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Triarylmethanols bearing bulky aryl groups and the NOESY/EXSY experimental observation of two-ring-flip mechanism for helicity reversal of molecular propellers

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Abstract

Triarylmethanols – the direct precursors of persistent trityl radicals – are racemic mixtures of chiral three-bladed molecular propellers. Depending on bulkiness of aryl groups they exhibit various liabilities to interconversion, the half- life time of room temperature racemization varying in a range between 8.4 hours and 1.32 years. NOESY/EXSY experiment performed on two representative models strongly supports the two-ring flip mechanism for the configurational interchange.

Keywords

chirality; triarylmethanols; 2D NOESY/EXSY; epimerization mechanism; activation parameters

Introduction

The recent invention of persistent triarylmethyl radicals (trityls, TAMs)^[1] stimulated a significant progress in application of low-frequency EPR for *in vivo* detection of free radicals^[2], 3D EPR imaging^[3], dynamic nuclear polarization,^[4] and developing some new techniques, *e.g.* designed for studies of molecular diffusion in micro-heterogeneous systems.^[5] The carbon-centered radicals show high solubility in water and stability towards various oxidoreductants presented in mammals blood. Due to inherent sterical crowding they exhibit a single and very narrow EPR line with line-width reversibly broadening parallel to increase of oxygen concentration. Giving trityls a serious advantage over traditional spin probes, these features are especially important for provision of accurate and precise measuring the spatial distribution of molecular oxygen in living systems.

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Supporting Information (see also the footnote on the first page of this article): ¹H spectra of compounds **3** and **6**; 2D NOESY/EXSY studies of interconversion of *M*- and *P*-enantiomers, and computational methods and data.

The strong interest to trityls stimulated much efforts in optimization of synthetic strategies,^[5,6] and synthesis of derivatives, which could show improved properties or are intended to fit new applications. Recently some new trityl structures were developed: those that combine functions of oxygen sensitivity and pH probe,^[7] ester derivatives with increased ability to penetrate cell membranes to enable intracellular delivery,^[8,9] dual function trityl-nitroxide biradicals for oxymetric studies and measuring the redox status,^[10] and those that contain linkers suitable for conjugation with biological targets.^[11]

X-Band pulsed ENDOR spectroscopy and DFT quantum chemistry calculations revealed the propeller-shaped geometry of tris(8-carboxyl-2,2,6,6-tetramethylbenzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methyl sodium salt (alias Finland trityl, Fig.1) with all three aryl rings of a given molecule having the same mode of twist.^[12] The direct proof of helicoidal geometry followed from X-ray crystallographic study of Finland trityl methyl ester (Fig.1), for which the structure of molecular propeller of regular C_3 symmetry was firmly determined.^[10]

Against the background of these broad-scale studies, surprisingly little is known on the structural properties and molecular dynamics of sterically crowded triarylmethanols – the direct precursors of trityl radicals. The general agreement^[13] that triarylmethyl systems exist as racemic mixtures of *M*- and *P*-propeller structures (Fig. 2) implicates that the triarylmethanols might demonstrate chiral properties, provided the steric bulk is large enough to prevent the aryl rings from free rotation around the corresponding carbon-carbon bonds connected to a central carbon.

It means that in the case of slow interconversion between enantiomeric *M*- and *P*-helices both of them potentially could be isolated as individual forms useful for their further transformation to corresponding chiral trityls. The outlined hypothetical strategy looks attractive. But however promising it may look, it is not worth much unless the kinetic investigation confirmed the validity of approach. This is why we aimed the present work to a thorough study of kinetics of conformational equilibrium using NMR techniques as a tool and placing the special emphasis on mechanism of isomerization.

Results and Discussion

The room temperature ^1H and ^{13}C NMR spectra (see the Experimental section and Supporting Information, SI, for the details) of a series of sterically crowded triarylmethanols **1–6** (Fig 3) are in good agreement with the concept of symmetrical propeller-shaped geometry. Indeed, in the upfield region they are sufficiently distinct to display equal in intensity, sharp and narrow singlet lines corresponding to four separate types of methyl (compounds **1–5**) or *tert*-butyl substituents (compound **6**). Each type represents one of four side-ring substituents with its own intrinsic spatial environment and therefore unique NMR shielding, and combines three methyl or *tert*-butyl groups, one from each of three equivalent aryl moieties. Two experimentally observed resonances derive from geminal side-groups located at position distal to central hydroxyl group. Two remaining singlets correspond to a pair of geminal substituents lying at proximal position. To illustrate, shown on Fig. 3 is the assignment of ^1H NMR spectrum of **1**.

