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Extraordinary Radical Scavengers: 4-Mercaptostilbenes

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Abstract: In the past decade, there was a great deal of interest and excitement in developing more active antioxidants and cancer chemoprevention agents than resveratrol, a naturally occurring stilbene. In this work, eight resveratrol-directed 4-mercaptostilbenes were constructed based on the inspiration that thiophenol should be a stronger radical scavenger than phenol, and their reaction rates with galvinoxyl (GO•) and 2,2-diphenyl-1-picrylhydrazyl (DPPH•) radicals in methanol and ethyl acetate were measured by using stopped-flow UV/Vis spectroscopy at 25 °C. Kinetic analysis demonstrates that 4-mercaptostilbenes are extraordinary radical scavengers, and the substitution of the 4-SH group for the 4-OH group in the stilbene scaffold is an important strategy to improve the radical-scavenging activity of resveratrol. Surprisingly, in methanol, some of the 4-mercaptostilbenes are 10^4-times more active than resveratrol, dozens of times to hundreds of times more effective than known antioxidants (α-tocopherol, ascorbic acid, quercetin, and trolox). The detailed radical-scavenging mechanisms were discussed based on acidified-kinetic analysis. Addition of acetic acid remarkably reduced the GO• and DPPH• radical-scavenging rates of the 4-mercaptostilbenes in methanol, a solvent that supports ionization, suggesting that the reactions proceed mainly through a sequential proton loss electron transfer mechanism. In contrast, an interesting acid-promoted kinetics was observed for the reactions of the 4-mercaptostilbenes with DPPH• in ethyl acetate, a solvent that weakly supports ionization. The increased ratio in rates is closely correlated with the electron-rich environment in the molecules, suggesting that the acceleration could benefit from the contribution of the electron transfer from the 4-mercaptostilbenes and DPPH•. However, the addition of acetic acid had no influence on the GO•-scavenging rates of the 4-mercaptostilbenes in ethyl acetate, due to the occurrence of the direct hydrogen atom transfer. Our results show that the radical-scavenging activity and mechanisms of 4-mercaptostilbenes depends significantly on the molecular structure and acidity, the nature of the attacking radical, and the ionizing capacity of the solvent.

Keywords: antioxidants · mercaptostilbenes · radical reactions · reaction mechanisms · resveratrol · scavengers

Introduction

Stilbenes are a small family of plant secondary metabolites derived from the phenylpropanoid pathway with numerous implications in plant disease resistance and human health.[1] One of the most extensively studied stilbenes is resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a phytoalexin in grapes and other food products, endowed with a surprising array of biological activities against various disease states including cancer, cardiovascular disease, and aging.[2] The truly unique biochemical profile of resveratrol has been attributed to its intrinsic antioxidant ability, because free radical-mediated oxidative damage to biomolecules (e.g., DNA, proteins, and lipids) has been suggested to be a major factor in the development of cancer, atherosclerosis, and aging.[3] Therefore, in the past decade, considerable effort has been devoted to the development of free radical scavengers (antioxidants) that are more effective than resveratrol, and the mechanistic studies on the related free radical-scavenging reactions.[4] In this context, we have also found that structural modifications in the stilbene scaffold of resveratrol including the introduction of electron-donating groups at the positions *ortho* and *para* to the 4-OH or 4′-OH group,[5] construction of the hybrid molecules by incorporating a chroman moiety of vitamin E,[6] and elongation of the conjugated double bond links,[7] are the important strategies to improve the radical-scavenging activity of this parent molecule.

Depending on the nature of the attacking radical, the solvent used, and the molecular structure, the formal abstraction of an hydrogen atom from an antioxidant (AH) by a free radical (X•) can occur by at least four different chemical pathways: direct (single-step) hydrogen atom transfer

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Supporting information (including the synthetic procedures, ^{1}H and ^{13}C NMR, HRMS (ESI), EI-MS spectra, and HPLC analysis (Table S1) of the 4-mercaptostilbenes; stability of the 4-mercaptostilbenes (Figure S1); spectral and kinetic measurements (Figure S2 and Tables S2 and S3), and measurements for the pK_a values of the 4-mercaptostilbenes and the 4-hydroxystilbenes (Figure S3)) for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103897.

[HAT, Eq. (1)], proton-coupled electron transfer [PCET Eq. (2)], sequential proton loss electron transfer [SPLET, Eq. (3)], and electron transfer then proton transfer [ETPT, Eq. (4)].[8] Generally speaking, for a given radical and solvent, the rate of HAT (including PCET) is strictly controlled by the bond dissociation enthalpy (BDE) of the A–H bond. The weaker the strength of the A–H bond, the faster is the HAT process. SPLET is essentially differentiated from HAT by the fact that it occurs when AH first loses a proton to form the corresponding anion (A^-) followed by rapid electron transfer to an electron-deficient radical in an ionizing solvents. This makes the amount (the acid dissociation constant, pK_a, of AH) and oxidation (ionization) potential of this anion (A^-) the key parameters in SPLET. ETPT also consists of a stepwise process involving first electron transfer from AH to an electrophilic radical and then proton transfer from the radical cation ($AH^{\bullet+}$) to the radical anion (X^-). Obviously, the oxidation (ionization) potential of AH plays a pivotal role in ETPT. All of the four different mechanisms eventually lead to the same net result ($A^\bullet$ and XH); thus, free radical-scavenging activity of an antioxidant is governed by the resonance stabilization of the resulting radical ($A^\bullet$).

