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1,1,2,2-tetracyanocyclopropane (TCCP) as supramolecular synthon

Antonio Bauzá,[a] Antonio Frontera,[a,]* Tiddo J. Mooibroek[b,]*

[a] Department of Chemistry Universitat de les Illes Balears
Crta. de Valldemossa km 7.5, 07122 Palma (Baleares), SPAIN
E-mail: toni.frontera@uib.es; Fax: (+) 34 971 173426

[b] School of Chemistry of the University of Bristol
Cantock's Close, BS8 1TS, Bristol, UK
E-mail: tiddomooibroek@gmail.com

Abstract

The 1,1,2,2-tetracyanocyclopropane (TCCP) unit presents a synthetically accessible and versatile synthon that can interact with lone-pair or π-electrons by 'non-covalent Carbon bonding'. Complexes of TCCP with common small molecules, anions, aromatics like fullerenes, amino acids and nucleobases were computed at the DFT BP86-D3/def2-TZVP level of theory. Binding energies vary between about -10 kcal/mol for neutral guests and -15 to -50 kcal/mol for anionic species. This is comparable to strong and very strong hydrogen bonding respectively. Thus, in addition to synthons that contain polarized hydrogen or halogen atoms, TCCP presents a new supramolecular synthon that awaits experimental exploitation.

Introduction

Living matter is for a great part governed by intermolecular recognition phenomena such as substrate/inhibitor/protein binding,[1-4] signalling events[5-8] and cell-cell interactions.[9-11] Intramolecular phenomena such as the folding of proteins[12-14] or DNA/RNA[15-18] are governed by the same physical forces. The design and synthesis of molecules that can influence such processes are the basis of many inquiries in supramolecular chemistry,[19-23] molecular biology[24-27] and pharmacology.[28-30] Underpinning the design process is knowing which molecular fragments will engage in favourable intermolecular interactions, i.e. knowing which supramolecular synthons one can use.[31-33] Prominent among these are synthons that rely on hydrogen bonding or aromatic interactions, such as nucleosides, amino acids and sugars. Chemical modification of such natural synthons is common practice,[34-37] while artificial supramolecular synthons that rely on other types of intermolecular interactions are rare. Halogen bonding is a noticeable exception,[38] but in principle Chalcogen,[39-41] Pnictogen,[42-45] or Tetrel[46-49] bonding interactions could similarly be exploited. That these interactions are not yet extensively used in (biochemical) research may in part be due to their novelty. Indeed, these interactions have only been studied in detail in the past decade or so.[46,50-55] A major obstacle of their exploitation, however, is the synthetic accessibility of identified supramolecular synthons. In particular, the problem is how to incorporate a given synthon in a larger molecular framework. For example, the Sulphur atom in SO_2 and SO_3 can participate in Chalcogen bonding interactions,[56] but these entities lack a convenient chemical anchor point.

We have recently highlighted that sp^3 hybridized carbon –the most abundant Tetrel atom– can be a supramolecular synthon.[47,48] More specifically, the 1,1,2,2-tetracyanocyclopropane (TCCP) motif (Scheme 1) was identified as an electron poor bowl, apt to accommodate an electron rich guest.[47] Two convenient (high yielding) synthetic routes towards this motif are shown in Scheme 1: reaction of a primary or secondary alkyl halide with tetracyanoethelene (left);[57-60] and reaction of an aldehyde or ketone with malonitrile (right).[61,62] In both instances, numerous variations of the R-

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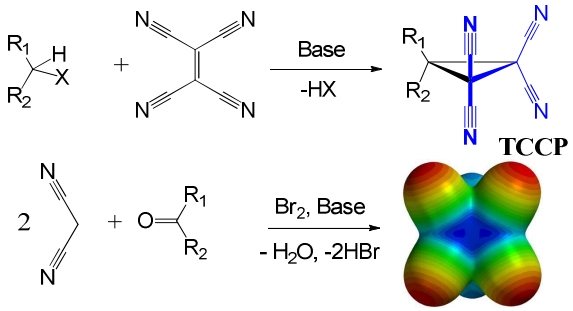
bearing moieties are readily available and provide a convenient way to obtain a practically infinite amount of TCCP derivatives. Thus, TCCP provides a rather unique case of a synthetically versatile and accessible supramolecular synthon that awaits utilization by the molecular scientists.



Scheme 1. Synthetic routes to 1,1,2,2-tetracyanocyclopropane (TCCP) structures. The molecular electrostatic potential map of 3,3'-dimehtyl-TCCP was computed at the DFT-B3LYP-6-31G* level of theory and the color code spans from –130 (red) to +150 (blue) kcal/mol.[63]

Anticipating the experimental exploitation of TCCP, we here report on a comprehensive theoretical investigation of the binding interactions of a model for TCCP derivatives (where R_1 = R_2 = H) with three classes of compounds; commonly encountered small (neutral) molecules, common anions, and several aromatic systems including Nature's aromatic building blocks.