In accordance with prediction for the regular propeller-shaped geometry two side-ring carbon atoms of SCS fragments and all six carbons belonging to aryl moieties are detected separately in ^{13}C NMR spectra. Besides, the ^1H NMR spectrum of ester **3** revealed the AB pattern arisen from diastereotopic methylenic protons of acetoxymethyl groups. In the spectra of analogous esters **4** and **5** the diagnostic multiplets of methylene groups positioned in the proximity to carboxyl function exhibit the fine splitting caused by coupling between

geminal methylenic protons with further splitting into quartet or triplet due to coupling with protons of adjacent methyl or CH₂N groups. As expected, decoupling the resonances of adjacent protons causes the complex multiplets to collapse to the classical AB systems (see Experimental). It is evident that the observed effects of diastereotopicity could be accounted for the presence of helicity with its influence being strong enough for spreading from the helical core even to remote parts of the molecule. The sharpness of NMR peaks, their distinct appearance for topologically equivalent protons and carbon atoms, and the observed effect of diastereotopicity are indicative of regular propeller-shaped geometry with interconversion of *M*- and *P*-isomers being negligibly slow on the NMR timescale.

Increasing the temperature could enhance the rate of isomerization to the level of secure registration. To this end we studied ¹H NMR spectra of triarylmethanol **1** in a temperature range between 25 and 150 °C. Except for detection of small downfield drift of distinct resonances of methyl protons and narrowing the region of their appearance, the DNMR failed to reveal the measurable broadening of spectra signals. Thus NOESY/EXSY spectroscopy was the next technique we applied to follow the kinetics of interconversion.

The region showing the resonances of methyl groups (1.50 – 2.00 ppm, Fig.4) was chosen for measurements. In a temperature range 25–90 °C, four singlet resonances were observed for the methyl protons without measurable exchange but with NOE correlation, resolving two pairs of geminal methyl groups (A+B) and (C+D) respectively.

At higher temperatures 100 °C, the enantiomerization became rapid enough to produce additional cross-peaks in NOESY spectra and display the exchange with participation of protons A becoming either B or C. The same was observed for protons D, which gave the cross-peaks with C and B. At 150 °C, where magnetization transfer due to exchange significantly predominates over that due to cross relaxation, for the first pair of simultaneous interconversions (A ↔ B and A ↔ C) the ratio of integral intensities of the corresponding cross peaks almost exactly equals to 2:1. The second pair exhibits the same distribution of statistical weights of 2:1 for transformations D ↔ C and D ↔ B respectively. A typical NOESY/EXSY ¹H NMR spectrum is presented on Fig. 4.

While the process of isomerization can in principle involve four different pathways (zero-, one-, two-, and three-ring flip paths), the two- and three-ring flip paths are generally considered the most preferable rotational mechanisms for C₃-symmetric propellers (Fig.5). The participation of zero- and one-ring flips is not seen as probable since the inherent lateral interaction between bulky aryl moieties would give an enormous contribution to the transition state energy.^[14]

Our NOESY/EXSY experimental data are consistent with these reasons. Moreover, they revealed the only plausible mechanism. Indeed, of four alternative mechanisms the only, *i.e.* the two-ring flip pathway, is in quantitative agreement with the observed distribution of cross-peaks intensities. Following this pathway two rings rotate in conrotatory direction around the axes connecting central carbon atom and corresponding C(1)_{aryl} carbons to cause exchange with participation of a total of eight methyl groups, which means conversion of A to B (D to C) and *vice versa*. The only remaining ring bearing four methyl groups rotates in disrotatory direction to produce exchange between A and C (D and B).

The expected ratio of methyl groups participating in two opposite rotations is equal to 8:4 (*i.e.* 2:1) and thus perfectly fit the distribution of cross-peaks integral intensities in experimental NOESY/EXSY spectra. The remaining three mechanisms gave predictions, which are not compatible with the experimentally observed pattern, so they may be quickly denied. For instance, the synchronous conrotatory twisting of all three aryl substituents

would give only two complementary cross-peaks with equal statistical weights of 3 and 3 (in arbitrary units) for both transformations A → B and D → C (Fig. 6).

