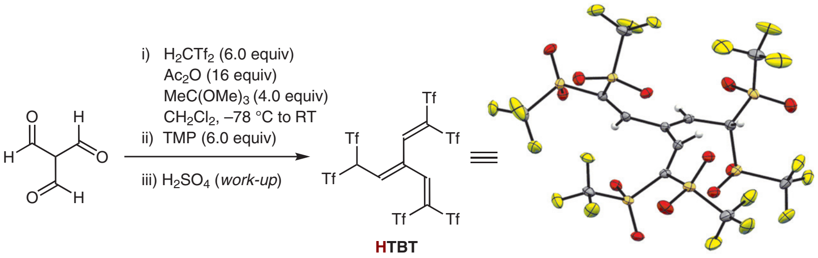
A Dendralenic C–H Acid

Denis Höfler
Richard Goddard
Nils Nöthling
Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470, Mülheim an der Ruhr, Germany
list@kofo.mpg.de

Published as part of the *30 Years SYNLETT – Pearl Anniversary Issue*

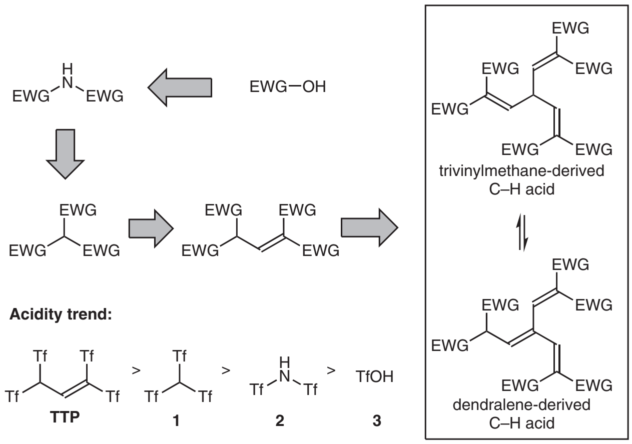


Received: 16.01.2019
Accepted after revision: 01.02.2019
Published online: 14.02.2019
DOI: 10.1055/s-0037-1612246; Art ID: st-2018-r0028-l

Abstract The design and synthesis of a strong, dendralenic C–H acid is described. Crystal structure analyses confirm the proposed structure. Despite the moderate stability of our motif, an application to Brønsted acid catalysis has been explored.

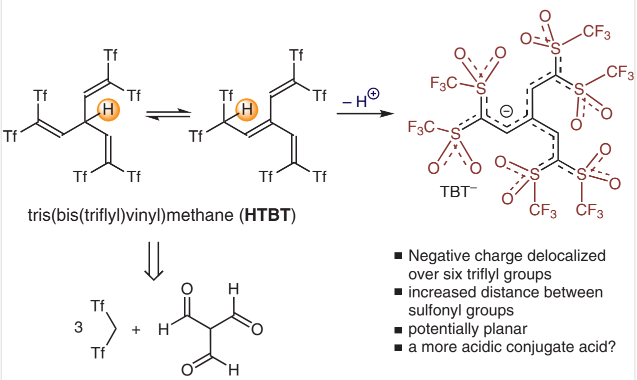
Key words dendralenic C–H acids, cross-conjugated acids, triflyl groups, strong acids, non-coordinating anions, Brønsted acids

In contrast to N–H- and O–H-based Brønsted acids, C–H acids enable the incorporation of a greater number of electron-withdrawing groups (EWGs) by virtue of carbon's higher valency. Experimental and estimated pK_a values of the simple trifluoromethanesulfonyl (triflyl, Tf) containing O–H, N–H, and C–H acids suggest that their acidity directly correlates with the number of electron-withdrawing groups (Scheme 1). Accordingly, tris(triflyl)methane (**1**) should be the strongest acid in the series, and indeed it shows a high reactivity in Brønsted and Lewis acid catalysis.[1] Still more electron-withdrawing groups can be introduced by choosing allylic C–H acid frameworks. This notion led to the design of 1,1,3,3-tetratriflylpropene (**TTP**), which showed a remarkable acidity and catalytic activity.[1d] In the search for still stronger acids, we sought to further increase the number of EWGs, which led to our interest in triene-derived C–H acids.[2] Purely hydrocarbon-based C–H acid scaffolds on the basis of fluorene and dibenzofluorene have already been realized by Kuhn and the latter showed a remarkable pK_a value of 5.9 (in water).[3] Depending on the location of the acidic proton, either trivinylmethane or dendralene-derived C–H acids are possible.



