Facile and High-Yielding Synthesis of TAM Biradicals and Monofunctional TAM Radicals

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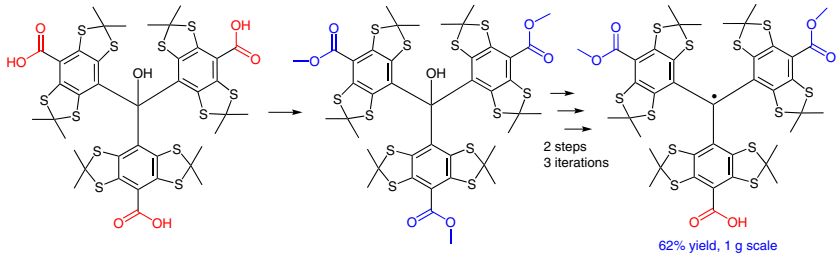

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Abstract Facile and high-yielding procedures for the synthesis of monocarboxylic acid derivatives of triarylmethyl radicals (TAM) were developed. Reaction of methyl thioglycolate with tris(2,3,5,6-tetrathiaaryl)methyl cation smoothly afforded the monosubstituted TAM derivative, which was hydrolyzed to a monocarboxylic acid, with the TAM moiety attached to thioglycolic acid via the sulfur atom. Alternatively, the diamagnetic tricarboxylic acid precursor of Finland trityl was transformed to a trimethyl ester and partially hydrolyzed under controlled conditions. The diester product was isolated, and the remaining fractions were converted back into the trimethyl ester for production of more diester. The first representatives of TAM biradicals with different TAM cores and interspin distances were obtained by reaction of these new TAM monocaboxylic acids with *N*,*N*′-dimethylethylenediamine.

Key words free radicals, persistent triarylmethyls, TAM derivatives, spin labels, biradicals

Tris(2,3,5,6-tetrathiaaryl)methyl radicals (TAM, trityls)[1] have recently emerged as highly promising alternatives to nitroxide radicals. These new carbon-centered radicals offer notable advantages over nitroxides with: much longer T_1 and T_2 relaxation times for magnetic resonance; higher stability toward redox agents present in living tissues and blood plasma, and much sharper EPR signals. These properties make TAM particularly attractive for numerous applications in biology;[2] for 3D EPR high-resolution imaging,[3] production of dynamic nuclear polarization (DNP),[4] and measurement of nanometer distances by site-directed spin labeling and pulsed ESR dipolar spectroscopy;[5] and in analytical chemistry[6] and material science.[7]

The growing interest in TAM has inspired intense research on their synthesis, which resulted in efficient and facile approaches for the widely used, simple, C_3-symmetric TAM, such as tris{8-carboxy-2,2,6,6-tetramethylbenzo[1,2-