$$AH+X^\bullet \rightarrow A^\bullet+XH \quad (1)$$

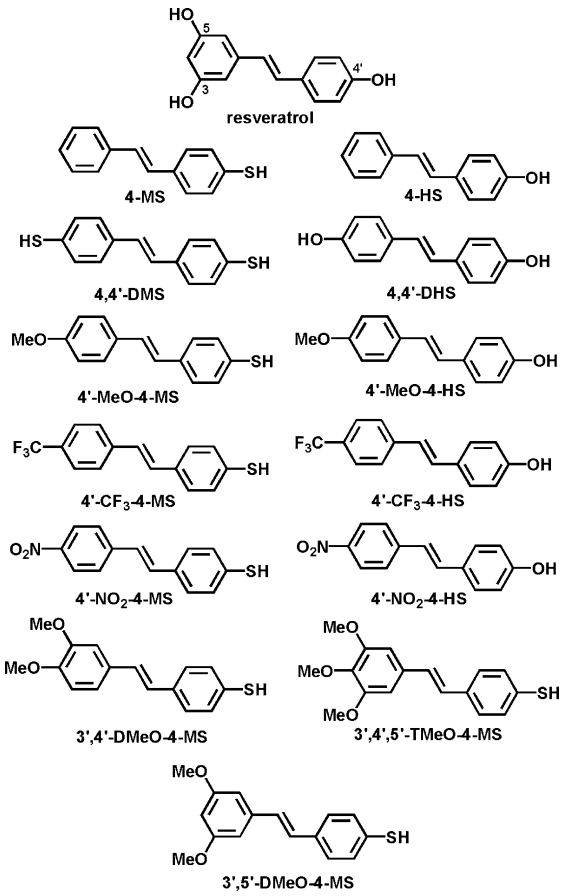
$$AH+X^\bullet \rightarrow [AH\cdots X^\bullet] \rightarrow [AH^{\bullet+}\cdots X^-] \rightarrow A^\bullet+XH \quad (2)$$

$$AH \xrightarrow{-H^+} A^- \xrightarrow{+X^\bullet} A^\bullet+X^- \xrightarrow{+H^+} A^\bullet+XH \quad (3)$$

$$AH+X^\bullet \rightarrow AH^{\bullet+}+X^- \rightarrow A^\bullet+XH \quad (4)$$

Understanding the above mechanisms is of great importance for designing a well free radical scavenger. The significant difference of the BDE between O–H (369.4–378.2 kJ mol^{-1})[9] and S–H (331.0–349.4 kJ mol^{-1})[10] for phenol (ArOH; Ar = aryl) and thiophenol (ArSH) makes the latter more susceptible to a HAT reaction than the former. The pK_a values of ArOH and ArSH have been reported to be 10.0 and 6.6,[11] respectively; Additionally, the reduction potentials (E^o($ArO^\bullet$/ArO^-) and E^o($ArS^\bullet$/ArS^-)) relative to the normal hydrogen electrode (NHE) for phenoxyl ($ArO^\bullet$) and phenylthiyl ($ArS^\bullet$) radicals are 0.79[12] and 0.69 V,[13] respectively. This indicates clearly that there is a high amount of ArS^- in ionizing solvents and that it is a stronger electron donor than ArO^-. Consequently, in comparison with ArOH, ArSH should exhibit increased reactivity towards electrophilic radicals by SPLET mechanism in ionizing solvents. Furthermore, a comparison of the reduction potentials (E^o($ArO^\bullet$,H^+/ArOH) and E^o($ArS^\bullet$,H^+/ArSH) being 1.38 and 1.08 V versus NHE, respectively)[13] for $ArO^\bullet$ and $ArS^\bullet$, suggests that ArSH is more active than ArOH in ETPT reactions. Taken together, these data support the notion that no matter what kind of mechanism is employed, ArSH should be a more effective radical scavenger than ArOH.

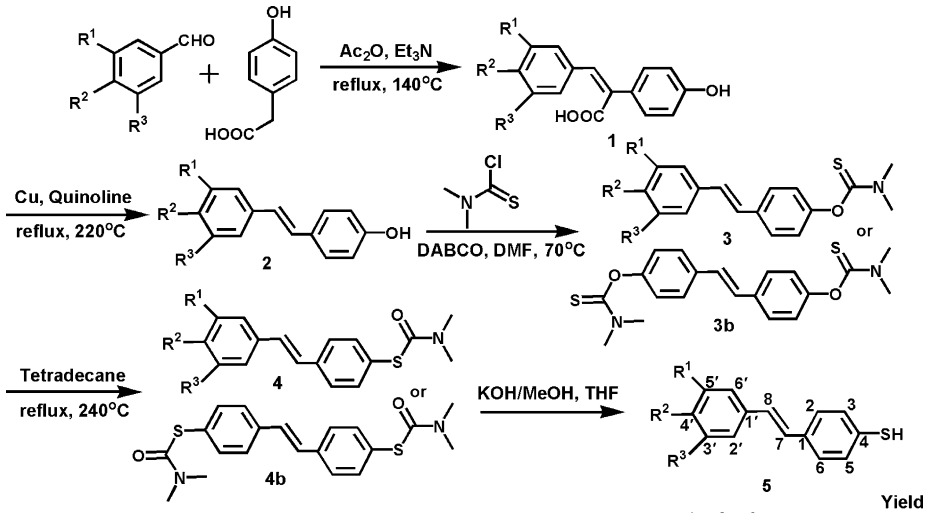
Inspired by the above data, we believe that direct attachment of the mercapto group to the aromatic ring of stilbene is an effective strategy to improve the radical-scavenging activity of resveratrol. In view of the fact that the 4′-OH group in the stilbene scaffold of resveratrol is more active than the 3- and 5-OH groups for radical-scavenging reaction,[4g,h,j,l,m,5] we report herein the synthesis of eight 4-mercaptostilbenes (Scheme 1) with the introduction of electron-donating (ED) and electron-withdrawing (EW) groups, and the quantitative kinetic and mechanistic study of the scavenging reaction of them against galvinoxyl ($GO^\bullet$) and 2,2-diphenyl-1-picrylhydrazyl ($DPPH^\bullet$) radicals in ethyl acetate and methanol. To our knowledge, there is no reported quantitative determination of the radical-scavenging activity of mercaptostilbenes, and we indeed found that all of these 4-mercaptostilbenes exhibit much more effective radical-scavenging activity than the corresponding 4-hydroxystilbenes, and surprisingly, some of them show about 10^4-fold increased radical-scavenging activity in methanol relative to naturally-occurring resveratrol (see below).



Scheme 1. Molecular structures of resveratrol, 4-mercaptostilbenes, and 4-hydroxystilbenes (MS = mercaptostilbene, HS = hydroxystilbene, DMS = dimercaptostilbene, DHS = dihydroxystilbene, DMeO = dimethoxy, TMeO = trimethoxy).

