

TCIMAIL

number **162**



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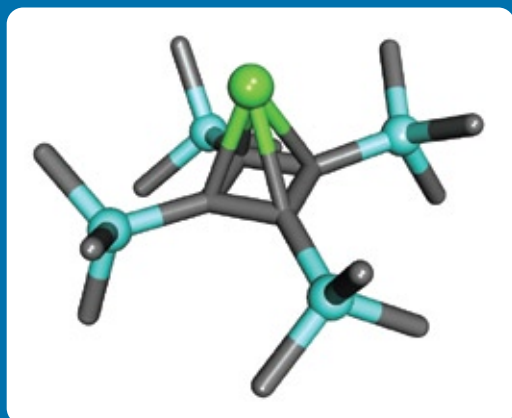
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Molecular Regular Polygons

Kentaro Sato

The hexagonal molecule of benzene composed of six carbon and six hydrogen atoms is one of the most beautiful structures in organic chemistry. Commonly known as the “turtle shell,” the structure is regarded as a symbol of the field. The shape was born from the balance between the attractive and the repulsive atomic forces and is a reflection of the fundamental laws of nature.

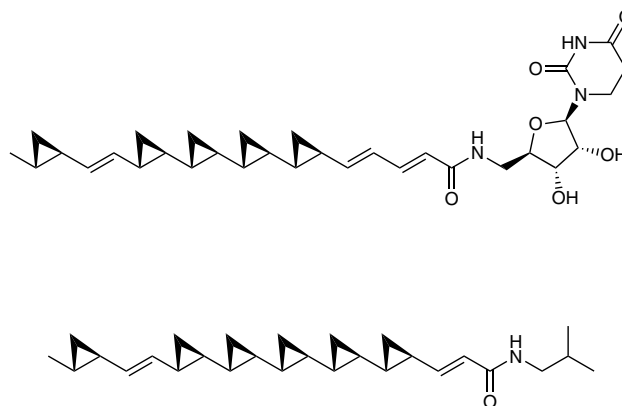
The structure of organic molecules follows simple rules of atomic connectivity and there are some very impressive polygonal examples besides benzene. In this article, let us put a spotlight on carbon-based equilateral polygonal molecular structures.

Regular Triangles

The smallest cyclic molecules made of three carbon atoms, called cyclopropanes, are of course triangular. As a

single unsubstituted compound, cyclopropane is a gas with a boiling point of -33 degrees Celsius. It was once used as an inhalation anesthetic for the sedating property, but is no longer used because of the flammability and the potential explosiveness.

Cyclopropane units are sometimes found as part of the structures of natural products such as terpenes. Among them, the two compounds that stand out are FR900848 and U-106305, both of which were discovered by pharmaceutical companies as drug candidates. As you can see, they feature a uniquely repetitive array of cyclopropane units. It is interesting to note that these two compounds that share this distinctive substructure were isolated from completely different organisms and also have completely different biological activities.



FR900848 (top), U-106305 (bottom)

It is a shame that these compounds have been called only by these alphabetical and numerical codes, as is always the case in pharmaceutical industry. However, the former compound has been named “jawsamycin” recently. Not surprisingly, the naming compares the alignment of triangles to the shark jaw.

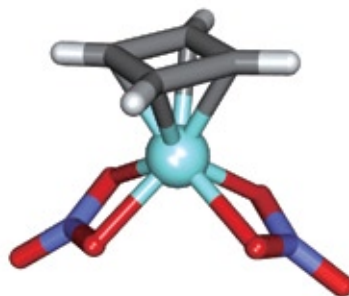
Squares

Introductory organic chemistry textbooks teach that four-membered ring and bigger cycloalkanes cannot have a planar conformation because of the bond angles. Annulenes, which are cyclic compounds composed of alternating single and double bonds, can take planar shapes but do not easily become equilateral polygons except for benzene.

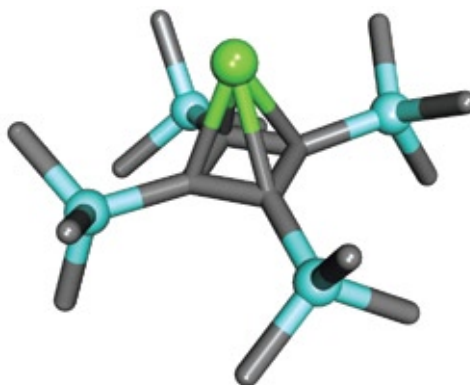
[4]Annulene, also known as cyclobutadiene, is highly strained and electronically antiaromatic with its 4π system. These properties make the molecule extremely unstable and its isolation as a pure form impossible. Based on spectroscopic analysis, it has been shown that the four carbon-carbon bonds of cyclobutadiene are not all equivalent and the structure is actually rectangular.