Scheme 1 Lead structures for the design of trivinylmethane-derived and highly conjugated dendralene-derived C–H acids

These considerations led to the design of tris(bis(triflyl)vinyl)methane (**HTBT**).[4] Irrespective of the location of the acidic proton on **HTBT**, only one anion should be obtained (**TBT**, after deprotonation) with a highly delocalized negative charge and a possible C_3-symmetry (Scheme 2). Furthermore, the peripheral location of the triflyl groups may enable a planar structure of the anion. As a result of this enhanced planarization and the greater number of electron-withdrawing groups, the acidity of **HTBT** was expected to be significantly higher in comparison to the related allylic C–H acid **TTP**. Synthetic access to **HTBT** was envisaged from triformylmethane and bis(triflyl)methane, as Yanai and coworkers[5] have already demonstrated that bis(triflyl)methane reacts with a variety of aldehydes in a self-promoted Knoevenagel-type condensation reaction.

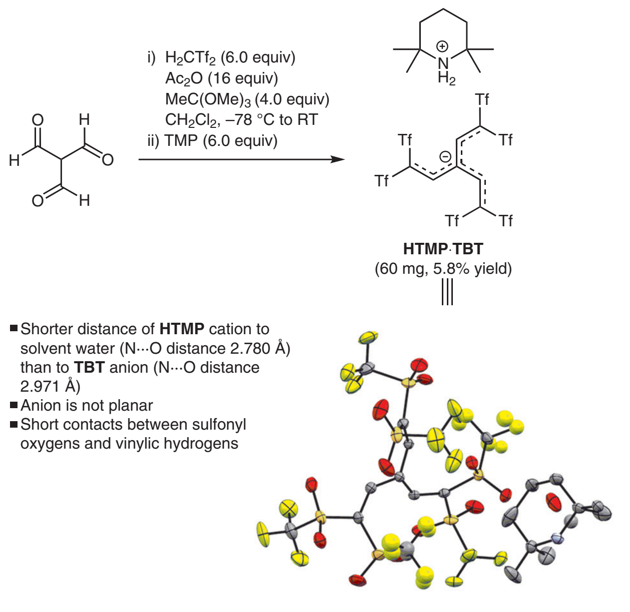


- Negative charge delocalized over six triflyl groups
- increased distance between sulfonyl groups
- potentially planar
- a more acidic conjugate acid?

Scheme 2 Design and retrosynthesis of the tris(bistriflylvinyl)methane (**HTBT**) and its anion **TBT**. The synthesis of triformylmethane has been previously described[6]

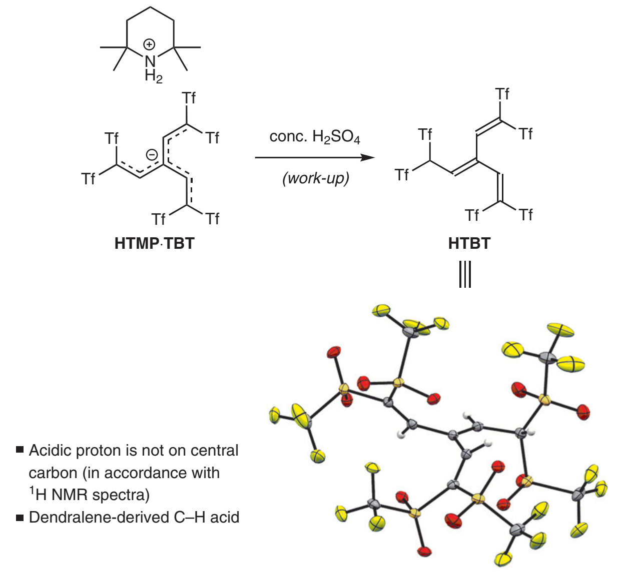
While our first attempts at the synthesis of **HTBT** led to the formation of a purely organic tricarbanion salt,[2] we found that by condensing triformylmethane[7] with bis(triflyl)methane followed by treatment with 2,2,6,6-tetramethylpiperidine (TMP), the desired HTMP salt of **TBT** (**HTMP·TBT**) was obtained in poor yield (Scheme 3).[8] Interestingly, crystal structure analysis of this ion pair revealed that the HTMP cation formed a slightly shorter N–H···O hydrogen bond to solvent water (N···O, 2.780(4) Å), which was introduced during the crystallization, than to the negatively charged **TBT** anion (N···O, 2.971(3) Å). Despite the increased distance between the triflyl groups, the **TBT** anion adopts a slightly non-planar chiral conformation. We assume that this may be due to the short contacts between the vinylic hydrogen atoms and the sulfonyl oxygen atoms. While we observe a local C_3-symmetry around the central carbon atom with similar bond lengths and torsion angles (see the Supporting Information), no global C_3-symmetry was observed in the **TBT** anion.