Results and Discussion

Synthesis of the 4-mercaptostilbenes: Construction of 4-mercaptostilbenes was accomplished by the conversion of phenol to thiophenol with reference to a previously reported procedure with some modifications[14] (Scheme 2). The conversion involved a three-step procedure of thiocarbamoylation and Newan–Kwart-rearrangement, followed by cleavage under hydrolytic conditions. These compounds investigated were *trans*-4-mercaptostilbene (4-MS), *trans*-4′,4-dimercaptostilbene (4′,4-DMS), *trans*-4′-methoxy-4-mercaptostilbene (4′-MeO-4-MS), *trans*-3′,4′-dimethoxy-4-mercaptostilbene (3′,4′-DMeO-4-MS), *trans*-3′,5′-dimethoxy-4-mercaptostilbene (3′,5′-DMeO-4-MS), *trans*-3′,4′,5′-trimethoxy-4-mercaptostilbene (3′,4′,5′-TMeO-4-MS), *trans*-4′-trifluoromethyl-4-mercaptostilbene (4′-CF_3-4-MS), and *trans*-4′-nitro-4-mercaptostilbene (4′-NO_2-4-MS), among which 4′-MeO-4-MS, 3′,4′-DMeO-4-MS, 3′,4′,5′-TMeO-4-MS, and 4′-CF_3-4-MS are the new compounds (Scheme 1), and only the 3′,5′-DMeO-4-MS was previously used in the studies of algicidal activity[14c] and inhibitory activity against colon cancer cell.[15]



Scheme 2. Synthesis of 4-mercaptostilbenes (Ac = acyl, DABCO = 1,4-diazobicyclo[2.2.2]octane).

Stability of the 4-mercaptostilbenes: Generally, the molecules with lower ionization potential are endowed with higher electron transfer ability, but very low ionization potentials also lead to their air instability due to the direct reaction with oxygen, thereby limiting their radical-scavenging efficacy. Thus, we first examined the stability of the 4-mercaptostilbenes towards air in DMSO at 30 °C by monitoring their typical UV absorbance. The 4-mercaptostilbenes showed no signs of decomposition over a 10 h period (see Figure S1 in the Supporting Information), and they were also stable in either solid or solution form under air during the following experiments.

Radical-scavenging activity of the 4-mercaptostilbenes: GO• and DPPH• are relatively stable oxygen and nitrogen radicals, as the prototypic models for peroxyl radicals, respectively, and have been widely used to screen the relative radical-scavenging ability.[8l,16] We next tested the radical-scavenging property of the 4-mercaptostilbenes in ethyl acetate and methanol by using the two kinds of radicals. The selection for two types of solvents is based on their significantly different ionizing ability, as ethyl acetate has a much lower dielectric constant ($\varepsilon = 6.02$)[17] than methanol ($\varepsilon = 32.63$)[17] and hence, has a lower ability to support ionization of the substrate. The second-order rate constants (k) of GO• and DPPH•-scavenging reactions of 4-mercaptostilbenes at 25 °C were measured by monitoring the decrease in absorbance at $\lambda = 428$ and 517 nm, respectively, by using the stopped-flow technique (see Figure S2 in the Supporting Information). The rate constants obtained are listed in Table 1 together with the values for known antioxidants (α-tocopherol, ascorbic acid, quercetin, and trolox) and our previous data for 4-hydroxystilbenes (Scheme 1),[5] which are given for comparison. As can be seen from the k values in Table 1 the GO•- and DPPH•-scavenging activity of the 4-mercaptostilbenes in ethyl acetate follows the sequences of 4′,4-DMS > 3′,4′-DMeO-4-MS > 4′-MeO-4-MS > 3′,4′,5′-TMeO-4-MS ≈ 3′,5′-DMeO-4-MS > 4-MS > 4′-CF_3-4-MS and 3′,4′-DMeO-4-MS > 3′,4′,5′-TMeO-4-MS > 4′,4-DMS > 3′,5′-DMeO-4-MS ≈ 4′-MeO-4-MS > 4-MS > 4′-NO_2-4-MS > 4′-CF_3-4-MS, respectively, whereas the order in methanol is 3′,4′-DMeO-4-MS > 4′,4-DMS > 4′-MeO-4-MS > 3′,4′,5′-TMeO-4-MS > 4-MS > 3′,5′-DMeO-4-MS > 4′-CF_3-4-MS and 3′,4′-DMeO-4-MS > 4′,4-DMS > 4′-MeO-4-MS > 3′,5′-DMeO-4-MS ≈ 3′,4′,5′-TMeO-4-MS > 4′-NO_2-4-MS > 4-MS > 4′-CF_3-4-MS, respectively. Although these activity sequences are not completely consistent, the k values increase generally with the introduction of ED groups (methoxy and mercapto) at the position *para* to the 4-SH and decrease with the introduction of EW groups (nitro and trifluoromethyl) with the exception of 4′-NO_2-4-MS in the case of

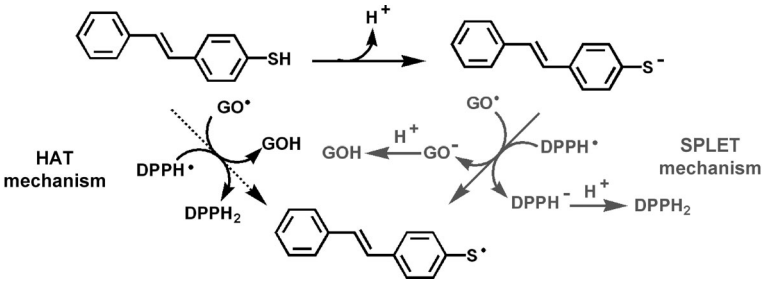
Table 1. Rate constants for radical-scavenging reaction of 4-mercaptostilbenes at 25 °C.[a]