Processing the intensities of the cross and diagonal peaks in the 2D NOESY/EXSY spectra gave values of rate constants k_{enant} for first order enantiomerization at various temperatures lying in range between 100 and 150 °C (see SI). The dependence of $\ln(k_{enant}h/k_B T)$ on $1/T$ (eq. 1) gave the enthalpy of activation $H^\ddagger$ and entropy of activation $S^\ddagger$ presented in Table 1.

$$\ln \frac{k_{enant}h}{k_B T} = \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT} \quad (1)$$

The experimental enthalpy of activation (95.3 ± 1.8 kJ/mole = 22.7 ± 0.4 kcal/mole) fit satisfactorily well the energy barrier of 27.1 kcal/mole calculated for the two-ring flip mechanism of isomerization (see SI).^[15] In addition to the former arguments the detection of this close agreement gives one more reason in support of synchronous conrotatory rotation of only two of three aryl rings in the course of formation of TS.

Our work was in state of completion, when J. Marchand-Brynaert et al. published the results of their studies of rotational isomerism of trityl **7** (Fig. 7), the paramagnetic analogue of **1**.^[16] The experimental and calculated activation enthalpies resulted from our kinetic studies match fairly well the value of $H^\ddagger$, which may be derived from the original literature data reported for **7**. In accordance with eq. 1 we processed the primary kinetic data reported for **7** to obtain after subsequent linear regression fitting the values 79.7 ± 2.0 kJ/mole and -103.5 ± 6.5 J/mole×K for $H^\ddagger$ and $S^\ddagger$ respectively. It is worthy of note that irrespective of magnetic nature of compound the major contribution to $G^\ddagger$ is accounted for the enthalpy factor, with the absolute value of entropy contribution ($T S^\ddagger$) being relatively low compared with that of $H^\ddagger$, e.g. at 298 K in the case of diamagnetic triarylmethanol **1** $H^\ddagger = 95.3$ kJ/mole vs. $T S^\ddagger = 5.93$ kJ/mole.

The rate constant of enantiomerization calculated for triarylmethanol **1**, using Eyring equation and data of Table 1, is 1.143×10^{-5} sec⁻¹ at 25 °C (DMSO solution). This means much shorter half-life for racemization ($t_{1/2} = \ln 2 / k_{enant,298} = 8.4$ h) in comparison with that for the paramagnetic analogue (28.6 days in ethyl acetate solution^[16]), but it is sufficient to provide the isolation of enantiomerically pure isomers of **1** with of the use of CSP HPLC technique. Thus, a procedure applied by authors of ref. 16 to resolution of racemic triarylmethanol **1** (column temperature 25 °C, elution over 10 min, immediate freezing the collected fractions at -78 °C) potentially must afford the individual stereoisomers of **1** with optical purity better than 99% ee. In fact it was 100 % ee within error limits of CD optical density measurements.^[16]

The analogous NOESY technique and methods for processing the 2D spectra were applied to follow the kinetics of enantiomerization of triarylmethanol **6**. The upfield region showing the resonances of *tert*-butyl groups (0.90 – 1.20 ppm) was chosen for measurements. This compound bearing twelve bulky and heavy *tert*-butyl groups demonstrated but very limited liability to isomerization. Therefore, NOESY/EXSY managed to detect the exchange cross-peaks suitable for measurement but still very weak at the only temperature of 149.4 °C. The experimental rate constant k_{con} corresponding to rotation in conrotatory direction was estimated (see SI) to be 7.42×10^{-3} sec⁻¹ at 149.4 °C. This gave the value of Gibbs activation energy of 121.9 kJ/mole. Under the assumption of small entropy contribution to $G^\ddagger$ (and hence a weak dependence of $G^\ddagger$ on temperature shown in fact for analogous triarylmethanol **1**) one could estimate the half-life for racemization of **6** at 25 °C: 1.36 years

with the first order rate constant of racemization $k_{rac} = 6k_{con}$ being equal to $1.62 \times 10^{-8} \text{ sec}^{-1}$.

It seems reasonable to suggest that kinetic characteristics of racemization of sterically hindered helical triarylmethanols strongly depend on the nature (and thus mass and bulkiness) of side-ring substituents. The nature of solvent and substituents located at para-positions of aryl rings may also be of key importance. To gain a better insight into the subject we perform a detailed investigation varying the above factors. The study is currently in progress and its results will be published elsewhere.