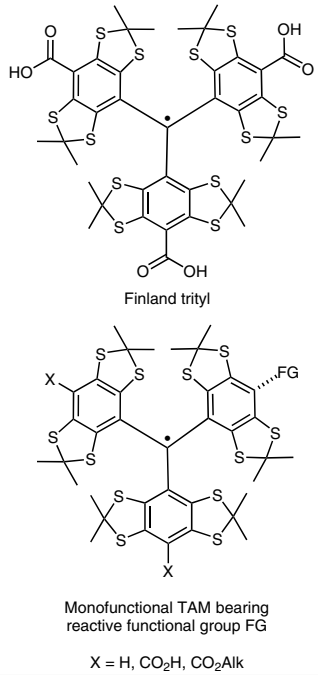
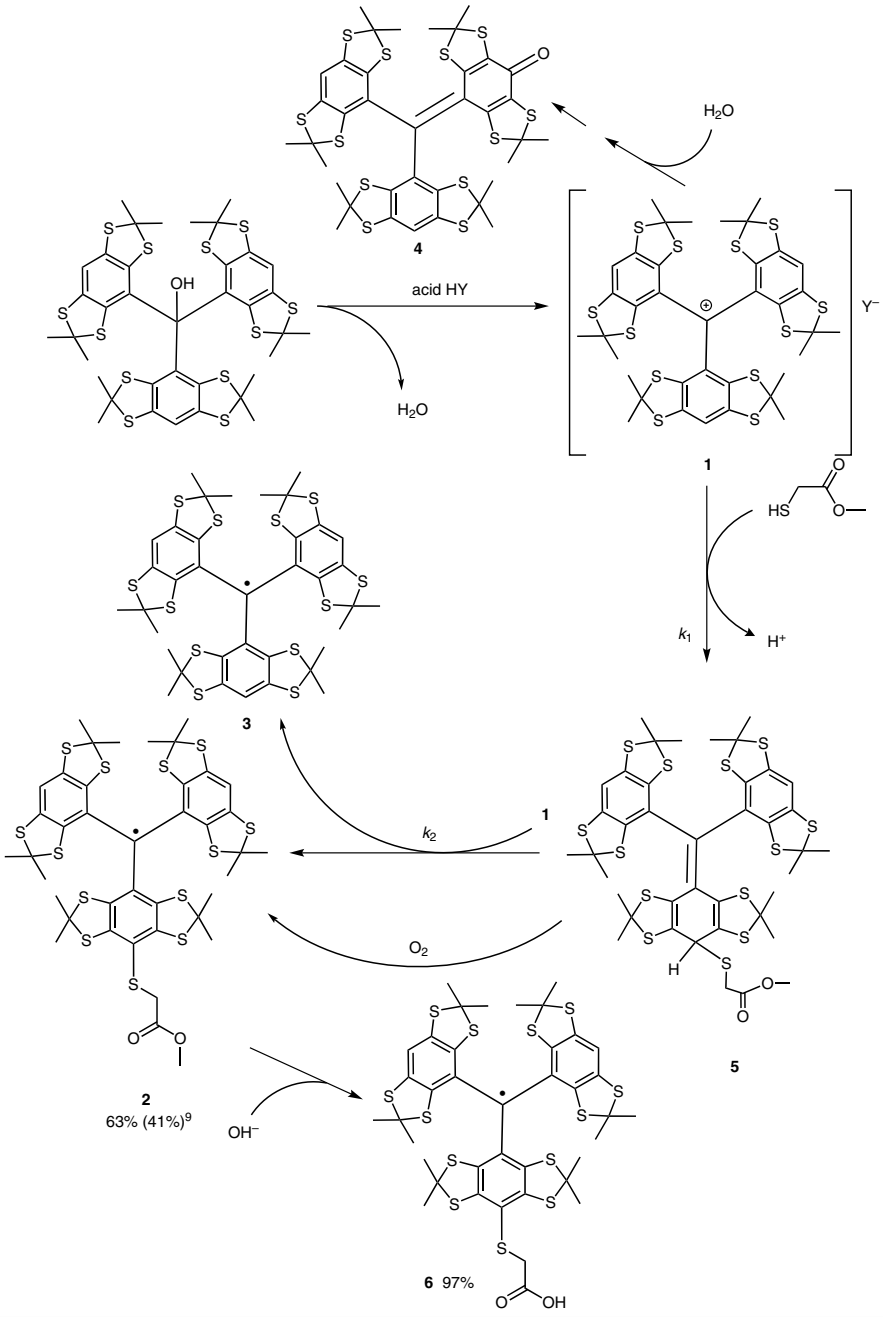


Figure 1 Finland trityl radical (symmetric tricarboxylic acid) and monofunctional TAM derivatives bearing a specific reactive functional group[9]



Scheme 1 Synthesis of TAM monobasic acid **6**. Proposed rationale for concurrent formation of TAM **3** and monofunctional TAM **2**.[9]

d:4,5-*d*]bis[1,3] dithiol-4-yl}methyl (Finland trityl, see Figure 1).[8]