A work-up with concentrated H_2SO_4 finally delivered **HTBT** as the free acid (Scheme 4).[9] NMR spectroscopic investigations and single-crystal structure analysis of **HTBT** confirmed the location of the acidic proton not on the central carbon atom, as in the crystal of bullvalene, but between two triflyl groups. As a result, **HTBT** can be considered a cross-conjugated, dendralenic C–H acid. Due to the low stability of **HTBT** at room temperature and at –25 °C no satisfactory yield could be determined. We would expect the stability of such acids to be increased in a non-coordinating and non-polar solvent, as a degradation pathway via a nucleophilic attack can be prevented. However, we are yet to identify such a solvent system that is also capable of solubilizing **HTBT**.



- Shorter distance of **HTMP** cation to solvent water (N···O distance 2.780 Å) than to **TBT** anion (N···O distance 2.971 Å)
- Anion is not planar
- Short contacts between sulfonyl oxygens and vinylic hydrogens

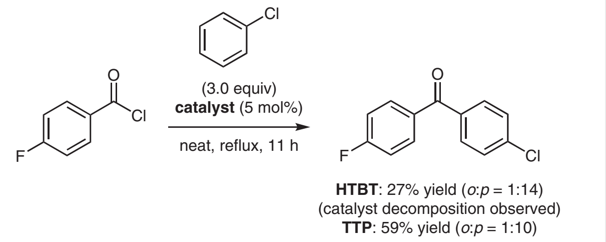
Scheme 3 Synthesis of **HTMP·TBT**. HTMP = 2,2,6,6-tetramethylpiperidinium



- Acidic proton is not on central carbon (in accordance with ^{1}H NMR spectra)
- Dendralene-derived C–H acid

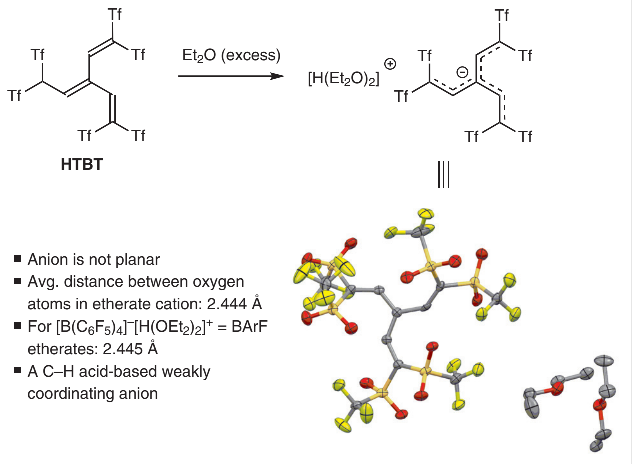
Scheme 4 Synthesis of **HTBT**. Due to the low stability of **HTBT** no yields could be determined

Despite the inherent low stability of **HTBT**, we attempted to directly employ freshly prepared **HTBT** for a benchmark Brønsted acid catalyzed Friedel–Crafts acylation reaction of weakly reactive chlorobenzene with *p*-fluorobenzoyl chloride (Scheme 5).[1d,10] While **TTP** provided higher yields, **HTBT** was also able to catalyze this transformation.



Scheme 5 Application of **HTBT** to the Friedel–Crafts acylation reaction of chlorobenzene with *p*-fluorobenzoyl chloride and a comparison with **TTP**

The acidity of **HTBT** is sufficient to protonate ethers thus allowing its transformation into an etherate salt when an excess of Et_2O was added (Scheme 6).[11] Single-crystal structure analysis revealed that the **TBT** anion neither adopts an idealized C_3-symmetry nor a planar conformation, which is in accordance with our previous findings. Interestingly, the oxonium proton prefers to coordinate to the oxygen atom of a second ether molecule rather than to one of the negatively charged triflyl oxygen atoms on the **TBT** carbanion. We were intrigued to find that the distances between the oxygen atoms of both Et_2O molecules are almost identical to those found in BArF etherates with the molecular formula $[B(C_6F_5)_4]^-[H(OEt_2)_2]^+$.[12] Consequently, a similar anion coordination can be assumed, thus classifying the **TBT** anion as a weakly coordinating anion.