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Results

For our enquiries we conducted computations based on density functional theory (DFT) at the BP86-D3/def2-TZVP level of theory and Table 1 summarized the results of the interaction of TCCP with common small molecules. For several of these molecule pairs, *ab initio* calculations at the MP2/def2-TZVP level of theory were also conducted (denoted 'a' in Table 1) to validate our use of the more economical DFT approach. The comparative results are given in the supplementary material (Table S1) and are in excellent agreement: computed distances differ less than 3% and computed energies typically less than 10%. In all cases, the minimized complex was subjected to an 'atoms in molecules' (AIM) analysis in order to identify atoms engaging in bonding contacts.[64] Graphical renderings of these analyses are depicted in Figure S1, and Figure 1 shows representative examples for some complexes with small neutral molecules.

The complexation energy with the control guest methane (-2.3 kcal/mol) is very small and methane actually is not located in the electron poor binding pocket of TCCP (see Figure S1). All other guests do engage in tetrel bonding with the $C_2(CN)_4$ pocket, although in several structures additional hydrogen bonding with TCCP's N-atom(s) is also observed (i.e. in **4**-**6**, **8**, **10**, **11**, **20**). These additional forces might explain the increased stability of these complexes over other, very similar ones. For example, the [H_2O···TCCP] pair **3** has an energy of -8.45 kcal/mol, solely due to O···C tetrel bonding interactions, while the additional hydrogen bonds with dimethyl ether (**4**), 1,4-dioxane (**5**) and THF (**6**) result in energies of about -11 kcal/mol. The energies of other small molecules with O-donors (**7**-**16**) are very similar, between about -7 and -10 kcal/mol. The strongest of these that do not have additional H-bonding according to AIM are trimethylphosphaneoxide **14** (-14.0 kcal/mol) and dimethylsulfoxide **16** (-12.2 kcal/mol). This is in line with the increased polarization of O in these molecules.

Other small molecules considered where an atom other than oxygen functions as electron donor (**17**-**28**) gave very similar energies, ranging between about -5 to about -10 kcal/mol. Carbon monoxide (**17**) and dinitrogen (**18**) displayed the lowest predicted energies at about -3 kcal/mol.

Interestingly, the series with H_2O (**3**; -8.5 kcal/mol, 2.82 Å) H_2S (**23**; -4.5 kcal/mol, 3.40 Å), H_3N (**19**; -9.4 kcal/mol, 3.00 Å) and H_3P (**25**; -4.9 kcal/mol, 3.57 Å) suggest that TCCP prefers 'hard' over 'soft' donor atoms, while the trend might also result from the longer distance required by the 'soft' second-row donors.

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Table 1. Interaction energies (ΔE), minimum contact distances (D) and densities of bond critical points (ρ) estimated at the DFT BP86-D3/def2-TZVP level of theory of complexes involving TCCP and several small molecules.

Complex	Guest	ΔE (kcal/mol)	D (Å)	ρ 100 (a.u.)
Control				
1	CH_4 [a]	-2.3	3.167[a]	0.470
O-donor atom(s)				
2	CO_2 [a,c]	-3.7	2.952	0.735
3	H_2O [a]	-8.5	2.819	1.094
4	$(CH_3)_2O$ [a,b]	-10.0	2.836	1.096
5	1,4-dioxane[b]	-11.4	2.824	1.129
6	THF[b]	-11.2	2.778	1.223
7	$(CH_3)_2CO$	-7.7	2.729	1.210
8	EtOAc[b]	-10.8	2.752	1.190
9	Urea	-11.1	2.687	1.310
10	Lactame[b]	-13.4	2.759	1.220
11	$(CH_3)_2NC(O)H$ [b]	-15.1	2.769	1.210
12	CH_3NO_2	-7.5	3.103	0.850
13	H_3PO [a]	-10.3	2.727	1.231
14	$(CH_3)_3PO$ [a]	-14.0	2.645	1.470
15	H_2SO [a]	-9.2	2.686	1.244
16	$(CH_3)_2SO$ [a]	-12.2	2.622	1.437
Other-donor atoms				
17	$\underline{C}O$ [a,c]	-3.2	3.302	0.599
18	N_2 [a,c]	-2.6	3.168	0.604
19	NH_3 [a]	-9.4	3.003	1.046
20	$N(CH_3)_3$ [a,b]	-11.2	3.177	0.831
21	CH_3CN	-7.3	2.962	0.963
22	Pyridine[d]	-9.5	3.010	1.025
23	H_2S [a]	-4.5	3.400	0.654
24	$S(CH_3)_2$ [a]	-7.7	3.266	0.876
25	PH_3 [a]	-4.9	3.567	0.665
26	$P(CH_3)_3$ [a]	-9.8	3.404	0.967
27	CH_2Cl_2	-4.9	3.968	0.580
28	CCl_4 [c]	-4.2	3.686	0.558

a) Complex also computed at the MP2/def2-TZVP level of theory, as detailed in Table S1. b) Also XH···NC(TCCP) hydrogen bonding present according to AIM analysis c) Alternate orientation also considered (respectively marked **2'/17'/18'/28'** in Figure S1) but found to be less stable. d) Another geometry where pyridine interacts with its π-cloud is less stable at -7.08 kcal/mol (see also complex 54 in Table 3).