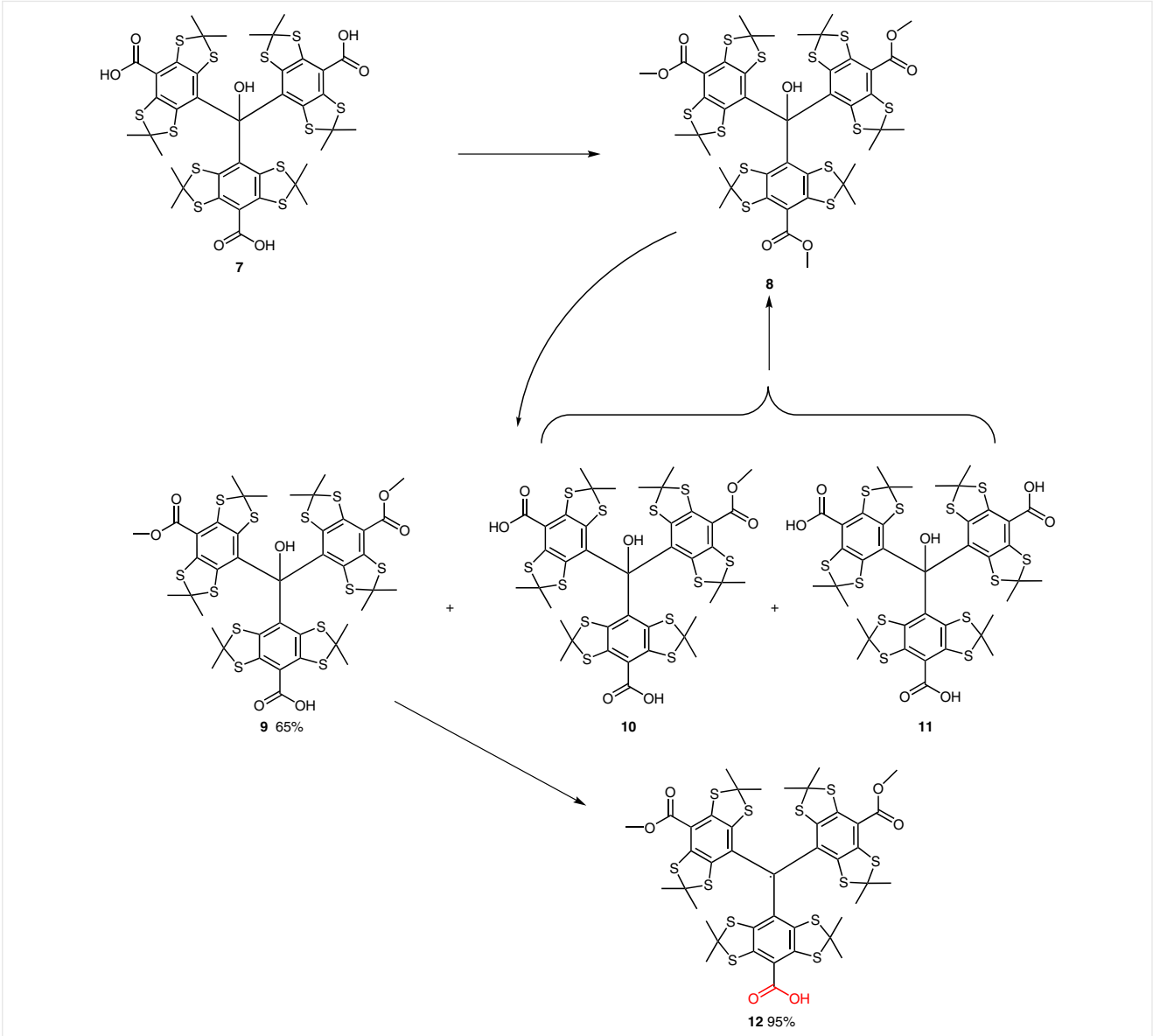
Despite this progress, surprisingly little has been reported on the synthesis of monofunctional trityl derivatives,[9] especially those which possess a specific reactive functional group (FG) to enable expanded use of TAM. These monofunctional TAM derivatives enable the X substituent (Figure 1) to control properties of the TAM core, for example, charge, solubility, hyperfine structure; while the FG provides a single reactive site necessary for constructing spin-labeling reagents, chemical sensors, biradicals, etc. We require precisely these reagents for our ongoing studies of TAM biradicals as new multispin systems designed for use as DNP agents.

Herein we report the practical, simple, and high-yield syntheses of two monofunctional TAM having different X (H or CO_2Me) groups and different carboxylic acid groups (SCH_2CO_2H or CO_2H) as FG. Both of the monofunctional TAM acids are used to construct biradicals. The different FG allowed simple variation of interspin distances in the product biradicals.

Quite recently, we generated monosubstituted TAM by reaction of tris(2,3,5,6-tetrathiaaryl)methyl cations with C-, N- P-, and S-nucleophiles.[9] In particular, the reaction of methyl thioglycolate with the cation **1** readily produced the functionalized TAM **2** (41%) along with two less-abundant byproducts – the unsubstituted TAM **3** and the quinonemethide **4**. This set of reactions is the basis for synthesis of one biradical.

The mechanistic interpretation of these reactions involves two parallel reaction paths (Scheme 1).[9] Both paths start with addition of thiol to cation **1** to produce the intermediate **5**. The single-electron oxidation of **5** by cation **1** yields the unsubstituted symmetric TAM **3**[10] and the desired monofunctional TAM **2** in the first path. The oxidation of intermediate **5** by atmospheric oxygen during workup of the final reaction mixture is the second path to **2**.[9]

These new reactions of formal aromatic nucleophilic substitution and oxidation can be used directly in the syn-



Scheme 2 Synthesis of TAM monobasic acid **12** with the zero-length spacer between TAM core and carboxyl group

thesis of the target monocarboxylic acid **6**, but the first path results in substantial loss of starting material as **3**. To improve the yield, it seemed reasonable to search for conditions which favor the formation of intermediate **5** while minimizing the *in situ* oxidation of **5** by the cation **1**, for example, k_1[**Th**]>>k_2[**1**], where [**Th**] stands for concentration of thiol.