	k [L mol^{-1} s^{-1}] (GO•)		k [L mol^{-1} s^{-1}] (DPPH•)	
	ethyl acetate[b]	methanol[c]	ethyl acetate[b]	methanol[c]
resveratrol	(15.6±0.2)	(46.9±1.5)	(1.03±0.02)	$(2.09\pm0.01)\times10^{2}$
4-MS	(50.3±0.9)	$(8.89\pm0.02)\times10^{5}$	(18.0±0.1)	$(8.81\pm0.08)\times10^{5}$
4,4′-DMS	$(1.05\pm0.01)\times10^{2}$	$(1.50\pm0.01)\times10^{6}$	(24.6±1.6)	$(1.90\pm0.01)\times10^{6}$
4′-MeO-4-MS	(86.0±0.9)	$(1.07\pm0.01)\times10^{6}$	(19.2±0.3)	$(1.40\pm0.02)\times10^{6}$
3′,4′-DMeO-4-MS	(94.7±5.1)	$(1.70\pm0.01)\times10^{6}$	(28.7±0.1)	$(2.08\pm0.03)\times10^{6}$
3′,5′-DMeO-4-MS	(61.8±5.4)	$(8.54\pm0.03)\times10^{5}$	(21.1±0.6)	$(1.06\pm0.03)\times10^{6}$
3′,4′,5′-TMeO-4-MS	(62.7±2.8)	$(9.69\pm0.02)\times10^{5}$	(27.6±0.2)	$(1.02\pm0.02)\times10^{6}$
4′-CF_3-4-MS	(27.6±0.7)	$(3.20\pm0.01)\times10^{5}$	(9.95±0.49)	$(6.87\pm0.08)\times10^{5}$
4′-NO_2-4-MS	[d]	[d]	(16.7±0.8)	$(9.48\pm0.21)\times10^{5}$
trolox		$(7.65\pm0.01)\times10^{4}$		$(9.99\pm0.01)\times10^{2}$
quercetin		$(1.36\pm0.01)\times10^{4}$		$(1.32\pm0.02)\times10^{4}$
ascorbic acid		$(4.33\pm0.02)\times10^{4}$		$(3.22\pm0.01)\times10^{4}$
α-tocopherol		$(2.51\pm0.01)\times10^{3}$		$(1.71\pm0.02)\times10^{3}$
4-HS	9.7[e]	(88.7±1.7)[b]	0.6[e]	$(2.93\pm0.02)\times10^{2}$[b]
4,4′-DHS	108.6[e]	$(1.22\pm0.01)\times10^{3}$[b]	6.4[e]	$(1.48\pm0.14)\times10^{4}$[b]
4′-MeO-4-HS	33.0[e]	$(3.88\pm0.01)\times10^{2}$[b]	1.9[e]	$(2.04\pm0.15)\times10^{3}$[b]
4′-CF_3-4-HS	3.2[e]	(10.9±0.5)[b]	0.7[e]	(94.1±5.4)[b]
4′-NO_2-4-HS			0.3[e]	(21.1±1.2)[b]

[a] All of the rate constants were detected by the stopped-flow technique and data are expressed as the mean ±SD for three determinations. [b] Detected by following the pseudo-first-order decay of radical. [c] Detected using second-order kinetics with the concentration ratio of compound and radical being 1:1. [d] Reaction rate could not be measured for spectral overlapping. [e] Cited from reference [5].

DPPH•/methanol. A comparison of the k values of the 4-mercaptostilbenes and their corresponding 4-hydroxystilbenes in ethyl acetate and methanol clearly indicates that the GO•- and DPPH•-scavenging activity of the former is much more active than the latter, highlighting the importance of the substitution of the 4-SH group for the 4-OH group in the stilbene scaffold. A striking feature of our data is that in methanol, the acceleration of the GO•- and DPPH•-scavenging reaction for some of the 4-mercaptostilbenes, such as 3′,4′-DMeO-4-MS, 4′,4-DMS, and 4′-MeO-4-MS, in comparison to resveratrol reaches about four orders of magnitude. Additionally, the radical-scavenging activity of 4′,4-DMS, 3′,4′-DMeO-4-MS, and 4′-MeO-4-MS in methanol also increases dozens of times to hundreds of times over that of the known antioxidants (α-tocopherol, ascorbic acid, quercetin, and trolox). For example, the k value of 3′,4′-DMeO-4-MS (1.70×10^{6} M^{-1} s^{-1}) for the GO•-scavenging reaction in methanol is approximately 3.6×10^{4}, 677, 39, 125, and 22 times larger than that of resveratrol (46.9 M^{-1} s^{-1}), α-tocopherol (2.51×10^{3} M^{-1} s^{-1}), ascorbic acid (4.33×10^{4} M^{-1} s^{-1}), quercetin (1.36×10^{4} M^{-1} s^{-1}), and trolox (7.65×10^{4} M^{-1} s^{-1}), respectively.

Effect of added acetic acid on the radical-scavenging reactions of the 4-mercaptostilbenes in methanol: The k values for the GO•- and DPPH•-scavenging reactions of the 4-mercaptostilbenes in methanol are roughly four orders of magnitude larger than that in ethyl acetate (see Table 1). This remarkable kinetic difference between methanol and ethyl acetate should arise from the different mechanisms. Litwinienko and Ingold have observed previously an abnormal increase of the rate constants for the DPPH•-scavenging reaction of phenols in alcoholic media, and clearly demonstrated by comparing the kinetic differences between acidified alcoholic and nonalcoholic solvents that this is attributed to partial ionization of phenols and a very fast electron transfer from the phenolate anion to DPPH• (SPLET).[8a] These excellent studies[8a] together with our recent results for hydroxystilbenes[5] indicate that in methanol, a solvent which supports ionization, the GO•- and DPPH•-scavenging reaction of the 4-mercaptostilbenes may occur primarily by the SPLET mechanism. To further elucidate this point, we examined the effect of added acetic acid on the GO•- and DPPH•-scavenging reaction of the 4-mercaptostilbenes in methanol (Figure 1). As shown in Figure 1, all of the rate constants for 4′-MeO-4-MS, 4-MS, and 4′-CF_3-4-MS including resveratrol in methanol decreased remarkably, with an increasing acetic acid concentration, to reach the different limiting values (see also Tables S2 A and B in the Supporting Information). This outcome strongly suggests that in nonacidified methanol, the observed kinetic data of the 4-mercaptostilbenes are a cooperation result of SPLET and HAT reactions, and the kinetics is mostly governed by the former (the actual electron donor is the thiolate anion), whereas the addition of acetic acid remarkably reduces the rate by eliminating the SPLET mechanism to only leave the HAT mechanism due to the suppression of ionization for the acid compounds (Scheme 3).