However, cyclobutadiene can be the ligand of organometallic complexes with metals such as iron. In these cases, the four-membered ring accepts a pair of electrons from the metal to complete the 6π aromatic system. In the iron complexes, it is known that all of the carbon-carbon bonds become equivalent and cyclobutadiene coordinates as a square.

In 2013, a compound called pyramidane was synthesized by V. Y. Lee and Akira Sekiguchi and the structure was determined by X-ray analysis. The molecule's shape is literally pyramidal, with its structure composed of germanium or tin atom positioned at the apex and the four carbon atoms forming the square base. Each of the four carbon atoms is bonded to a trimethylsilyl group that protects the sensitive complex against decomposition. What an absolutely amazing creation!



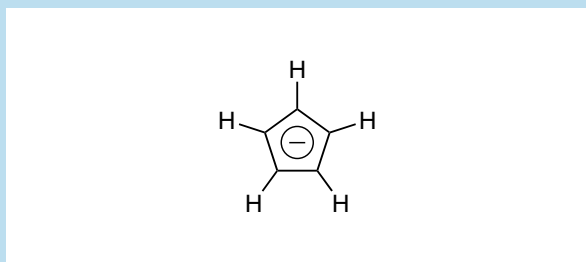
An example of cyclobutadiene organometallic complex



Pyramidane

Regular Pentagons

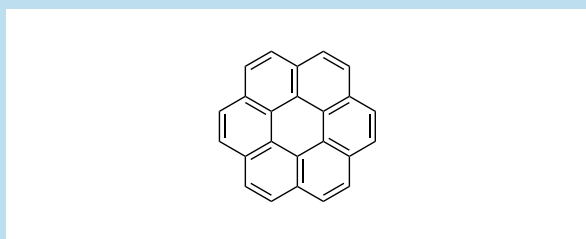
As for equilateral five-membered ring compounds, cyclopentadienyl anion is well-known. The cyclopentadienyl anion formed by the deprotonation of cyclopentadiene is a 6π electronic system that shows aromatic character. The five carbon atoms are equivalent and the molecule has a shape of regular pentagon. When it binds to transition metals, the resulting compounds are generally called metallocenes. Metallocenes are familiar compounds to us today, but their early discoveries were so impactful that they triggered the emergence of a new genre called organometallic chemistry.



Cyclopentadienyl anion

Regular Hexagons

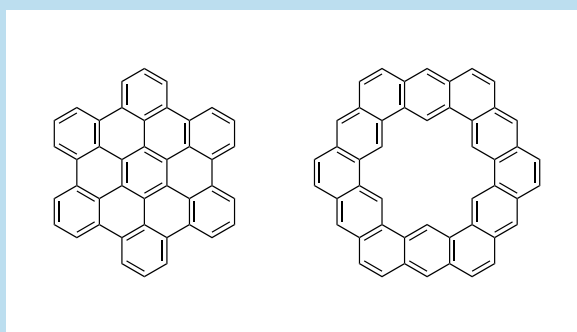
As mentioned in the beginning, benzene is a symbolic compound possessing regular hexagonal structure. There are a number of compounds in which several benzene rings are fused to form a larger hexagonal structure as a whole. The compound consisting of seven fused benzene rings is called coronene after the corona of the Sun.



Coronene

Coronene is found in coal tar and also known to form during petroleum cracking processes. Interestingly, the mineral ore called Karpatite produced in places like Ukraine contains coronene as its main constituent.

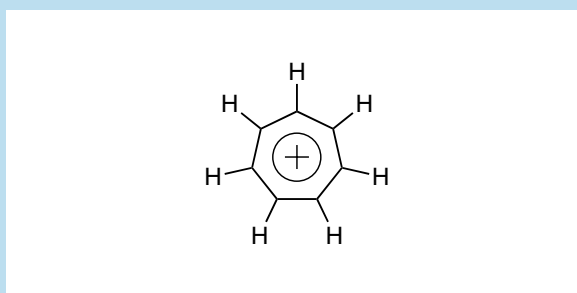
Hexabenzocoronene, which is coronene plus six additional fused benzene units, is considered a trendy material in recent nanotechnology research. Kekulene, which you could call “the benzene made of benzenes,” was synthesized in 1978 for the first time. Needless to say, this macrocyclic aromatic compound was named after August Kekulé, the German chemist who proposed the six-membered ring structure of benzene.