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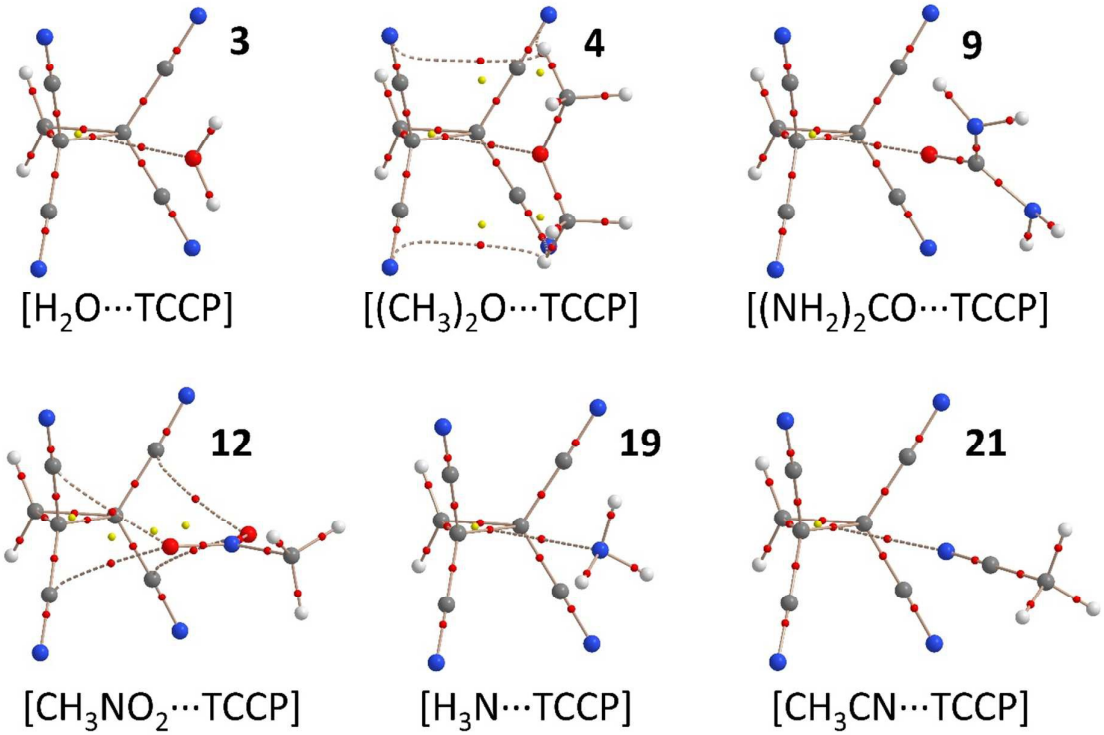

Figure 1. Molecular geometries of representative complexes of TCCP with small molecules, as computed at the BP86-D3/def2-TZVP level of theory (see also Table 1). The small red dots denote the bond-critical points according to an AIM analysis.

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All anionic guests appears to sit comfortably within the electron poor bowl shape of TCCP, and are held in place solely by one or multiple Tetrel bonding interactions, as evidenced by the AIM analyses (see Figure 2 for representative examples, but also Figure S1). The interacting energies are summarized in Table 2, and range typically from -19.4 kcal/mol for SCN^- (**43**) to -32.8 kcal/mol for acetate (**32**). The two complexes with the largest energies (**37** and **38**) concern dianions (SO_4^{2-} = -68.9 kcal/mol; SO_3^{2-} = -88.1 kcal/mol). The latter (**38**) might well have some covalent character; the C-C≡N angles (143°) deviate significantly from the ~170-180° observed in the monoanionic complexes. The C-C≡N angles in **37** are about 164˚, indicating that there is much less covalent character.

From the series with hydroxide **29** (-57.7 kcal/mol) > formate **30** ≈ acetate **31** ≈ hydrogen carbonate **32** (about -30 kcal/mol) > perchlorate **33** (-18.6 kcal/mol) it seems evident that the interacting energies decrease when the negative charge becomes more spread out over a larger anion (although the hydride result (**39**) breaks this trend, likely due to the short distance). The anions where a N-donor atom formally bears the negative charge (**40**-**43**) bind weaker (about -20-25 kcal/mol) than the small anions with O-donor atoms (e.g. formate **30** with -31.8 kcal/mol). In the series with halogen donor atoms (**44**-**49**) there is a clear trend with energies ranging from -52.1 kcal/mol for F^- (**44**) to -14.8 kcal/mol for PF_6^- (**49**).