Scheme 3. Radical-scavenging mechanisms of 4-mercaptostilbene in methanol: HAT mechanism (dot line) and SPLET mechanism (solid line).

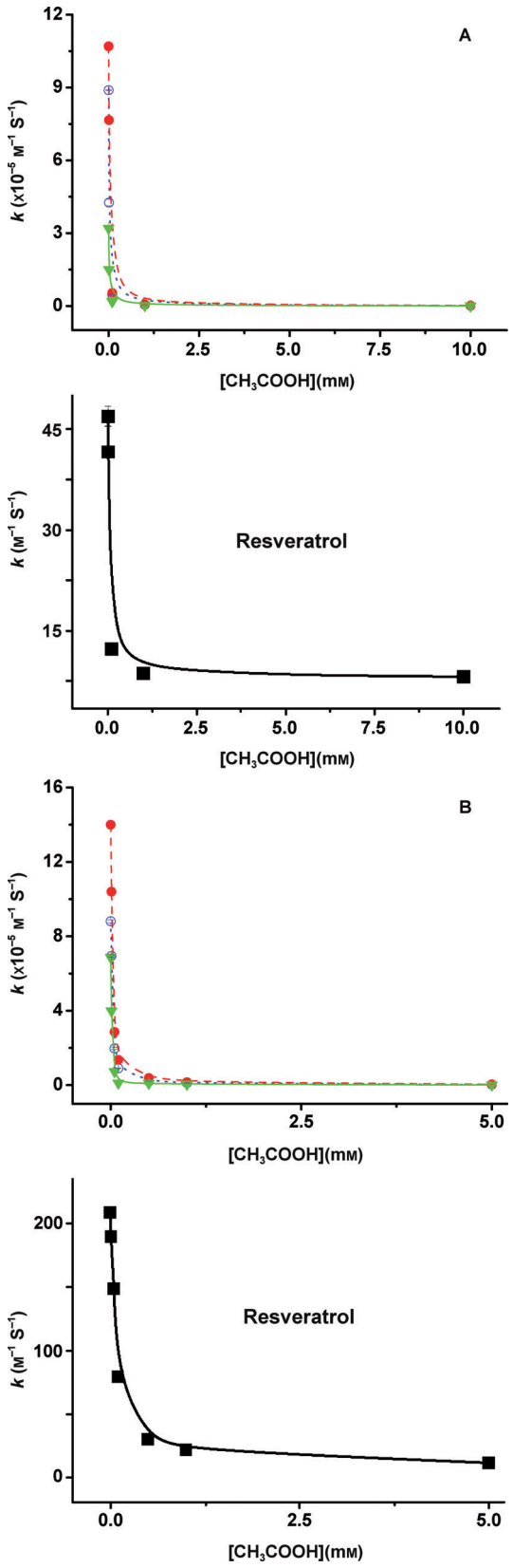


Figure 1. Effect of added acetic acid on the GO•- (A) and DPPH•-scavenging (B) rate of 4-mercaptostilbenes (○=4-MS, ●=4′-MeO-4-MS, ▼=4′-CF_3-4-MS) or resveratrol (■) in methanol.

Acidity constants of the 4-mercaptostilbenes: Recently, Litwinienko and co-workers have determined the pK_a values and DPPH•-scavenging rate of multi-hydroxyl flavonoids and demonstrated clearly that the kinetics and reaction sites in alcoholic media are noticeably affected by the acidity of the hydroxyl groups.[8c] Consequently, the acidity of the HS group in the 4-mercaptostilbenes is of great importance for the kinetics of their SPLET reactions with GO• and DPPH• in methanol that support ionization. We also determined the pK_a values of the 4-mercaptostilbenes and their corresponding 4-hydroxystilbenes in methanol/phosphate-buffered saline (PBS; pH 7.4) (v/v=2:1) by monitoring their UV/Vis absorption changes with different pH values (Figures 2 and

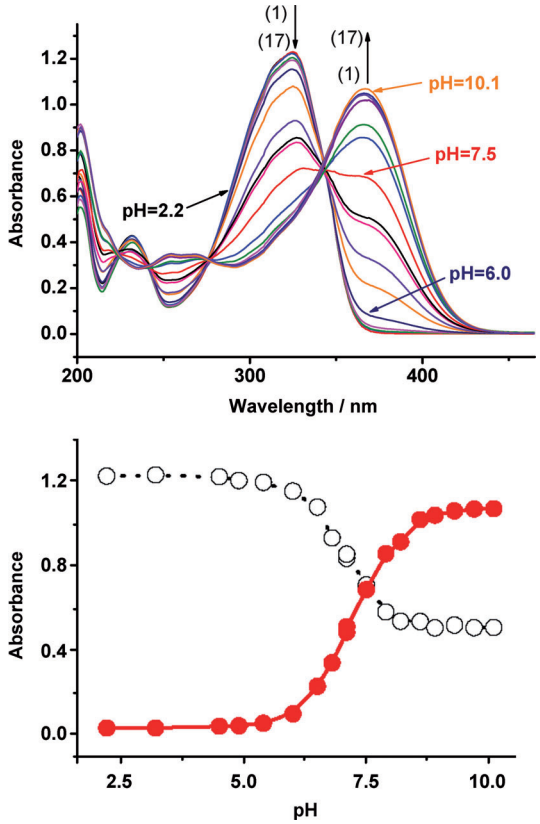


Figure 2. Top: Absorption spectra of 4′-CF_3-4-MS in methanol/PBS (v/v, 2:1) as a function of the pH. Curves 1–17 correspond to pH 2.2, 3.2, 4.5, 4.9, 5.4, 6.0, 6.5, 6.8, 7.1, 7.5, 7.9, 8.2, 8.6, 8.9, 9.3, 9.7, and 10.1, respectively. Bottom: Titration curves at λ=325 (dot line) and 366 nm (solid line).