- Anion is not planar
- Avg. distance between oxygen atoms in etherate cation: 2.444 Å
- For $[B(C_6F_5)_4]^-[H(OEt_2)_2]^+$ = BArF etherates: 2.445 Å
- A C–H acid-based weakly coordinating anion

Scheme 6 Conversion of **HTBT** into the diethyl ether–diethyloxonium salt **TBT·H(OEt$_2$)$_2$** and structural comparison with related BArF etherates[12]

In summary, we have designed and developed a synthesis of the cross-conjugated dendralenic C–H acid **HTBT**. Several crystal structures confirmed our design and revealed that the **TBT** anion adopts a non-planar and chiral conformation. Despite its low stability, **HTBT** was found to catalyze a Friedel–Crafts acylation reaction of chlorobenzene. A structural comparison with related BArF etherates indicates that the **TBT** anion may be classified as a C–H-acid-based weakly coordinating anion.

Acknowledgment

Generous support by the Max-Planck-Society, the Deutsche Forschungsgemeinschaft (Leibniz Award to B.L. and Cluster of Excellence RESOLV, EXC 1069), and the European Research Council (Advanced Grant 'C–H Acids for Organic Synthesis, CHAOS') is gratefully acknowledged. We also thank Jennifer Arlt for her technical support and the members of our analytical departments for their excellent service. We acknowledge DESY (Hamburg, Germany), a member of the Helmholtz Association HGF, for the provision of experimental facilities. Parts of this research were carried out at PETRA III and we would like to thank Anja Burkhardt, Eva Crosas, and Sebastian Günther for assistance in using the P11 beamline.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612246.

References and Notes

(1) (a) Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Yu.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391. (b) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L. *J. Am. Chem. Soc.* **1994**, *116*, 3047. (c) Turowsky, L.; Seppelt, K. *Inorg. Chem.* **1988**, *27*, 2135. (d) Höfler, D.; van Gemmeren, M.; Wedemann, P.; Kaupmees, K.; Leito, I.; Leutzsch, M.; Lingnau, J. B.; List, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 1411. (e) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2000**, 80. (f) For a description of pentacarboxycyclopentadiene-derived acids, see: Gheewala, C. D.; Radtke, M. A.; Hui, J.; Hon, A. B.; Lambert, T. H. *Org. Lett.* **2017**, *19*, 4227; and references cited therein.

(2) Höfler, D.; Goddard, R.; Lingnau, J. B.; Nöthling, N.; List, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 8326.

(3) Kuhn, R.; Rewicki, D. *Angew. Chem.* **1967**, *79*, 648.

(4) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. (b) Hendrickson, J. B.; Giga, A.; Wareing, J. *J. Am. Chem. Soc.* **1974**, *96*, 2275.

(5) (a) Yanai, H.; Egawa, S.; Taguchi, T. *Tetrahedron Lett.* **2013**, *54*, 2160. (b) Yanai, H.; Egawa, S.; Yamada, K.; Ono, J.; Aoki, M.; Matsumoto, T.; Taguchi, T. *Asian J. Org. Chem.* **2014**, *3*, 556.

(6) (a) Arnold, Z.; Budesinsky, M. *J. Org. Chem.* **1988**, *53*, 5352. (b) Krasnaya, Z. A.; Smirnova, Y. V.; Krystal, G. V.; Bogdanov, V. S. *Mendeleev Commun.* **1996**, *6*, 17. (c) Buděšínský, M.; Fiedler, P.; Arnold, Z. *Synthesis* **1989**, 858.

(7) Triformylmethane was prepared in two steps from commercially available bromoacetic acid following our recently reported procedure, see Ref. 2.

(8) **HTMP·TBT**
A Schlenk flask was charged with bis(triflyl)methane (1.7 g, 6.0 mmol, 6.0 equiv) and dry CH_2Cl_2 (1 mL) was added under argon. The colorless, clear solution so obtained was cooled to –78 °C in an acetone/dry ice bath. Triformylmethane (0.10 g, 1.0 mmol)