Conclusions

Sterically hindered triarylmethanols – the precursors of persistent trityl radicals – are racemic mixtures of molecular propellers possessing the chiral C_3 axes. NOESY/EXSY spectra are compatible with the only mechanism of their configurational isomerism – the two-ring flip scheme. Depending on bulkiness of aryl groups the half-life time of room temperature racemization may vary in a broad range between 8.4 hours and 1.36 years.

Experimental Section

General

^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (^1H : 400 MHz, ^{13}C : 100 MHz) and Bruker AV-600 spectrometer (^1H : 600 MHz, ^{13}C : 150 MHz). Chemical shifts (scale) are given in ppm with reference to residual signals of chloroform- D_1 (^1H : 7.26, ^{13}C : 77.16) or DMSO- D_6 (^1H : 2.50, ^{13}C : 39.52). IR spectra were recorded on a Bruker Tensor 27 and Bruker Vector 22 FTIR spectrometers in KBr pellets, wavenumber values are given in cm^{-1} . Electrospray ionization mass spectra ESI/MS were recorded using hybrid quadrupole/time-of-flight Bruker micrOTOF-Q spectrometer with methanol used as a solvent and scanning the spectra in m/z range 100–3000 in positive and negative ionization modes. Analytical HPLC analyses were carried out with an Agilent 1100 Series instrument equipped with ZORBAX Eclipse XDB C8 column with methanol eluent followed by methanol with addition of 0.1 % (v/v) trifluoroacetic acid. Preparative column chromatography was performed using 60–200 μm silica gel purchased from Acros. Chemicals were purchased from Aldrich and Acros and were used without further purification.

Two-dimensional nuclear Overhauser enhancement (2D NOESY) experiments were performed on a Bruker AV-600 spectrometer using the standard three-pulse sequence, standard 5mm NMR tubes and DMSO- D_6 as a solvent. NOESY spectra were acquired at a number of temperatures between +100 and +150 °C (373 and 422 K) depending on the sample. The temperature in range 23 – 150 °C was calibrated with reference to a standard sample of ethylene glycol and melting point of naphthalene (80°C). The NOESY mixing times t_m were adjusted to match the rate of the exchange process. Eight accumulations and t_2 (F_2 dimension) $\times$ t_1 (F_1 dimension) = 1024 $\times$ 128 sampling data points array were used. The data point array F_2 (F_2 dimension) $\times$ F_1 (F_1 dimension) = 2048 $\times$ 2048 was used in the Fourier transformation after the zero filling. The rate constants k_{ex} of rings rotation were calculated using integral intensities of cross peaks and diagonal peaks, see Section 2 of SI.

The Priroda program package^[17] was used in *ab initio* energy calculations and geometry optimization. The DFT method (PBE functional^[18], 22 (cc-pCVTZ) basis^[19]) without zero point energy correction was applied to single point energy calculations. Geometry optimization was carried out at the PBE/ 1 (cc-pVDZ) level of theory.

The calculations of chemical shifts were performed by the method GIAO/PBE/ 22 for each of 64 accessible ground state conformers. The procedure of averaging over all energy levels within approximation of Maxwell-Boltzman distribution and thermal equilibrium of isomeric species afforded mean values of chemical shifts, which are presented in Section 3 of SI.

Tris(2,2,6,6-tetramethylbenzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methanol (1)

was synthesized by analogy with known literature protocol.^[6b] White powder: mp > 260 °C (gradually decomposed). Found: C, 50.52; H, 4.37. C₃₇H₄₀O₁S₁₂ requires C, 50.19; H, 4.55. IR (KBr): = 3364 (m), 2957 (m), 2914 (m), 1450 (s), 1371 (s), 1294 (m), 1248 (m), 1194 (m), 1151 (s), 785 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 1.67 (s, 9H, CH₃), 1.72 (s, 9H, CH₃), 1.80 (s, 9H, CH₃), 1.82 (s, 9H, CH₃), 6.20 (s, 1H, OH), 7.17 (s, 3H, CH); ¹³C NMR (100 MHz, CDCl₃): 27.74 (CH₃), 29.29 (CH₃), 32.38 (CH₃), 34.93 (CH₃), 63.49 (SCS), 64.18 (SCS), 83.28 (COH), 118.30 (CH), 131.99 (C), 137.38 (C), 137.97 (C), 138.47 (C), 139.36 (C).