In general the interaction energies reported in Tables 1 and 2 are in good agreement with the MEP values of the guest molecules on their negative regions. For instance in the neutral O/N Lewis bases the MEP values vary from –58 kcal/mol [for $(CH_3)_3PO$] to –12 kcal/mol (for N_2). Moreover, for the mono-anionic guests, the MEP values vary from –216 kcal/mol (F^-) to –125 kcal/mol (PF_6^-), in line with the interaction energies observed for their corresponding complexes. The SO_3^{2-} dianionic guest exhibits the most negative MEP value (–247 kcal/mol) and the largest interaction energy (see Table 2).

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Table 2. Interaction energies (ΔE), minimum contact distances (D) and densities of bond critical points (ρ) estimated at the DFT BP86-D3/def2-TZVP level of theory of complexes involving TCCP and several anions.

Complex	Guest	ΔE (kcal/mol)	D (Å)	ρ·100 (a.u.)
Anions with O-donor atoms and hydride				
29	HO^-	-57.7	2.286	2.850
30	HCO_2^-	-31.8	2.720	1.890
31	$CH_3CO_2^-$	-32.8	2.700	1.940
32	$HOCO_2^-$	-29.5	2.720	1.860
33	ClO_4^-	-18.6	2.810	1.410
34	NO_3^-	-26.0	2.748	1.690
35	$H_2PO_4^-$	-29.2	2.737	1.890
36	HSO_4^-	-24.1	2.764	1.740
37	SO_4^{2-}	-65.9	2.482	2.810
38	SO_3^{2-}	-88.1	2.520	7.490
39	H^-	-43.4	2.409	1.680
Anions with N-donor atoms				
40	N_3^-	-26.3	2.558	1.910
41	OCN^-	-25.6	2.831	2.120
42	CN^-	-22.6	2.696	1.670
43	SCN^-	-19.4	2.681	1.670
Anions with halogen donor atoms				
44	F^-	-52.1	2.311	2.800
45	Cl^-	-30.4	2.907	1.650
46	Br^-	-24.8	3.104	1.410
47	I^-	-19.6	3.369	1.160
48	BF_4^-	-17.2	2.755	1.350
49	PF_6^-	-14.8	2.857	1.200

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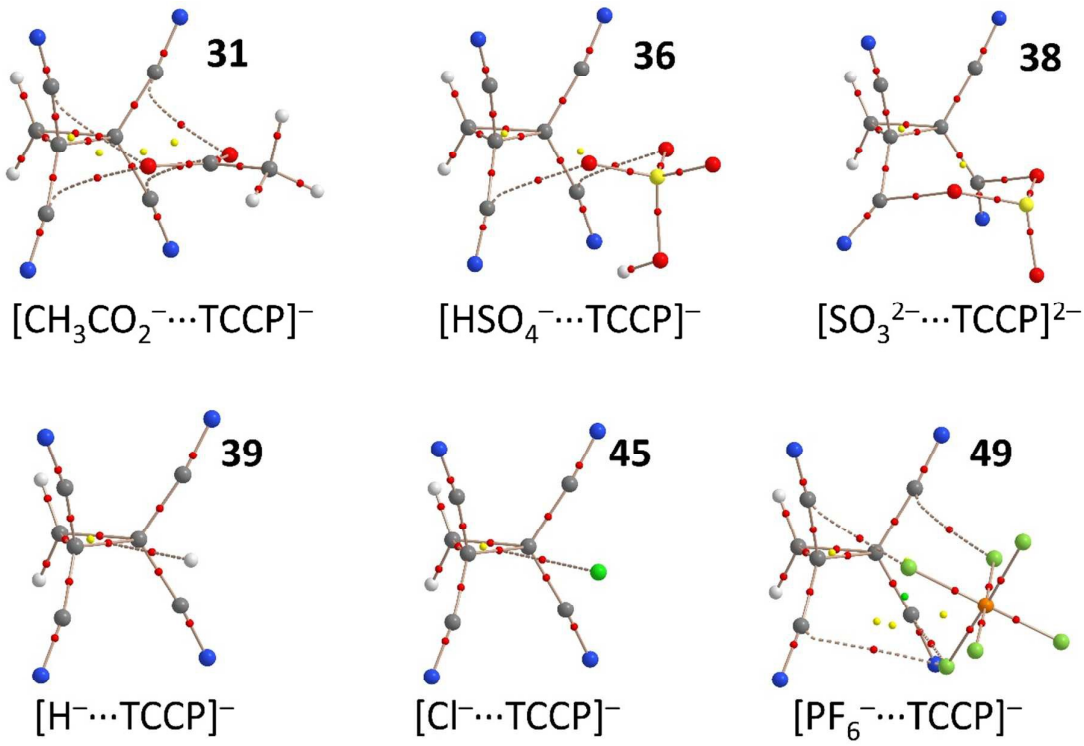

Figure 2. Molecular geometries of representative complexes of TCCP with anions, as computed at the BP86-D3/def2-TZVP level of theory (see also Table 2). The small red dots denote the bond-critical points according to an AIM analysis.