A systematic testing of solvents (dichloromethane, diethyl ether, tetrahydrofuran, dimethylformamide, toluene) and variation of reaction time and temperature gave rise to a notably revised and improved procedure, in which a concentrated solution of cation **1**[11] in dichloromethane (CH_2Cl_2) was added slowly at –20 °C to a toluene solution with a large excess (20 equiv) of methyl thioglycolate. The overnight reaction afforded the monofunctional TAM **2** in 63% yield, the unsubstituted TAM **3** was isolated as a minor byproduct (18%).[12] Finally, the ester **2** was hydrolyzed with LiOH as a mild base[13] to give the target monocarboxylic acid TAM **6** in quantitative yield.[14]

The SCH_2 group in **6** interrupts the π conjugation and delocalization of the unpaired electron spin from the TAM moiety onto the carboxyl group, as well as lessening steric effects from the bulky TAM. But we are also interested in biradicals with short linkages between TAM. The ready availability of diamagnetic tricarboxylic acid **7**[15] suggested a method for synthesis of a different TAM monocaboxylic acid without an intervening SCH_2 group (Scheme 2).

The trimethyl ester **8**, prepared from the triacid **7** by known literature method,[16] was hydrolyzed with 1.55 molar equivalents of LiOH.[17] The monocarboxylic acid **9** was isolated from the reaction mixture by column chromatography. The remaining di- and tricarboxylic acid byproducts **10** and **11** were also collected and converted back into precursor **8**. The regenerated triester **8** was again used to produce additional product **9** with an overall 65% yield after three iterations.[18,19] As the final step, **9** was converted into cation by addition of excess trifluoromethane sulfonic acid and then reduced with $SnCl_2$ to the target monocaboxylic acid TAM **12** in 95% yield.[18]

The carboxyl function in **6** and **12** provides a convenient FG for building these TAM into multispin systems. We turned to the synthesis of symmetrical diamides, in which TAM can be connected by linkers of varying length. Both monocarboxylic acid TAM readily afforded the required biradicals **13**[20] and **14**[21] (Scheme 3).

In summary, we have developed practical, high-yielding, and simple synthetic approaches for preparation of two monocarboxylic acids containing a TAM subunit with different substituent X groups. The first representatives of TAM biradicals have been synthesized from these monocarboxylic acids.

We believe that such monofunctional TAM reagents provide an important new route for constructing dynamic nuclear polarization reagents and chemical sensors; and for the site-directed spin-labeling of biopolymers. Such studies are ongoing in our laboratories.

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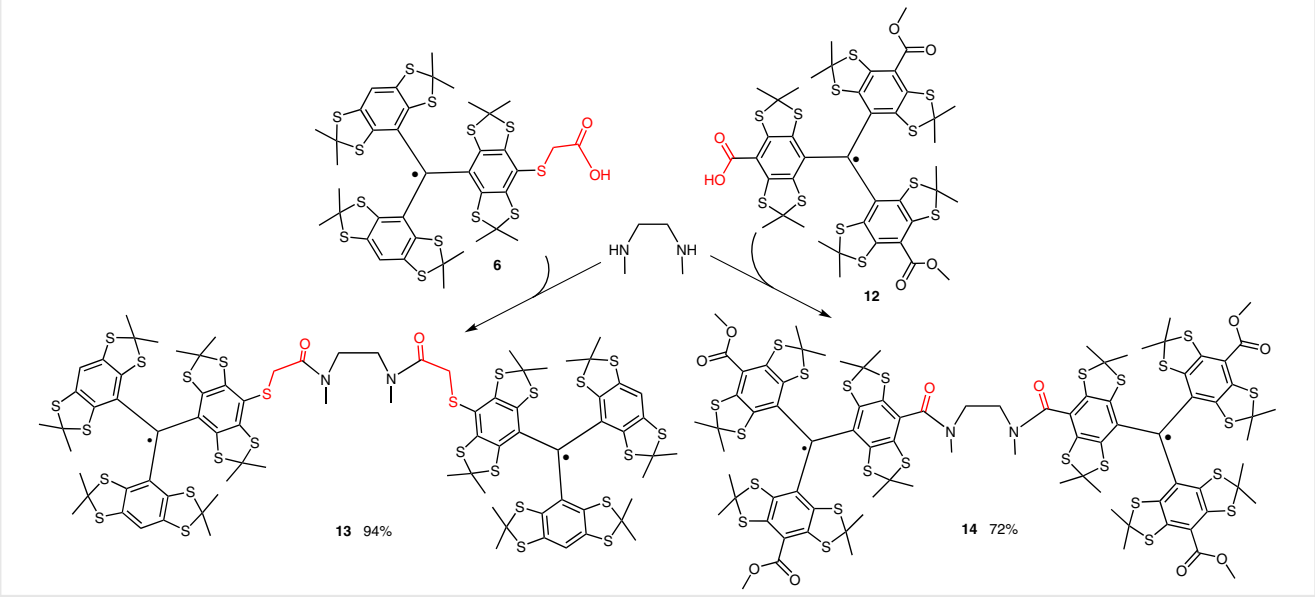