Tris(8-carboxyl-2,2,6,6-tetramethylbenzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methanol (2)

To a stirred suspension of **1** (1.500 g, 1.69 mmol) in n-hexane (1.70 mL) and freshly distilled anhydrous TMEDA (7.2 mL) cooled to -78 °C was added 2.5 M solution of butyl lithium in hexane (6.8 mL, 16.9 mmol), dropwise over 10 min under argon. After stirring for 20 min the cooling bath was removed, and reaction was left stirring at room temperature for 2 h. The mixture gradually turned to a dark-brown solution and then to thick pale-brown slurry. Anhydrous toluene (18 mL) was added. The resulting viscous solution was stirred for 30 min and then transferred onto solid carbon dioxide (350 g) and left to attain ambient temperature. Solvents and TMEDA were evaporated *in vacuo*. The resulting solid cake was shaken with toluene (20 mL), which was evaporated again to remove residual TMEDA.

Ether (60 mL), water (50 mL) and 2M NaOH (10 mL) were added. The biphasic mixture was vigorously shaken and transferred to a separatory funnel. Water phase was separated, and organic phase was extracted three times with 0.2M NaOH (10 mL). The combined water extract was left standing for 5 h at room temperature, filtered through paper and acidified to pH 2 by slow addition of 4M aqueous hydrochloric acid to give a greenish-yellow slurry. After 2 h the solid was collected on filter, washed with 0.1 M aqueous HCl (4 × 10 mL) and dried *in vacuo*. The dry residue was heated at reflux for 5 min with a mixture of toluene (15 mL) and acetonitrile (2 mL) to cause fast formation of clear solution followed by crystallization. After standing in refrigerator for 2 h the lemon-yellow solid was collected on filter, washed with cold toluene (3 × 2 mL) and dried *in vacuo*. Yield: 1.030 g, 60 %. The product may contain residual toluene (5–12 mol %). HPLC purity > 95 %. Mp > 300 °C (gradually turned black, decomposition). Found: C, 46.86; H, 4.04; S, 37.44. C₄₀H₄₀O₇S₁₂ requires C, 47.21; H, 3.96; S, 37.82. MS (ESI, *m/z*): 1014.9307 (measured), 1014.9344 (calcd for C₄₀H₃₉O₇S₁₂ [M-H⁺]⁻). IR (KBr): = 3348 (s), 2963 (m), 2918 (m), 2860 (m), 1686 (s), 1452 (m), 1366 (m), 1317 (m), 1261 (m), 1223 (s), 1167 (m), 727 (w) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): 1.60 (s, 9H, CH₃), 1.62 (s, 9H, CH₃), 1.69 (s, 9H, CH₃), 1.72 (s, 9H, CH₃), 6.79 (s, 1H, OH). ¹³C NMR (100 MHz, DMSO-d₆): 27.58 (CH₃), 28.62 (CH₃), 31.40 (CH₃), 33.96 (CH₃), 60.74 (SCS), 60.83 (SCS), 83.60 (COH), 122.11 (C), 133.40 (C), 138.33 (C), 139.87 (C), 140.60 (C), 140.94 (C), 166.08 (CO₂H).

Tris(8-acethoxymethylcarbonyl-2,2,6,6-tetramethylbenzo-[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methanol (3)

Trityl **2** (0.100 g, 0.100 mmol) and solution of triethylamine (0.030 g, 0.300 mmol) in anhydrous DCM (1.0 mL) were placed to a 5 mL Wheaton vial, and the mixture was stirred at 25 °C for 10 min until dark-green homogeneous solution was obtained. A solution of