S3 in the Supporting Information). As exemplified in Figure 2, upon increase of the pH from 2.2 to 10.1 the absorption band of 4′-CF_3-4-MS at λ=325 nm gradually decreased along with the appearance of a new absorption band at λ=366 nm. The isosbestic point at λ=344 nm suggests a ground state acid–base equilibrium involving the neutral (λ=325 nm) and anionic (λ=366 nm) forms of 4′-CF_3-4-MS. From the inflection point of the spectrophotometric titration curves (Figure 2, bottom), its pK_a value of 7.14 was obtained. The pK_a values of other compounds are presented in Table 2. As can be seen from Table 2, all 4-mer-

Table 2. The pK_a values of 4-mercaptostilbenes and 4-hydroxystilbenes in methanol/phosphate-buffered saline (v/v = 2:1).[a]

4-Mercaptostilbene	pK_a	4-Hydroxystilbene	pK_a
4-MS	(7.32±0.02)	4-HS	(10.9±0.1)
4′-MeO-4-MS	(7.43±0.03)	4′-MeO-4-HS	(10.8±0.1)
4′-CF_3-4-MS	(7.14±0.07)	4′-CF_3-4-HS	(10.5±0.1)
4′-NO_2-4-MS	(7.00±0.05)	4′-NO_2-4-HS	(10.3±0.1)

[a] Data are expressed as the mean ±SD for three determinations.

captostilbenes are three orders of magnitude more acidic than their corresponding 4-hydroxystilbenes, which is closely correlated with the remarkable increase of radical-scavenging rate constants in methanol for the former compared with the latter. Moreover, the above-mentioned exception, that is, the relatively high DPPH•-scavenging rate constants of 4′-NO_2-4-MS ($9.48\times10^5\,M^{-1}s^{-1}$) compared with 4-MS ($8.81\times10^5\,M^{-1}s^{-1}$) in methanol also confirm a crucial role of the acidity in the SPLET reaction. However, it should be pointed out that the introduction of EW groups (nitro and trifluoromethyl) can augment the acidity of 4-mercaptostilbenes, as indicated by the pK_a values from Table 2, and hence increase the concentration of thiolate anion, but this stabilizing effect on the anion will decrease its oxidation potential and electron transfer ability. This paradox effect on the contribution of SPLET results in the experimental fact that the most acidic compounds (4′-NO_2-4-MS and 4′-CF_3-4-MS) are not the most effective radical scavengers, in contrast, 3′,4′-DMeO-4-MS, 4′,4-DMS, and 4′-MeO-4-MS are the most active ones among the 4-mercaptostilbenes examined.

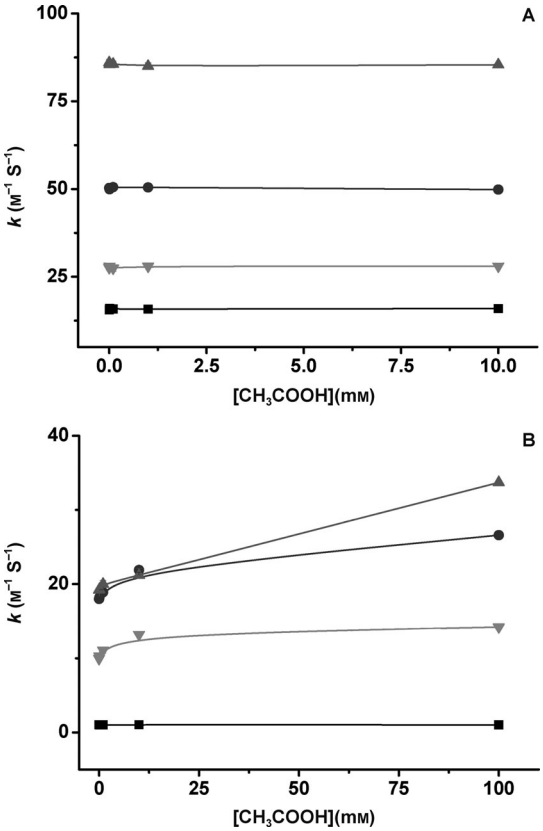
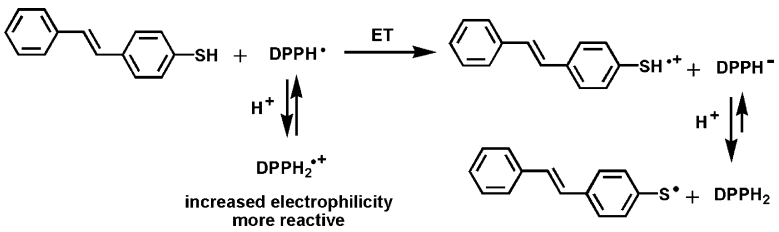


Figure 3. Effect of added acetic acid on the GO•- (A) and DPPH•-scavenging (B) rate of 4-mercaptostilbenes (▲ = 4′-MeO-4-MS, ● = 4-MS, ▼ = 4′-CF_3-4-MS) or resveratrol (■) in ethyl acetate.

Effect of added acetic acid on the radical-scavenging reactions of the 4-mercaptostilbenes in ethyl acetate: To rationalize the reaction mechanism of the 4-mercaptostilbenes in a solvent that weakly supports ionization, we finally investigated the effect of added acetic acid on their radical-scavenging rate in ethyl acetate. As expected, each of the 4-mercaptostilbenes and resveratrol showed a constant GO•-scavenging rate in the presence of acid (Figure 3 A). Consequently, only the HAT reaction takes place under the present condition. However, in the case of DPPH•, an interesting acid-promoted reaction kinetics was observed for 4′-MeO-4-MS, 4-MS, and 4′-CF_3-4-MS. Specifically, their reaction rate constants increased somewhat by 76, 48, and 43%, respectively, when the concentration of acetic acid was 100 mmol L^{-1} (Figure 3 B and Table S3 A in the Supporting Information). It is also noticeable that the ratios increase with increasing the electron-rich environment in the molecules, that is, the electron richer the molecule, the larger is the increased ratio of the k value, as demonstrated by the three 4-mercaptostilbenes. This might be indicative of a propensity toward the ETPT mechanism rather than the HAT mechanism in the case of 4-mercaptostilbenes/DPPH• reactions in ethyl acetate (Scheme 4). In other words, the ETPT reaction might contribute to the increased rate in the presence of acid. Recently, unexpected acid-promoted kinetics has also been found in reactions of peroxyl radicals with phenols in acetonitrile,[8b] and reactions of DPPH• with bilirubin ester and dipyrrinone in methanol.[8f] The acid-promoted kinetics can be understood because the protonation of DPPH• can be initiated by the addition of acid, leading to an increase in the electrophilicity of the radical and hence, facilitating the electron-transfer step;[8b,f] additionally, the equilibrium toward $DPPH_2$ can be promoted by the pres-