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As it appears from the data collected in Table 3, small isolated π-systems like ethene (**50**) and ethyne (**51**) bind to TCCP with about -5 kcal/mol. Small conjugated systems such as benzene (**53**) bind even stronger (about -7 kcal/mol), while larger condensed hydrocarbons (**55**-**60**) such as pyrene (**58**) bind stronger still (about -10 kcal/mol). As is apparent from the AIM analyses shown in Figure 3, all these complexes are held together mainly by tetrel bonding interactions (in some cases perhaps stabilized by weak CN···HC polar contacts).

It is interesting to note that the binding energy peaks at coronene (**60**; -12.6 kcal/mol), which can be seen as a model for graphene. Likewise, the binding energies calculated with several fullerenes (**61**-**64**) are substantial and strongest for a model of carbon nanotube (12,0) at -12.6 kcal/mol (**64**).

Also noteworthy is the positioning of TCCP over pyrene in **58** and triphenylene in **59**; apparently TCCP prefers the periphery over the center. It is known what Li^+ also preferentially binds to a peripheral ring in large condensed hydrocarbons.[65] However, in **60** the TCCP sits perfectly above the center of the coronene.

Encouraged by the energies computed with small molecules and aromatic systems, we expected that Nature's aromatic building blocks could bind to TCCP as well. The computational verifications of this expectation are listed in Table 3 as complexes **65**-**73** and Figure 4 shows the molecular structure and AIM analysis of several representative examples. Models of tyrosine **65** (-8.1 kcal/mol) and tryptophan **66** (-11.7 kcal/mol) interact much like condensed hydrocarbons, binding to TCCP with their π-electrons. Histidine **67** (-11.6 kcal/mol) seems to prefer binding to TCCP with its N-atom. When protonated, histidine moves away from TCCP's electron poor binding pocket and instead establishes a strong hydrogen bond with one of the N-atoms in TCCP. The binding energies computed with the nucleobases (**69**-**73**) are very similar at about -11 kcal/mol. Adenine (**69**) and guanine (**70**) bind with their π-surfaces, while the thymine (**71**), cytosine (**72**) and uracil (**73**) interact with their lone-pair electrons on O and/or N and additional hydrogen bonding.

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Table 3. Interaction energies (ΔE), minimum contact distances (D) and densities of bond critical points (ρ) estimated at the DFT BP86-D3/def2-TZVP level of theory of complexes involving TCCP and several π-systems.

Complex	Guest	ΔE (kcal/mol)	D (Å)	ρ·100 (a.u.)
Simple isolated π-systems (control)				
50	Ethene	-5.6	3.458	0.531
51	Ethyne	-4.3	3.431	0.528
Simple extended π-systems				
52	Cyclobutadiene	-6.9	3.502	0.660
53	Benzene	-8.5	3.601	0.649
54	Pyridine[a]	-7.1	3.697	0.629
Larger extended π-systems				
55	Naphtalene	-8.5	3.800	0.222
56	Antracene	-10.1	3.727	0.585
57	Phenantrene	-11.4	3.600	0.527
58	Pyrene	-11.9	3.581	0.710
59	Triphenylene	-11.8	3.665	0.657
60	Coronene	-12.6	3.698	0.692
Fullerenes				
61	C60	-7.7	3.762	0.672
62	CNT (8,0)	-11.6	3.545	0.723
63	CNT (10,0)	-12.3	3.540	0.710
64	CNT (12,0)	-12.7	3.549	0.686
Nature's aromatic building bocks				
65	Model of Tyr	-8.1	3.650	0.671
66	Model of Trp	-11.7	3.627	0.693
67	Model of His[b]	-11.6	2.928	1.159
68	Model of His^{+}[b]	-17.6	1.841[a]	3.500
69	Adenine	-11.2	3.710	0.643
70	Guanine	-11.3	3.228	0.598
71	Thymine[b]	-11.5	2.767	1.217
72	Cytosine[b]	-14.4	2.925	1.432
73	Uracil[b]	-10.6	2.787	1.160

a) Another geometry where pyridine interacts with its N-atom is more stable at -9.5 kcal/mol (see also complex **22** Table 1). b) No interaction with the π-system.