Hexabenzocoronene (Left), Kekulene (Right)

Regular Heptagons

We have so far seen four-, five-, and six-membered ring examples with 6π electronic system, so let us move on to analogous seven-membered rings. The chemical species called tropylium cation ($C_7H_7^+$) is the most famous one, which is synthesized from cycloheptatriene (by Lewis acidic treatment, for example).

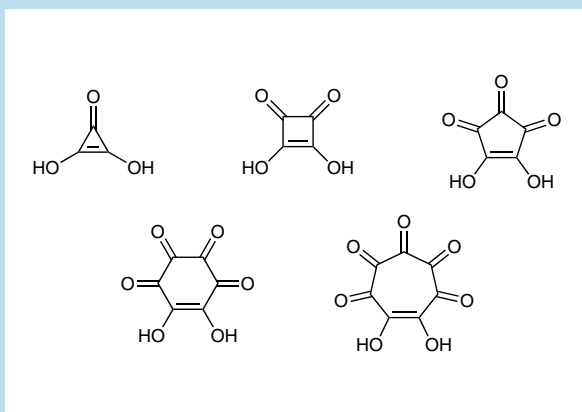


Tropylium cation

Carbon-based seven-membered ring structure attracts a special interest in the field of recent nano-carbon science. The infinite extension of fused six-membered rings would result in a large flat structure known as graphene. On the other hand, when both five- and six-membered rings are available, the carbon atoms tend to form round and finite structures such as fullerene.

When seven-membered rings are also available, the resulting nano-scale structures tend to adopt bent and curled shapes. For example, nanotubes containing seven-membered rings can have bent and branched substructures. In terms of the application of carbon materials to electronic devices and other nano-scale materials, the ability to incorporate seven-membered rings may become a key factor.

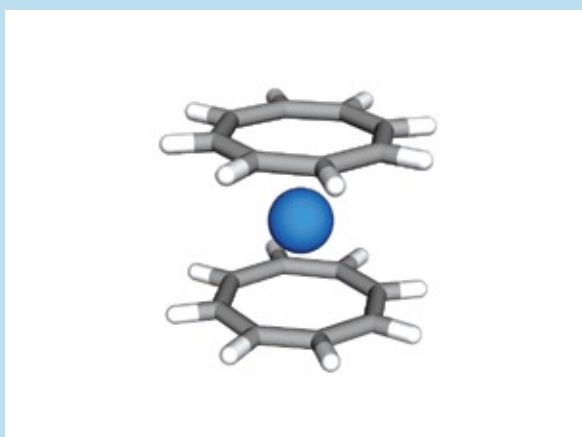
Let us look through compounds of the slightly different family. As shown below, oxo-carbon acids with the ring sizes from three to seven are known. Upon releasing two protons, these compounds become regular polygonal structures by delocalizing the charges. Because the dianions are stabilized by aromaticity, these oxo-acids show exceptionally strong acidities for compounds only made of C, H, and O.



Oxo-carbon acids

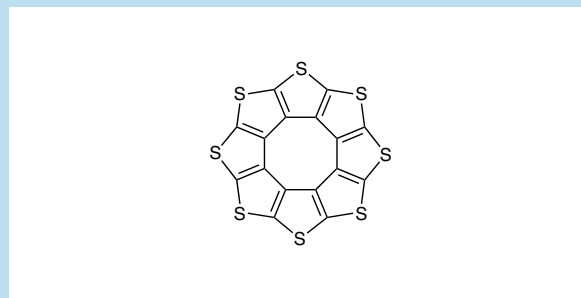
Regular Octagons

Cyclooctatetraene ([8]annulene) does not assume flat conformation unlike benzene and related aromatic compounds. The flat structure would be an 8π antiaromatic system, therefore the boat-shape becomes a more stable structure. However, the dianion formed by treatment with reducing agents is a 10π aromatic system that can exist as a flat regular octagon. Also, in some organometallic complexes containing cyclooctatetraene, the ligand is known to coordinate with the metal center as a flat regular octagon.



