MS (ESI): m/z 185.0 $[M]^+$. HRMS (ESI): Calcd for $C_{12}H_{13}N_2$: 185.1073. Found: 185.1072.

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14 CCDC 1402336 contains the supplementary crystallographic data for compound **1**. Copy of the data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.CCDC.cam.ac.uk/data_request/cif.

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