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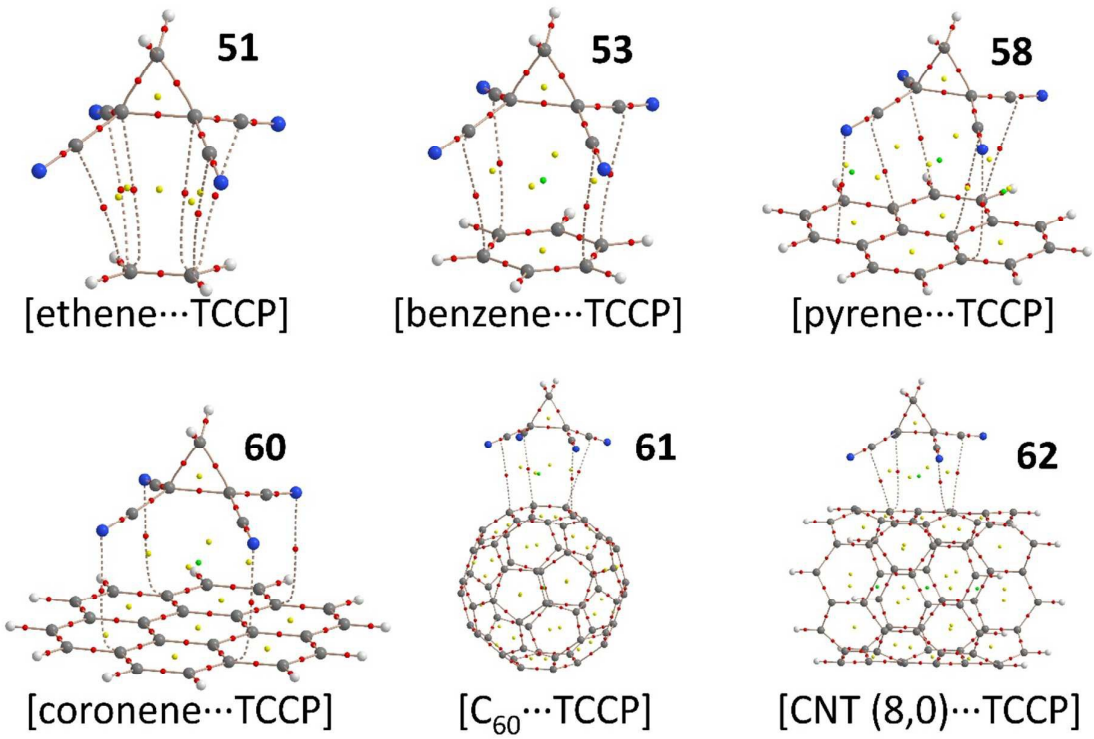

Figure 3. Molecular geometries of representative complexes of TCCP with π-systems, as computed at the BP86-D3/def2-TZVP level of theory (see also Table 3). The small red dots denote the bond-critical points according to an AIM analysis.

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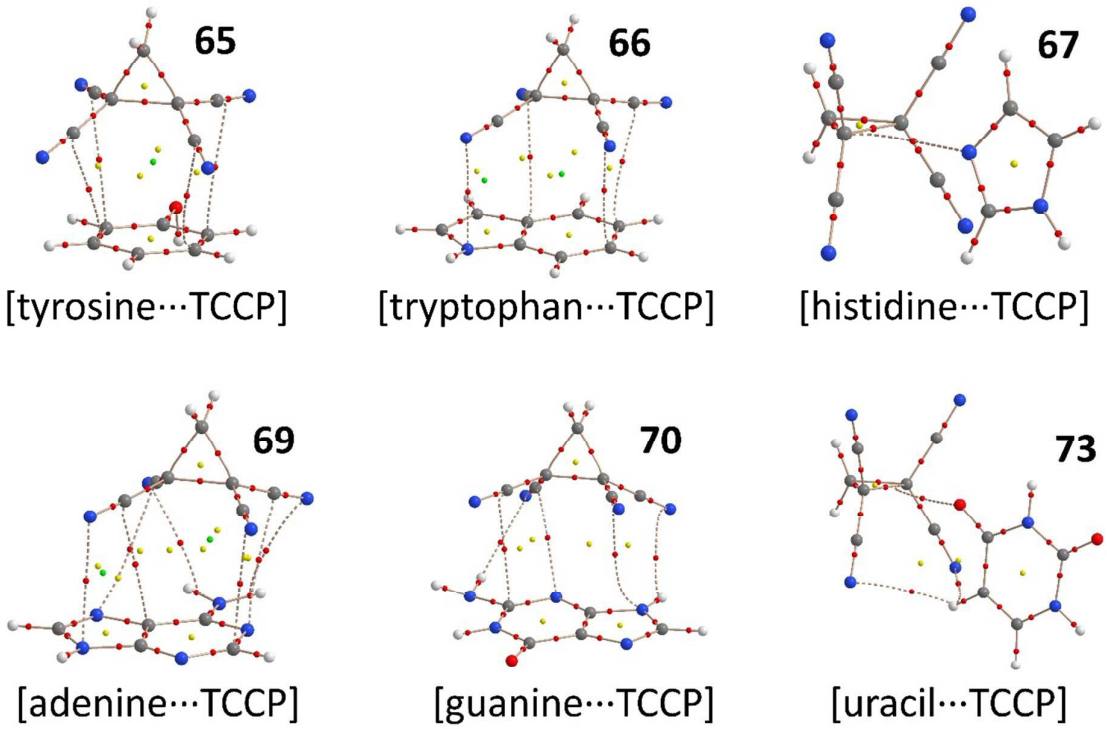