Uranocene $[U(C_8H_8)_2]$

In 2006, a neutral compound containing equilateral octagonal structure was synthesized. This compound composed of eight fused thiophene units looked like sunflower, so it was named “sulflower” by combining sulfur and flower.

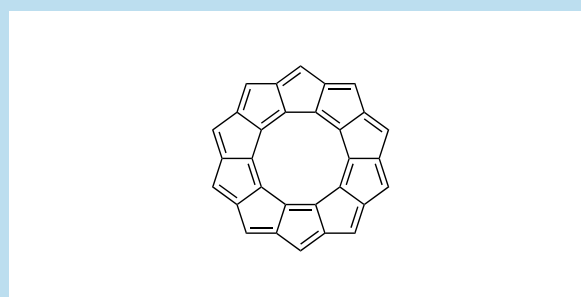


Sulflower

Regular Decagons and Beyond

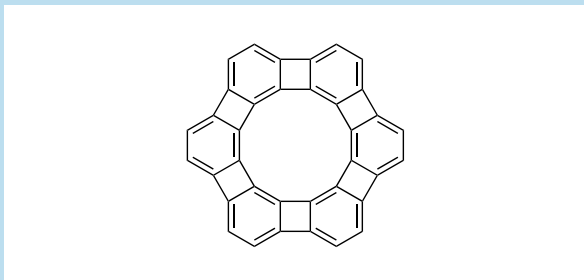
One could think of regular polygonal molecules larger than eight, but those would be unlikely to exist as flat molecules considering that the ideal bond angle of sp^2 carbon is 120 degrees. One possibility is to make them as an inner structure by surrounding it with small ring units like sulflower.

For instance, there is a structure called [10.5]coronene, which consists of five-membered rings positioned on each side of a decagon. This structure has been of great theoretical interest for a long time but its synthesis has yet to be achieved.



[10.5]Coronene

One could also imagine a structure like the one shown below, which has six- and four-membered rings placed alternately on the sides of a dodecagon. This type of compounds composed of fused benzene and cyclopentadiene rings (known as [N]phenylenes) are widely known, but this particular compound has never been synthesized. It has been difficult because both the inner and outer rings (12π and 24π , respectively) are antiaromatic. For this reason, this molecule has a fitting nickname “antikekulene.”



Antikekulene

Seeing the gallery of these structures reminds us that symmetry is an important keyword in the world of molecules. Revisiting familiar organic compounds with geometric point of view can be refreshingly eye-opening and possibly gives you unexpected hints for your research.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2008-Present Freelance science writer. 2009-2012 Project assistant professor of the graduate school of Science, the University of Tokyo.

[Specialty] Organic chemistry

[Website] The Museum of Organic Chemistry <<http://www.org-chem.org/youki/MOC.html>>

Useful Cinchona Alkaloid Derived Catalysts

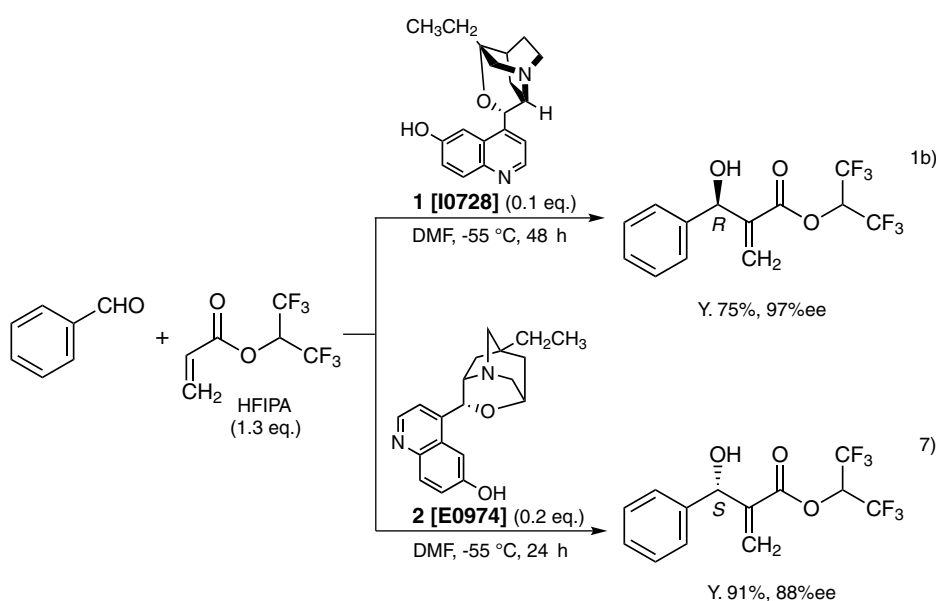
I0728 β -Isocupreidine (1)