bromomethyl acetate (0.055 g, 0.360 mmol) in anhydrous DCM (1.0 mL) was added, and the solution was stirred under argon at 25 °C for 45 h. The reaction was quenched by dropwise addition of 1 M hydrochloric acid (0.8 mL). The organic fraction was separated, and water phase was extracted with chloroform (3 × 1 mL). The combined organic extract was concentrated and then purified by column chromatography using silica gel and chloroform followed by mixed solvent methanol–chloroform (1:10) as eluent to give the title product as a yellow powder (0.113 g, 92 %). HPLC purity > 95 %. Mp > 230 °C (gradually decomposed). Found: C, 48.01; H, 4.43; S, 30.68. C₄₉H₅₂O₁₃S₁₂ requires C, 47.70; H, 4.25; S, 31.19. MS (ESI, *m/z*): 1254.9989 (measured), 1254.9954 (calcd for C₄₉H₅₂O₁₃S₁₂Na [M + Na]⁺). IR (KBr): = 3351 (m), 2963 (w), 2920 (w), 1769 (s), 1720 (s), 1452 (m), 1366 (m), 1315 (w), 1246 (s), 1207 (s), 1161 (m), 1128 (w), 1099 (m), 1049 (m), 1001 (s), 972 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 1.63 (s, 9H, CH₃), 1.64 (s, 9H, CH₃), 1.72 (s, 9H, CH₃), 1.75 (s, 9H, CH₃), 2.14 (s, 9H, CH₃CO₂), 5.97 (1H, upfield part of AB system, OCH^aH^b, J=5.6 Hz), 6.00 (1H, downfield part of AB system, OCH^aH^b, J=5.6 Hz), 6.74 (s, 1H, OH). The ¹H NMR spectrum is shown in SI.

¹³C NMR (100 MHz, CDCl₃): 20.91 (CH₃CO), 28.70 (CH₃), 29.32 (CH₃), 32.02 (CH₃), 34.04 (CH₃), 61.34 (SCS), 61.40 (SCS), 80.08 (OCH₂O), 84.48 (COH), 120.10 (C), 134.53 (C), 139.63 (C), 140.61 (C), 142.24 (C), 142.72 (C), 165.02 (C_{ar}CO₂), 169.55 (CH₃CO₂).

Tris(8-ethoxycarbonyl-2,2,6,6-tetramethylbenzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methanol (4)

was prepared in accordance with known literature protocol ^[5] (**Method A**). HPLC purity > 97%. Lemon-yellow powder: mp > 270 °C (gradually decomposed). Found: C, 50.22; H, 4.43. C₄₆H₅₂O₇S₁₂ requires C, 50.15; H, 4.76. IR (KBr): = 3354(m), 2974 (m), 2914 (w), 1707 (s), 1450 (m), 1369 (m), 1319 (m), 1246 (s), 1229 (s), 1167 (m), 1101 (m), 1024 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 1.43 (t, 9H, OCH₂CH₃, J=7.1 Hz), 1.63 (s, 18H, CH₃), 1.72 (s, 9H, CH₃), 1.74 (s, 9H, CH₃), 4.41 (m, 6H, OCH₂), 6.75 (s, 1H, OH). Irradiation applied to triplet at 1.43 ppm causes the ABX₃ multiplet at 4.41 ppm to collapse to AB system arisen solely from geminal coupling of methylenic protons: 4.39 (1H, OCH^aH^b, J=10.8 Hz), 4.42 (1H, OCH^aH^b, J=10.8 Hz).

¹³C NMR (100 MHz, CDCl₃): 14.41 (CH₂CH₃), 28.80 (CH₃), 29.36 (CH₃), 32.01 (CH₃), 33.98 (CH₃), 61.01 (SCS), 61.09 (SCS), 62.49 (OCH₂CH₃), 84.46 (COH), 121.45 (C), 134.14 (C), 139.40 (C), 140.50 (C), 141.59 (C), 142.00 (C), 166.34 (CO₂Et).

Triarylmethanol **4** was prepared also by alternative **Method B**. A mixture of triacid **2** (0.410 g, 0.403 mmol) and dry triethylamine (0.204 g, 2.01 mmol) in anhydrous chloroform (2 mL) was stirred at r.t. for 10 min. To resulting homogeneous solution dropwise over 20 min was added a solution of SOCl₂ (0.480 g, 4.03 mmol) in chloroform (0.5 mL). The mixture was refluxed for 2.5 h, stirred at r.t. overnight, and then concentrated to dryness to give an orange-yellow solid. Anhydrous ethanol (mL), chloroform (1 mL) and pyridine (0.039 g, 0.49 mmol) were added. The resulting mixture was stirred at 65 °C for 3.5 h and then overnight at r.t. After removal of solvents *in vacuo*, chloroform (5 mL) and water (3 mL) were added to a solid residue. The organic phase was separated, washed with 0.1 M aqueous HCl (2 mL), and water (4 mL), filtered through a short silica gel column, and concentrated *in vacuo* to give a title product **4** as a lemon-yellow powder. Yield: 0.444 g, 100 %.