Scheme 3 Synthesis of TAM biradicals **13** and **14**

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561299.

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(10) In addition, the symmetrical TAM **3** may also result from direct single-electron reduction (ref. 9) of cation **1** by methyl thioglycolate.

(11) Triarylmethanol – the precursor of cation **1** (Scheme 1) – is readily available in large scale (up to 10–20 g) and in high yield using the recently published protocol (Rogozhnikova et al.[8a]).

(12) Substitution of toluene with more polar solvents leads to a notable decrease in yield of TAM **2**: 41% (CH_2Cl_2), 16–22% (Et_2O, THF), 12% (DMF).

(13) LiOH as an alkaline reagent is strongly recommended: the use of NaOH or KOH resulted in poor yield and bad contamination of TAM **6**.

(14) **Synthesis of TAM 6**

Bis{2,2,6,6-tetramethylbenzo[1,2-*d*:4,5-d′]bis[1,3]dithiol-4-yl}{8-methoxycarbonylmethylthio-2,2,6,6-tetramethylbenzo[1,2-*d*;4,5-*d′*]bis[1,3]dithiol-4-yl}methyl (2)

A solution of cation 1 was prepared by stirring of solution of triarylmethanol precursor[8a] (0.276 g, 0.316 mmol) in anhydrous CH_2Cl_2 (2.5 mL) and CF_3SO_3H (0.060 g, 0.400 mmol, 1.26 equiv) at r.t. for 2.5 h under argon. Slowly, over 20 min, the resulting deep-green solution of cation 1 was added by syringe to a magnetically stirred and cooled (–20 °C) solution of methyl thioglycolate (0.335 g, 3.16 mmol, 20 equiv) in anhydrous toluene (15 mL). The mixture was stirred overnight at room temperature under argon. Water (10 mL) was added, and the mixture was stirred for 5 h at r.t. under air. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was filtered through a short cotton plug and concentrated in vacuo. The resulting solid was dissolved in toluene (20 mL), which was evaporated again to remove residual thioglycolate. Column chromatography on silica gel [hexane, then CH_2Cl_2–hexane (1:1 v/v), then CH_2Cl_2] afforded 3 (0.050 g, 18%), and the title compound 2 (0.194 g, 63%). Spectroscopic data for 2 are the same as in ref. 9.

Bis{2,2,6,6-tetramethylbenzo[1,2-*d*:4,5-*d′*]bis[1,3]dithiol-4-yl}{8-carboxymethylthio-2,2,6,6-tetramethylbenzo[1,2-*d*;4,5-*d′*]bis[1,3]dithiol-4-yl}methyl (6)

A mixture of TAM 2 (0.150 g, 0.154 mmol), LiOH monohydrate (0.019 g, 0.463 mmol, 3 equiv), and H_2O (1 mL) in THF (7.5 mL) was stirred at room temperature under argon overnight. The resulting deep-green solution was neutralized by addition of 2 M aq HCl (0.300 mL) and concentrated in vacuo. Subsequent column chromatography on silica gel [CH_2Cl_2, then CH_2Cl_2–MeOH (20:1 v/v), then CH_2Cl_2–MeOH (10:1 v/v)] gave TAM 6 (0.143 g, 97%).