Scheme 4. Proposed mechanism for the acid-promoted reaction of 4-mercaptostilbene with DPPH• in ethyl acetate.

ence of acid,[8f] as exemplified in Scheme 4. Such a contrast effect (constant and acceleration in the rate) of added acetic acid can be attributed to the fact that in contrast to GO$^{\bullet}$ (E^{o}_{red} vs. saturated calomel electrode (SCE) = 0.05 V),[18] DPPH$^{\bullet}$ has a relatively high reduction potential (E^{o}_{red} vs. SCE = 0.18 V),[18] is thereby prone to undergo electron-transfer reaction. Nevertheless, for resveratrol, no acceleration was observed even in the case of DPPH$^{\bullet}$ (Figure 3B) probably due to its high oxidation potential compared to the 4-mercaptostilbenes.

Conclusion

In conclusion, eight resveratrol-directed 4-mercaptostilbenes were constructed based on the inspiration that ArSH should be a stronger radical scavenger than ArOH. This work demonstrates that 4-mercaptostilbenes are extraordinary radical scavengers, and the substitution of the 4-SH group for the 4-OH group in the stilbene scaffold is an important strategy to improve the radical-scavenging activity of resveratrol. Most impressively, in methanol, some of the 4-mercaptostilbenes are 10^4-times more active than resveratrol, dozens of times to hundreds of times more effective than known antioxidants (α-tocopherol, ascorbic acid, quercetin, and trolox). Their radical-scavenging activity and mechanisms are strongly influenced by various factors including the molecular structure and acidity, the nature of the attacking radical, and the ionizing capacity of the solvent. Additionally, all of the synthesized 4-mercaptostilbenes have no smell, which is entirely different from the mercaptans. Based on the above-described results, the 4-mercaptostilbenes may be considered as a novel type of resveratrol-directed antioxidants.

Experimental Section

Materials: α-Tocopherol was purchased from Calbiochem. Quercetin and the 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) radical were purchased from Aldrich–Sigma. The galvinoxyl (GO$^{\bullet}$) radical, trolox, and ascorbic acid were obtained from Acros Organics. Methanol was of HPLC grade and used directly, whereas ethyl acetate and acetic acid were of analytical grade and purified by standard techniques.

Synthesis of compounds: The 4-mercaptostilbenes (**5**) were synthesized mainly referred to the published method[14a,b,c] and their structures and purity were confirmed by ^{1}H and ^{13}C NMR spectroscopy, HRMS (ESI), EI-MS, and HPLC (see the Supporting Information for all synthetic procedures).

***trans*-4-Mercaptostilbene (5a)**: Pale-yellow solid; m.p. 159–161 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 4.37 (s, 1H; SH), 7.21 (s, 2H; H7, H8), 7.26 (t, J = 7.2 Hz, 1H; H4′), 7.32 (d, J = 8.4 Hz, 2H; H3, H5), 7.36 (t, J = 7.2 Hz, 2H; H3′, H5′), 7.50 (d, J = 7.2 Hz, 2H; H2′, H6′), 7.58 ppm (d, J = 8.4 Hz, 2H; H2, H6); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 127.2, 127.3, 127.5, 127.8, 128.1, 128.3, 128.6, 129.0, 131.1, 134.7, 135.9, 137.5 ppm; MS: *m*:*z* (%): 212 (100), 178 (99.27), 89 (49.5).

***trans*-4,4′-Dimercaptostilbene (5b)**: Brown–yellow solid; m.p. 233–235 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.51 (s, 2H; SH), 7.12 (s, 2H; H7, H8), 7.28 (d, J = 8.0 Hz, 4H; H3, H5); 7.45 ppm (d, J = 8.0 Hz, 4H; H2, H6); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 127.0, 128.6, 131.6, 133.8 ppm; MS: *m/z* (%): 244 (100), 178 (61.18), 165 (28.79).

***trans*-4′-Methoxy-4-mercaptostilbene (5c)**: Pale-yellow solid; m.p. 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47 (s, 1H; SH), 3.83 (s, 3H; OCH_3), 6.90 (d, J = 8.0 Hz, 2H; H3′, H5′), 6.91 (d, J = 16.4 Hz, 1H; H8), 7.02 (d, J = 16.4 Hz, 1H; H7), 7.25 (d, J = 8.0 Hz, 2H; H2′, H6′), 7.36 (d, J = 8.0 Hz, 2H; H3, H5), 7.44 ppm (d, J = 8.0 Hz, 2H; H2, H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 114.2, 125.7, 126.9, 127.7, 128.0, 129.3, 129.7, 130.0, 135.4, 159.4 ppm.

***trans*-3′,4′-Dimethoxy-4-mercaptostilbene (5d)**: Pale-yellow solid; m.p. 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (s, 1H; SH), 3.90 (s, 3H; OCH_3), 3.94 (s, 3H; OCH_3), 6.86 (d, J = 8.4 Hz, 1H; H3′), 6.90 (d, J = 16.4 Hz, 1H; H8), 6.98–7.06 (m, 3H; 3H (H2′, H6′, H7′), 7.25 (d, J = 8.4 Hz, 2H; H3, H5), 7.37 ppm (d, J = 8.4 Hz, 2H; H2, H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 55.9, 108.7, 111.2, 119.9, 125.9, 126.8, 128.2, 129.4, 129.7, 130.3, 135.2, 148.9, 149.1 ppm; HRMS (ESI): *m*/*z* calcd for $[M+H]^+$: 273.0944; found: 274.2739.