Tris(8-(2-(morpholin-4-yl)ethyl)carbonyl-2,2,6,6-tetramethylbenzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl)methanol (5)

A solution of triacid **2** (0.050 g, 0.050 mmol) and 1,1-carbonyldiimidazole (0.041 g, 0.250 mmol) in anhydrous THF (1.5 mL) was stirred under argon in a 5 mL Wheaton vial at 55 °C

for 4 h. To resulting mixture was added a solution of 2-(morpholine-4-yl)ethanol (0.039 g, 0.300 mmol). The mixture was stirred for 1 h at room temperature, and sodium hydride (0.012 g of 60 % suspension in mineral oil, 0.300 mmol) was added portionwise. After stirring at r.t. for 24 h the mixture was transferred to evaporation flask and solvents were removed *in vacuo*. Chloroform (2 mL), water (2 mL) and brine (2 mL) were added. Organic phase was separated, washed with water (3 × 1 mL) and concentrated *in vacuo*. The solid residue was then purified by column chromatography using silica gel and chloroform as an eluent followed by mixed solution of methanol and chloroform (2:8) to afford the title product as yellow solid (0.072 g, 96 %). HPLC purity > 95 %. Mp > 200 °C (gradually decomposed). Found: C, 51.02; H, 5.46; N, 3.34. C₅₈H₇₃N₃O₁₀S₁₂ requires C, 51.34; H, 5.42; N, 3.10. MS (ESI, *m/z*): 1356.2001 (measured), 1356.2023 (calcd for C₅₈H₇₄N₃O₁₀S₁₂ [M+H]⁺). IR (KBr): = 3356 (m), 2957 (m), 2918 (m), 2853 (m), 1705 (s), 1452 (m), 1366 (m), 1312 (m), 1248 (s), 1225 (s), 1117 (s), 1016 (m) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): 1.63 (s, 18H, CH₃), 1.71 (s, 9H, CH₃), 1.75 (s, 9H, CH₃), 2.55 (bs, 12H, ring CH₂N), 2.79 (t, 6H, CH₂N, J=6.1 Hz), 3.68 (m, 12H, ring CH₂O), 4.46 (m, 6H, COOCH₂), 6.76 (s, 1H, OH). Decoupling the triplet at 2.79 ppm removes the multiplet at 4.46 ppm and leaves an AB system of methylene group adjacent to carboxyl function: 4.45 (1H, COOCH^aH^b, J=11.4 Hz), 4.47 (1H, COOCH^aH^b, J=11.4 Hz). ¹³C NMR (100 MHz, CDCl₃): 28.52 (CH₃), 29.09 (CH₃), 31.73 (CH₃), 33.69 (CH₃), 53.70 (ring CH₂N), 56.51 (CH₂N), 60.83 (SCS), 60.95 (SCS), 63.95 (OCH₂), 66.87 (ring CH₂O), 84.16 (COH), 121.06 (C), 133.90 (C), 139.15 (C), 140.24 (C), 141.37 (C), 141.79 (C), 166.00 (CO₂CH₂).

Tris(8-carboxyl-2,2,6,6-tetra(2-(1-*t*-butoxy-2,2-d₂-ethyl))-benzo[1,2-d;4,5-d']bis[1,3]dithiol-4-yl) methanol (6)

was prepared by analogy with known literature protocol.^[1d] Mp > 260 °C (decomposed). IR (KBr): = 3358 (m), 2972 (s), 2931 (m), 2870 (m), 1700 (m), 1472 (w), 1388 (m), 1362 (m), 1230 (s), 1194 (s), 1084 (s), 1020 (w), 861 (w) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): 0.97 (s, 27H, C(CH₃)), 1.04 (s, 27H, C(CH₃)), 1.07 (s, 27H, C(CH₃)), 1.10 (s, 27H, C(CH₃)), 1.80–2.30 (m, 2.57 H, residual protons, CH₂C), 3.15–3.55 (m, 24H, CH₂O), 7.04 (s, 1H, OH), 13.90 (broad s, 3H, COOH) (see SI). Within the error limits of ¹H NMR integration, compound **6** possessed the percentage of deuterium of 89.3±1.1 % for side-chain methylene groups adjacent to carbon atoms of sulfur-containing rings.