Data for 6

Fine black powder mp >280 °C (decomp.). HPLC purity 97%. ESI-MS: *m/z* calcd for $C_{39}H_{41}O_2S_{13}$ [M^+]: 956.9476; found: 956.93; *m/z* calcd for $C_{39}H_{40}O_2S_{13}$ [M – H^-]: 955.9403; found: 955.92. IR (KBr): ν = 2955 (s), 2920 (s), 2851 (m), 1707 (s), 1605 (m), 1450 (s), 1431 (m), 1383 (s), 1364 (vs), 1302 (s), 1244 (vs), 1167 (s), 1148 (vs), 1123 (m), 1103 (s), 1030 (m), 683 (m), 660 (m) cm^{-1}. EPR spectrum for 0.50 mM solution in deoxygenated MeOH: 1:2:1 triplet, α_H=2.263 G, peak-to-peak linewidth 66.5 μT, g = 2.0055. The resolved hyperfine splitting is from the ^1H at the *para* position on two of the aryl rings. The ^1H hyperfine splitting from the methyl groups of side rings is unresolved with hyperfine splitting constants expected to be similar to those of Finland trityl (less than 0.15 G[4d])..

(15) The tricarboxylic acid **7** is available in large scale (up to 5–10 g) and in high yield with the use of the recently published protocol (Rogozhnikova et al.[8a]).

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(17) Using MathCad 14.0 and fourth-order Runge–Kutta method with adaptive step size we studied a kinetic model of consecutive hydrolysis of triester. Under the assumption of independent hydrolysis of each of the three initial ester groups, the model predicts the maximum fraction of monocarboxylic acid (44.4%) for reaction of 1 equiv of triester with 1.42 equiv of hydroxide base. Variation of the amount of base in a range between 1.30 and 1.70 equiv results in small changes in the fraction of monocarboxylic acid (43.9–41.5%). For these reasons we chose to use 1.55 equiv of LiOH.

(18) **Synthesis of TAM 12**

Tris{8-[methoxycarbonyl]-2,2,6,6-tetramethylbenzo[1,2-*d*:4,5-*d′*]bis[1,3]dithiol-4-yl}methanol (8)

Prepared according to the method in ref. 16. HPLC purity >95%; mp >230 °C (gradual decomp.). Anal. Calcd for $C_{43}H_{46}O_7S_{12}$ (1059.60): C, 48.74; H, 4.38; S, 36.31. Found: C, 48.90; H, 4.49; S, 36.04. ESI-HRMS: *m/z* calcd for $C_{43}H_{46}O_7S_{12}$ [M$^+$]: 1057.9892; found: 1057.9898. IR (KBr): ν = 3313 (m), 2952 (m), 2912 (w), 1712 (s), 1506 (w), 1450 (m), 1433 (m), 1363 (m), 1315 (m), 1251 (s), 1220 (s), 1166 (m), 1105 (m), 1016 (m), 956 (w), 864 (w), 794 (w), 734 (w), 684 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 18 H, CH_3), 1.74 (s, 9 H, CH_3), 1.76 (s, 9 H, CH_3), 3.95 (s, 9 H, CH_3O), 6.78 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.74 (*C*H$_3$C), 29.30 (*C*H$_3$C), 31.98 (*C*H$_3$C), 33.92 (*C*H$_3$C), 52.50 (*C*H$_3$O), 61.01 (SCS), 61.12 (SCS), 84.38 (COH), 121.12 (C), 134.14 (C), 139.40 (C), 140.46 (C), 141.58 (C), 142.04 (C), 166.70 (CO_2) ppm

Bis{8-(methoxycarbonyl)-2,2,6,6-tetramethylbenzo[1,2-*d*:4,5-*d′*]bis[1,3]dithiol-4-yl}{8-carboxyl-2,2,6,6-tetramethylbenzo[1,2-*d*;4,5-*d′*]bis[1,3]dithiol-4-yl}methanol (9)

A mixture of triester **8** (0.865 g, 0.816 mmol), LiOH monohydrate (0.053 g, 1.26 mmol), and water (1 mL) in THF (5 mL) was stirred at room temperature for 48 h under argon. The resulting mixture was acidified by aq 2 M HCl to pH 4 and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (2 mL) and concentrated *in vacuo*. Column chromatography on silica gel (CH_2Cl_2–MeOH, 1:20, 1:10, 1:5 v/v) afforded the initial substrate (used further in repeated runs), a mixture of acids **10** and **11** (used for conversion to initial substrate by method of ref. 14) and the title monocarboxylic acid **9**. Three iterations afforded 0.553 g of **9** (65%) with partial recovery of precursor **8** (0.115 g, 14%).