Figure 4. Molecular geometries of complexes of TCCP with some of Nature's aromatic building blocks, as computed at the BP86-D3/def2-TZVP level of theory (see also Table 3). The small red dots denote the bond-critical points according to an AIM analysis.

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Next, we wondered how a host molecule with several appropriately-spaced TCCP units would interact with some size-complementary electron rich guests. To this end we conjured one bipodal and two tripodal claw-like hosts (Figure S2) in which the linking unit assures an appropriate space in between TCCP-moieties and also allows for the correct angles so that the $C_2(CN)_4$ 'binding pockets' can face each other. We computed interacting energies with a selection of guests (see Table 4). The molecular geometries of selected complexes are shown in Figure 5 (the whole series is shown in Figure S3). AIM analyses were also performed and revealed tetrel bonding in all cases (not shown due to congested graphics).

The bipodal host interacts with some neutral and 'flat' molecules with about –5 to –10 kcal/mol (**74**–**77**); while the interaction of the spherical halide anions is much larger varying between –30 and –70 kcal/mol (**78** – **81**). The two tripodal hosts seem to complement the tetrahedral anions BF_4^- (**82**, **85**), ClO_4^- (**83**, **86**) as well as the trigonal planar NO_3^- (**84**, **87**) with interacting energies of about –20 to –40 kcal/mol.

These energies are generally larger compared to the analogous interaction with a single TCCP unit (Tables 2 and 3). For example, **78** (-67.1 kcal/mol) is about 30% more stable than **44** (-52.08 kcal/mol) and **82** (-27.5 kcal/mol) is about 60% more stable than **48** (-17.17 kcal/mol). That the stabilization is not strictly additive is likely a result of some repulsive interactions in the complex (e.g. CN···NC), some strain on the conformation of the host (e.g. the Ar-C≡C-CH_2 units in **82** and **84** are not perfectly linear), and/or the decreased electronegativity of the guest upon binding to one TCCP moiety.

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Table 4. Interaction energies (ΔE) and minimum contact distances (D) estimated at the DFT BP86-D3/def2-TZVP level of theory of complexes involving host molecules with multiple TCCP-units.

Complex	Guest	ΔE (kcal/mol)[a]	D (Å)
Bipodal host			
74	H_2O	-5.6	3.226
75	H_2S	-5.7	3.466
76	Benzene	-12.4	3.622
77	Pyridine	-9.6	3.634
78	F^-	-67.1	2.489
79	Cl^-	-41.3	3.005
80	Br^-	-34.1	3.177
81	I^-	-27.0	3.411
Tripodal hosts			
82	BF_4^-	-27.5	3.403
83	ClO_4^-	-31.5	3.403
84	NO_3^-	-41.1	2.718
85	BF_4^-	-23.4	3.381
86	ClO_4^-	-22.2	2.811
87	NO_3^-	-22.9	2.649

a) Energies relative to unbound hosts in its energy minimal conformer (as estimated by a Monte Carlo MMFF simulation prior to the DFT minimum energy calculation). For geometries see Figure S2 (compounds **88**-**90**).