With the aim of unequivocal spectroscopy characterization of the core structure the unlabelled form of trityl **6**, i.e. **tris(8-carboxyl-2,2,6,6-tetra(2-(1-*t*-butoxyethyl))-benzo[1,2-d;4,5-d']bis[1,3]di-thiol-4-yl) methanol**, was synthesized. Mp > 260 °C (decomposed). Found: C, 58.42; H, 8.21. C₁₀₀H₁₆₀O₁₉S₁₂ requires C, 58.56; H, 7.86. MS (ESI, *m/z*): 2047.8187 (measured), 2047.8124 (calcd for C₁₀₀H₁₅₉O₁₉S₁₂ [M-H]⁻). IR (KBr): = 3364 (m), 2974 (s), 2932 (m), 2872 (m), 2595 (broad w), 1701 (m), 1474 (w), 1391 (m), 1364 (m), 1231 (s), 1196 (s), 1086 (s), 1020 (w), 862 (w) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): 0.98 (s, 27H, C(CH₃)), 1.06 (s, 27H, C(CH₃)), 1.09 (s, 27H, C(CH₃)), 1.11 (s, 27H, C(CH₃)), 1.85–2.32 (m, 24H, CH₂C), 3.18–3.54 (m, 24H, CH₂O), 7.02 (s, 1H, OH), 13.75 (broad s, 3H, COOH). ¹³C NMR (100.614 MHz, DMSO-d₆): 27.00 (C(CH₃)), 27.16 (C(CH₃)), 27.24 (C(CH₃)), 27.24 (C(CH₃)), 57.11 (CH₂C), 57.33 (CH₂C), 58.04 (CH₂C), 58.47 (CH₂C), 65.82 (SCS or OC(CH₃)), 65.82 (SCS or OC(CH₃)), 66.45 (OC(CH₃) or SCS), 66.45 (OC(CH₃) or SCS), 72.01 (OCH₂), 72.06 (OCH₂), 72.25 (OCH₂), 72.30 (OCH₂), 83.01 (COH), 121.92 (C), 133.16 (C), 137.90 (C), 139.86 (C), 140.23 (C), 140.94 (C), 166.77 (CO₂H).

Supplementary Material

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Acknowledgments

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Figure 1.
Structures of Finland trityls: sodium salt and methyl ester

Figure 2.
Interconversion of *M*- and *P* propellers

Figure 3.

a) Structures of triarylmethanols **1–6**. b) Geometry of **1** and assignment of experimental chemical shifts to methyl groups. Chemical shifts assignment was performed on the basis of quantum chemical calculation of nuclear shielding (see SI).

Figure 4.
Methyl region of 2D NOESY/EXSY ^1H NMR spectrum of triarylmethanol **1** (149.4 $^{\circ}\text{C}$).

Figure 5.
Alternative mechanisms of reversal of *M*-propeller to *P*-propeller

Zero-ring flip

	A	B	C	D
D		3		*
C	3		*	
B		*		3
A	*		3	

One-ring flip

	A	B	C	D
D		2	1	*
C	2		*	1
B	1	*		2
A	*	1	2	

Two-ring flip

	A	B	C	D
D		1	2	*
C	1		*	2
B	2	*		1
A	*	2	1	

Three-ring flip

	A	B	C	D
D			3	*
C			*	3
B	3	*		
A	*	3		

Figure 6.

Expected distributions of cross-peaks in 2D NOESY spectra of **1** for zero-, one-, two-, and three-ring flip pathways. Symbols * denote diagonal peaks. The off-diagonal digits stand for peak intensities measured in arbitrary units.

Figure 7.
Enantiomerization of trityl 7

Table 1Activation parameters (H , S , and G) for enantiomerization of **1** and **7**

Compound	H , kJ/mole	S , J/mole×K	G , 298 K, kJ/mole ^[a]
1 (DMSO solution)	95.3± 1.8	−19.9± 4.6	101.2 ± 3.3
7 ^[b] (ethyl acetate solution)	79.7 ± 2.0	−103.5 ± 6.5	110.6 ± 3.9

^[a]The maximal value of mean error is given^[b]Extracted from experimental data of ref. 16