Yellow powder; HPLC purity >95%; mp >200 °C (gradual decomp.). Anal. Calcd for $C_{42}H_{44}O_7S_{12}$ (1045.57): C, 48.25; H, 4.24; S, 36.80. Found: C, 48.57; H, 4.40; S, 36.45. ESI-HRMS: *m/z* calcd for $C_{42}H_{43}O_7S_{12}$ [M – H$^-$]: 1042.9663; found: 1042.9630. IR (KBr): ν = 3429 (m), 2954 (m), 2922 (m), 2854 (m), 1712 (s), 1585 (m), 1506 (m), 1452 (m), 1435 (m), 1382 (m), 1365 (s), 1336 (m), 1315 (m), 1249 (s), 1224 (s), 1166 (m), 1149 (m), 1103 (m), 1016 (m), 912 (w), 864 (w), 792 (w), 732 (w), 704 (w) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.55–1.72 (singlet signals of methyl groups, 36 H, CH_3), 3.87 (s, 6 H, CH_3O), 6.79 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ =27.16 (*C*H$_3$C), 27.70 (*C*H$_3$C), 27.73 (*C*H$_3$C), 27.83 (*C*H$_3$C), 28.50 (*C*H$_3$C), 29.46 (*C*H$_3$C), 30.60 (*C*H$_3$C), 31.22 (*C*H$_3$C), 32.23 (*C*H$_3$C), 33.54 (*C*H$_3$C), 33.86 (*C*H$_3$C), 52.23 (*C*H$_3$O), 59.32 (*SCS*), 59.90 (*SCS*), 60.40 (*SCS*), 60.64 (*SCS*), 60.83 (*SCS*), 60.89 (*SCS*), 83.47 (*COH*), 120.46 (C), 120.60 (C), 130.59 (C), 133.90 (C), 134.15 (C), 136.19 (C), 138.44 (C), 138.70 (C), 139.06 (C), 139.68 (C), 139.71 (C), 139.76 (C), 139.97 (C), 140.30 (C), 140.38 (C), 140.45(C), 140.59 (C), 165.53 (CO_2CH_3), 168.63 (CO_2H) ppm.

Bis{8-(methoxycarbonyl)-2,2,6,6-tetramethylbenzo[1,2-*d*:4,5-*d′*]bis[1,3]dithiol-4-yl}{8-carboxyl-2,2,6,6-tetramethylbenzo[1,2-*d*;4,5-*d′*]bis[1,3]dithiol-4-yl}methyl (12)To solution of **9** (0.115 g, 0.110 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a solution of TfOH (0.082 g, 0.550 mmol) in anhydrous MeCN (0.5 mL). The resulting deep-green solution was stirred under argon for 5 min at room temperature, after which a solution of $SnCl_2$ (0.022 g, 0.116 mmol) in anhydrous THF (1 mL) was added. After stirring under argon for 8 min at room temperature the mixture was quenched by addition of water (20 mL) followed by addition of CH_2Cl_2 (10 mL). The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was filtered through a short cotton plug and concentrated *in vacuo*. Column chromatography on silica gel [CH_2Cl_2, then CH_2Cl_2–MeOH (20:1 v/v)] afforded TAM **12** (0.107 g, 95%).

Fine black powder; mp >280 °C (decomp.). HPLC purity 98.6%. ESI-MS: *m/z* calcd for $C_{42}H_{43}O_6S_{12}$ [M$^+$]: 1026.9708; found: 1026.973; *m/z* calcd for $C_{42}H_{42}O_6S_{12}$ [M – H$^-$]: 1025.9635; found: 1025.959. IR (KBr): ν = 2953 (m), 2922 (m), 1706 (s), 1452 (m), 1433 (m), 1366 (m), 1273 (m), 1234 (vs), 1167 (m), 1148 (m), 1136 (m), 1111 (m), 864 (w), 721 (w) cm^{-1}. EPR spectrum for 0.50 mM solution in anaerobic MeOH: sept α_H = 0.0992 G (6 H), peak-to-peak linewidth 7.7 μT (Lorentzian) and 2.1 μT (Gaussian), g = 2.0056. The observed hyperfine splitting is caused by six-proton nuclei of $COOCH_3$ present at the *para* position on two of the aryl rings.

(19) The analogous series of iterations performed with trimethyl ester of the paramagnetic triacid (Finland trityl) was accompanied by formation by numerous high-molecular contaminants and resulted in lower isolated yield (51%) of TAM **12** after three repetitive runs.