***trans*-3′,5′-Dimethoxy-4-mercaptostilbene (5e)**: Pale-yellow solid; m.p. 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (s, 1H; SH), 3.85 (s, 6H; OCH_3), 6.42 (t, J = 2.4 Hz, 1H; H4′), 6.67 (d, J = 2.4 Hz, 2H; H2′, H6′), 6.99 (d, J = 16.4 Hz, 1H; H8), 7.04 (d, J = 16.4 Hz, 1H; H7), 7.27 (d, J = 8.0 Hz, 2H; H3, H5), 7.39 ppm (d, J = 8.0 Hz, 2H; H2, H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 100.2, 104.7, 127.4, 128.5, 128.6, 129.8, 130.4, 134.9, 139.4, 161.2 ppm; MS: *m*/*z* (%): 272 (100), 208 (22.08), 152 (24.27).

***trans*-3′,4′,5′-Trimethoxy-4-mercaptostilbene (5f)**: Pale-yellow solid; m.p. 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (s, 1H; SH), 3.87 (s, 3H; OCH_3), 3.91 (s, 6H; OCH_3), 6.72 (s, 2H; H2′, H6′), 6.93 (d, J = 16.0 Hz, 1H; H8), 6.99 (d, J = 16.0 Hz, 1H; H7), 7.25 (d, J = 8.0 Hz, 2H; H3, H5), 7.37 ppm (d, J = 8.0 Hz, 2H; H2, H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 60.9, 103.5, 127.0, 127.3, 128.3, 129.6, 129.9, 132.9, 134.8, 137.9, 153.4 ppm; HRMS (ESI): *m*/*z* calcd for $[M+H]^+$: 303.1049; found: 303.1043.

***trans*-4′-Trifluoromethyl-4-mercaptostilbene (5g)**: Pale-yellow solid; m.p. 179–181 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$), δ = 4.42 (s, 1H; SH), 7.29 (d, J = 16.4 Hz, 1H; H8), 7.34 (d, J = 8.0 Hz, 2H; H3, H5), 7.37 (d, J = 16.4 Hz, 1H; H7), 7.40 (d, J = 8.4 Hz, 2H; H2, H6), 7.69 (d, J = 8.4 Hz, 2H; H2′, H6′), 7.79 ppm (d, J = 8.4 Hz, 2H; H3′, H5′); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 126.0 (q, J = 270 Hz), 127.0 (q, J = 4 Hz), 127.9, 128.4, 129.0, 129.9 (q, J = 30 Hz), 130.4, 132.2, 133.7, 135.5, 143.0 ppm.

***trans*-4′-Nitro-4-mercaptostilbene (5h)**: Yellow solid; m.p. 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (s, 1H; SH), 7.08 (d, J = 16.0 Hz, 1H; H8), 7.19 (d, J = 16.0 Hz, 1H; H7), 7.28 (d, J = 8.4 Hz, 2H; H3, H5), 7.41 (d, J = 8.4 Hz, 2H; H2, H6), 7.60 (d, J = 8.8 Hz, 2H; H2′, H6′), 8.20 ppm (d, J = 8.8 Hz, 2H; H3′, H5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.1, 125.8, 126.7, 127.6, 129.4, 132.0, 132.4, 133.6, 143.7, 146.7 ppm; MS: *m*/*z* (%): 257 (100), 178 (83.05), 89 (41.95)

Stability of the 4-mercaptostilbenes: The stability of the 4-mercaptostilbenes (26.7 μmol L^{-1}) towards air in DMSO solution at 30 °C was monitored at the band maximum (λ(4-MS) = 331, (4′-MeO-4-MS) = 340, (3′,4′-DMeO-4-MS) = 346, (resveratrol) = 327 nm) by using UV/Vis spectroscopy.

Spectral and kinetic measurements

Pseudo-first-order kinetics: An aliquot of a 4-mercaptostilbene at more than 10-fold excess of the concentration of the radical, was rapidly mixed with GO$^{\bullet}$ (5 μmol L^{-1}) or DPPH$^{\bullet}$ (25 μmol L^{-1}) by using a stopped-flow SFA-20 accessory. The pseudo-first-order decay of GO$^{\bullet}$ (428 nm) or DPPH$^{\bullet}$ (517 nm) in ethyl acetate at 25 °C was monitored by using a Varian Cary 300 Spectrophotometer. The second-order rate constants (k) were obtained by the plots of the pseudo-first-order constants versus [4-mercaptostilbene]. The second-order rate constants in the presence of acid were determined in the same manner.

Second-order kinetics: As the radical-scavenging rates of the 4-mercaptostilbenes in methanol are very fast, their second-order rate constants (k) were measured by using second-order kinetics with the concentration ratio of the compound and the radical being 1:1 and the stopped-flow technique. The concentrations of GO$^{\bullet}$ and DPPH$^{\bullet}$ in methanol were measured from their molar extinction coefficient values, $\varepsilon = 1.153 \times 10^5$ (λ_{max} = 428) and 1.023×10^4 M^{-1} cm^{-1} (517 nm), respectively.

Measurements for pKa values of the 4-mercaptostilbenes and 4-hydroxystilbenes: The pKa values in methanol/PBS (v/v = 2:1) were measured using the spectrophotometric titration methods as described previously.[8c] A precision pH meter (Mettler Toledo EL20 pH-meter) was used with a combined pH glass electrode calibrated on primary pH standards for the mixed solvent. Briefly, small volumes of titrant (2 mol L^{-1} KOH or HCl in methanol/PBS) were used to adjust pH of the system (3 mL solution of the 40 μmol L 1 4-mercaptostilbenes or 4-hydroxystilbenes) to the appropriate values at 25 °C under a nitrogen atmosphere. After each addition of titrant and when the pH value was stable, 2 mL samples of titrated solution were transferred to quartz cuvettes (10 mm i.d.), and the UV/Vis spectra in the range 200–650 nm were recorded using a Varian Cary 300 Spectrophotometer.

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