was added and a slurry was obtained. Trimethyl orthoacetate (0.47 g, 3.9 mmol, 0.50 mL, 3.9 equiv) and acetic anhydride (1.6 g, 16 mmol, 1.5 mL, 16 equiv) were added and the reaction mixture was allowed to reach RT overnight. A dark red solution was obtained. All volatiles were removed under reduced pressure and the solid mixture so obtained was dissolved in CH_2Cl_2 (5 mL). 2,2,6,6-Tetramethylpiperidine (0.85 g, 6.0 mmol, 1.0 mL, 6.0 equiv) was added and the reaction mixture was subsequently concentrated under reduced pressure. Almost complete removal of all volatiles was achieved by dissolving in $CHCl_3$ and evaporation to dryness. The solid mixture was transferred to a separation funnel with $CHCl_3$ (20 mL) and washed with sat. aq $NaHCO_3$ (20 mL). Both phases were separated and the aq phase was washed with $CHCl_3$ (20 mL), acidified with aq HCl (conc.) to a pH of 1, and extracted with CH_2Cl_2 (20 mL). The pooled CH_2Cl_2 phases were concentrated under reduced pressure to give the TMP salt of the title compound as an orange solid (0.35 g). As this compound still contained significant amounts of bis(triflyl)methane, the solid mixture was dissolved in $CHCl_3$, washed with aq HCl (conc.), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The red solid so obtained was dissolved in $CHCl_3$ and all volatiles were removed under reduced pressure. This procedure was repeated once more with $CHCl_3$ and then with 1,2-dichloroethane. A red solid was obtained, which was triturated with $CHCl_3$ to give the TMP salt of the title compound as a yellow solid (60 mg, 0.058 mmol, 5.8% yield). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.31$ (s, 3 H), 5.61 (s, 2 H), 1.86–1.81 (m, 2 H), 1.75–1.72 (m, 4 H), 1.49 (s, 12 H). (^{14}N couplings can be observed in the ^{1}H NMR spectrum. However, the signals of NH_2 group was not sharp enough for an accurate determination of $^1J_{1H14N}$.) ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 165.51$, 119.82 (q, $^1J_{CF} = 328$ Hz), 114.79, 108.53, 59.94, 35.23, 27.87, 15.95; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -73.96$; HRMS (ESIneg): *m*/*z* [M – H$^+$] calcd for $C_{13}H_3O_{12}F_{18}S_6^-$: 884.7667; found: 884.7667. Single crystals suitable for structural analysis were obtained after dissolving the initially obtained orange solid [containing bis(triflyl)methane impurities] in $CHCl_3$ or 1,2-dichloroethane and slowly evaporating the solvent.

(9) **Synthesis of HTBT as the Free Acid**
HTMP·TBT (17 mg, 0.017 mmol) was dissolved in CH_2Cl_2 (10 mL) and conc. H_2SO_4 (10 mL) was added. The mixture was stirred at RT for 30 min and the sulfuric acid phase was removed using a Pasteur pipet. $BaCl_2$ (dry) was added and after stirring for 30 min, the solution was filtered and all volatiles were removed under reduced pressure. A yellowish solid was obtained. NMR spectra (^{1}H and ^{19}F) in $CDCl_3$ were acquired. After 3 d, ^{1}H and ^{19}F NMR spectra were acquired once again, but after this time period, all product signals had vanished due to deprotonation and decomposition. ^{1}H NMR (501 MHz, $CDCl_3$): $\delta = 8.80$ (t, $J = 1.7$ Hz, 1 H), 8.59 (t, $J = 1.7$ Hz, 1 H), 6.52 (d, $J = 10.9$ Hz, 1 H), 5.36 (d, $J = 10.9$ Hz, 1 H); ^{13}C NMR (126 MHz, CD_2Cl_2): $\delta = 162.66$, 158.32, 136.73, 123.98, 119.52 (q, $J = 331$ Hz), 76.06. (Due to the fast decomposition of the desired product and the observed ^{13}C to ^{19}F coupling, not all signals in the ^{13}C NMR spectrum were obtained.) ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -71.48$, –72.25, –72.52, –72.87, –73.00. The **HTMP·TBT** salt (0.017 g, 0.017 mmol) was dissolved in CH_2Cl_2 (10 mL) and conc. H_2SO_4 (10 mL) was added. The mixture was stirred at RT for 30 min and the sulfuric acid phase was removed. Treatment with $BaCl_2$ was omitted. After three months, single crystals of the title compound were obtained which were suitable for structure analysis.

(10) Höfler, D. *Ph.D. thesis*. Universität zu Köln: Germany **2018**.

(11) **Conversion of HTBT into the Etherate Salt**
HTMP·TBT (43 mg, 0.042 mmol) was dissolved in CH_2Cl_2 (10 mL) and conc. H_2SO_4 (10 mL) was added. The mixture was stirred at RT for 30 min and the sulfuric acid phase was removed. All volatiles were removed under reduced pressure and a colorless solid was obtained. Et_2O was added, which afforded a clear, yellow solution. All volatiles were removed under reduced pressure and a yellow solid was obtained. CH_2Cl_2 (10 mL) was added and the formation of a biphasic mixture was noticed. Slow evaporation over 14 d led to the formation of single crystals of the etherate salt, which were suitable for structure analysis.

(12) Jutzi, P.; Müller, C.; Stammler, A.; Stammler, H.-G. *Organometallics* **2000**, *19*, 1442.