(20) **Synthesis of Biradical 13**

A solution of dicyclohexylcarbodiimide (0.014 g, 0.067 mmol) in CH_2Cl_2 (0.5 mL) was added slowly with cooling on an ice-bath to a stirred solution of *N*-hydroxysuccinimide (0.081 g, 0.070 mmol) and TAM **6** (0.056 g, 0.058 mmol) in anhydrous CH_2Cl_2 (1 mL). The mixture was stirred under argon at room temperature for 4 h and then concentrated *in vacuo*. The resulting cake was dissolved in toluene (5 mL), the solution was filtered through a short cotton plug. Concentration of the filtrate *in vacuo* afforded the OSU derivative of TAM **6**. It was dissolved in 0.023 M solution of *N*,*N′*-dimethylethylenediamine in CH_2Cl_2 (1 mL, 0.023 mmol of diamine). The mixture was stirred under argon at room temperature for 36 h and quenched by addition of 0.01 M of aq HCl. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was filtered through a short cotton plug and concentrated *in vacuo*. Column chromatography on silica gel [CH_2Cl_2, then CH_2Cl_2–EtOAc (20:1 v/v), then CH_2Cl_2–EtOAc (10:1 v/v)] afforded the biradical **13** (0.042 g, 94% of initial diamine).

Data for 13

Fine dark brown powder; mp >280 °C. HPLC purity 94.6%. ESI-MS: *m/z* calcd for $C_{82}H_{90}N_2O_2S_{26}$ [M$^+$]: 1965.9741; found: 1965.975. IR (KBr): ν = 2955 (s), 2922 (s), 2853(m), 1734 (m), 1651 (vs), 1452 (s), 1433 (m), 1396 (m), 1383 (m), 1364 (s), 1302 (m), 1244 (vs), 1167 (s), 1150 (vs), 1103 (m), 847 (w), 685 (w) cm^{-1}. The EPR spectrum for a 0.50 mM solution of biradical **13** in degassed CH_2Cl_2 has five equally spaced lines caused by the hyperfine coupling to the four proton nuclei that are the X groups. The peak-to-peak line intensities appear to be in the ratio of 1:1:2:1:1 rather than the 1:4:6:4:1 expected for four

equivalent proton nuclei. However, the outer and center lines are noticeably sharper than the other two lines, a classic example of the alternating linewidth effect resulting from the limited tumbling rate (compared to the hyperfine anisotropy) of such a large molecule (>2 nm long) in solution. The hyperfine coupling (α_H = ca. 1 G) is about half that of **6**, showing that the electron spin–spin interaction between the TAM is much larger than the α_H = ca. 2 G of **6** (see Supporting Information).

(21) **Synthesis of Biradical 14**

To a stirred solution of TAM **12** (0.034 g, 0.033 mmol) and Et_3N (0.012 g, 0.116 mmol) in anhydrous $CHCl_3$ (1 mL) slowly was added a solution of $SOCl_2$ (0.027 g, 0.231 mmol) in $CHCl_3$ (0.2 mL). The mixture was stirred under argon at room temperature for 20 h and then concentrated *in vacuo*. The resulting cake was dissolved in toluene (5 mL), the solution was filtered through a short cotton plug. Concentration of the filtrate *in vacuo* afforded the chloroanhydride of **12**. It was dissolved in 0.023 M solution of *N*,*N*′-dimethylethylenediamine in CH_2Cl_2 (0.57 mL, 0.0132 mmol of diamine). Et_3N (0.010 g, 0.10 mmol) and 4-dimethylaminopyridine (0.004 g) were added. The mixture was stirred under argon at room temperature for 36 h and quenched by addition of 0.01 M of aq HCl. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was filtered through a short cotton plug and concentrated *in vacuo*. Column chromatography on silica gel [CH_2Cl_2, then CH_2Cl_2–EtOAc (30:1 v/v)] gave the biradical **14** (0.020 g, 72% of initial diamine).

Data for 14

Fine black powder; mp >280 °C. HPLC purity 96.6%. ESI-MS: *m/z* calcd for $C_{89}H_{94}N_2O_{10}S_{24}$ [M^+]: 2106.0205; found: 2106.021. IR (KBr): ν = 2953 (m), 2920 (m), 2860 (w), 1707 (s), 1641 (s), 1485 (m), 1452 (m), 1433 (m), 1366 (m), 1265 (s), 1236 (vs), 1167 (m), 1136 (m), 1109 (m), 1043 (m), 864 (w), 789 (w), 729 (w) cm^{-1}. The EPR spectrum for a 0.50 mM solution of biradical **14** in degassed CH_2Cl_2 consists of a single sharp line flanked by a pair of weak lines from natural abundance ^{13}C hyperfine (see Supporting Information). The hyperfine couplings from the methyl ester H are expected to produce at least 13 lines split by <0.1 G (based on the α_H of **12**). Each of those lines is further split into five lines by weak hyperfine interactions with the two N. The result is expected to be the single, unresolved line that is observed.