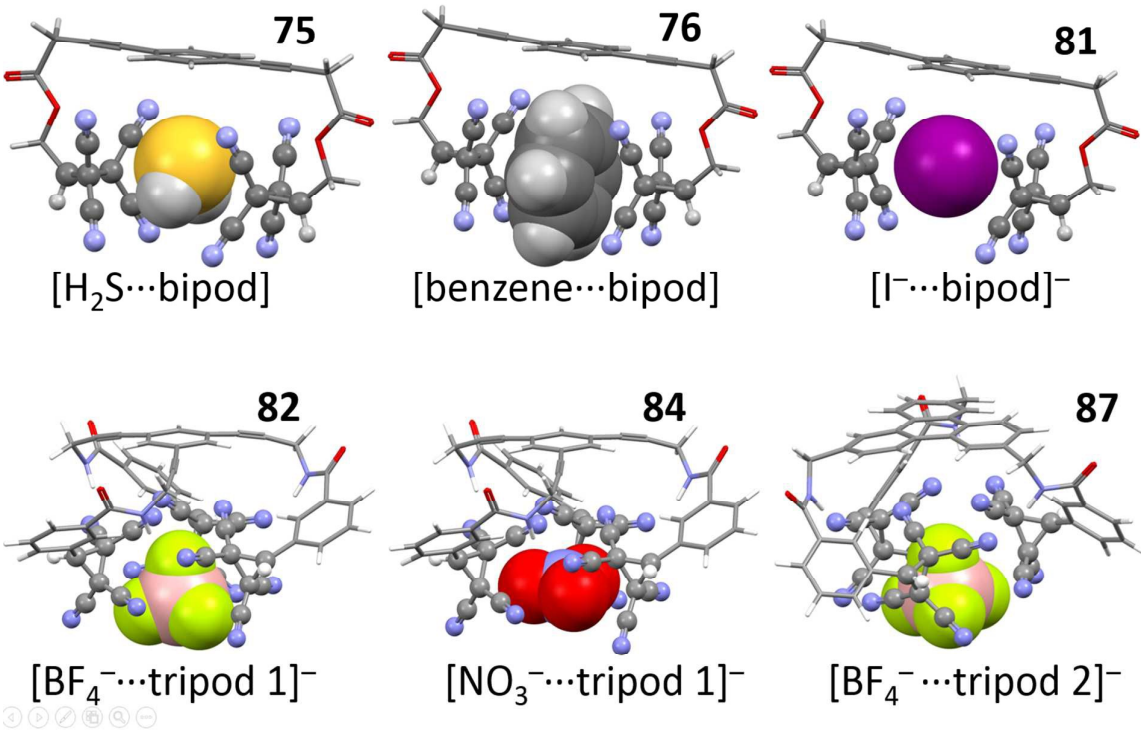

Figure 5. Molecular geometries of complexes of bipodal (top) and tripodal (bottom) TCCP-hosts with some electron rich guests, as computed at the BP86-D3/def2-TZVP level of theory (see also Table 4).

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Discussion and conclusions

From the above results it is clear that TCCP derivatives can accommodate a plethora of guest molecules that bear lone-pair electrons, π-electrons and/or a negative charge. The main mode of interaction with these electron rich entities is tetrel bonding with TCCP's electron deficient $C_2(CN)_4$ bowl. Hydrogen bonding with the cyano N-atoms may further stabilize the complex (e.g. complex **6** with THF).

The binding energies of about -10 kcal/mol observed with various neutral guest molecules are comparable in strength to strong hydrogen bonding involving charge-neutral H-bonding pairs.[66] The values of about -15 to -30 kcal/mol –typically observed with various anions– is truly remarkable because they are comparable in strength to very strong (ionic) hydrogen bonding.[66] The exceptionally large enthalpies computed for H^- (-43.4 kcal/mol) HO^- (-57.7 kcal/mol) and F^- (-52.1 kcal/mol) even far exceed the common benchmark for strong hydrogen bonding (about -35 kcal/mol).[66]

The large energies of formation computed between TCCP and (models of) fullerenes (about -10 kcal/mol) was somewhat expected, as TCCP's bowl-like shape and electron positive core are complementary to the concave shape and electron rich surface of fullerenes. This complementarity hints towards the potential of TCCP derivatives to act as facial amphiphiles to help mobilize these carbon isomorphs in solution.[67-70] Other charge-neutral supramolecular approaches for binding fullerenes indeed seem far less apt. For example, typical binding energies of hydrogen-π and halogen-π interactions are estimated at about 1-5 kcal/mol,[71,72] while not being shape-complementary to fullerenes at all.

Perhaps the most important result is the difference in geometric preferences of TCCP binding to (models of) amino acids and nucleobases. This implies that TCCP derivatives might selectively nest themselves in proteins and DNA/RNA-type molecules. In this context it is worth mentioning that TCCP derivatives are expected to be poorly hydrated in aqueous solution (no strong H-bond donors) and thus also interact with biomolecules by virtue of the hydrophobic effect. The potential of TCCP derivatives to bind strongly and selectively to biomolecules implies that TCCP might be engineered to influence the functioning of biomachineries, which in turn might have pharmacological implications. Additionally, the bipodal and tripodal TCCP hosts illustrate that strategically placed TCCP-units may greatly enhance the affinity for a guest molecule, just like multiple H-bond donors within a protein can result in high affinity binding to a ligand.

In summary we highlighted that TCCP is an accessible supramolecular synthon that acts as an 'electron sponge', mainly by virtue of tetrel bonding interactions. Its unique bowl-like shape, electron deficient core, and (presumed) hydrophobic character make TCCP-derivatives a promising new addition to the (bio)chemists toolbox (e.g. the PDB is void of TCCP-like ligands). As a result, following this theoretical exploration we anticipate that experimental exploitation of this unit will soon unveil its functional potential.

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