1g

E0974 α -Isocupreine (2)

100mg

A cinchona alkaloid derivative, β -isocupreidine (β -ICD, **1**), has been known as a catalyst which catalyzes reactions such as the Morita–Baylis–Hillman (MBH) reaction¹, aza-MBH reaction², Michael reaction³, electrophilic amination⁴, and [2+2] cycloaddition^{5,6} with high enantioselectivities. Recently, Hatakeyama, Ishihara, *et al.* have developed α -isocupreine (α -ICPN, **2**), a pseudoenantiomer of **1**, and reported the MBH reaction using **2**.⁷ According to their results, in the reaction of various aldehydes with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA), the catalyst **1** affords (*R*)-products, and the catalyst **2** affords the related (*S*)-isomers respectively, in good yields. Thus, both enantiomers can be obtained in various kinds of asymmetric reactions by using these two catalysts properly. This synthetic method has broad applicability to the synthesis of natural products.



Typical Procedure:

1 or **2** (0.1 or 0.2 mmol) is dissolved in THF (2 mL) and the solution is evaporated by rotary evaporation at room temperature. After repeating this operation three times, the amorphous residue is dried under vacuum at room temperature for 10 min. A solution of the dried **1** or **2** and aldehyde (1.0 mmol) in DMF is cooled to -55 °C, and HFIPA (1.3 mmol) is then added. After the mixture is stirred at -55 °C, the reaction is quenched by the addition of 0.1 M HCl (3 mL). The mixture is extracted with EtOAc, washed with saturated NaHCO₃ and brine, dried over MgSO₄, concentrated, and chromatographed on silica gel (hexane-EtOAc) to give the corresponding products.

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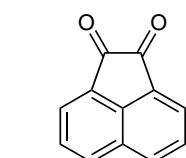
A Building Block for Organic Electronic Material Incorporating A Reactive 1,2-Diketone Moiety Forming Tetracene Derivatives

C2669 Cyclopenta[fg]tetracene-1,2-dione (1)

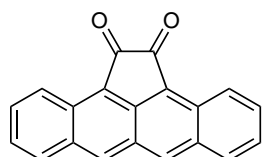
200mg, 1g

Acenes incorporating a linear-shaped structure with plural fused-benzene rings are useful materials for organic electronics. Accordingly, a building block for the acene derivative can be an important raw material to develop a new electronic material. In 2011, Matsuo *et al.* reported cyclopenta[fg]tetracene-1,2-dione (**1**) that is a tetracene derivative with a 1,2-diketone moiety. This has a more extended acene structure compared with those of acenaphthylene-1,2-dione and aceanthrylene-1,2-dione.¹⁾ **1** is particularly stable to oxidation compared with a normal tetracene, because there is an additional group on the unstable moiety of tetracene.

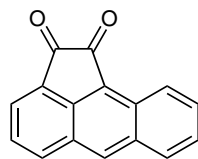
The single crystal X-ray analysis of **1** showed a highly planar structure of the molecule in the crystal, and there are π -stacking conformations between the planar molecules.¹⁾ Matsuo *et al.* reported that **1** reacted with 1,2-phenylenediamines to form several π -extended pyrazine derivatives.²⁾ Further introduction of a disulfide group to the pyrazine derivatives gave a low band gap material showing photoabsorption up to *ca.* 800 nm. Characteristics of organic field-effect transistors (OFET) fabricated by the pyrazine derivatives were also reported,²⁾ thus we can further expect synthetic development of a new tetracene-based material derived from **1** as a building block.



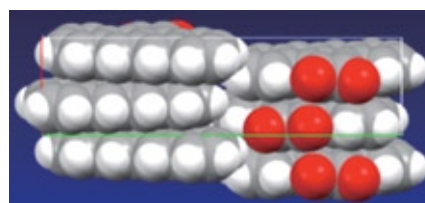
Acenaphthylene-1,2-dione



Cyclopenta[fg]tetracene-1,2-dione
(1)

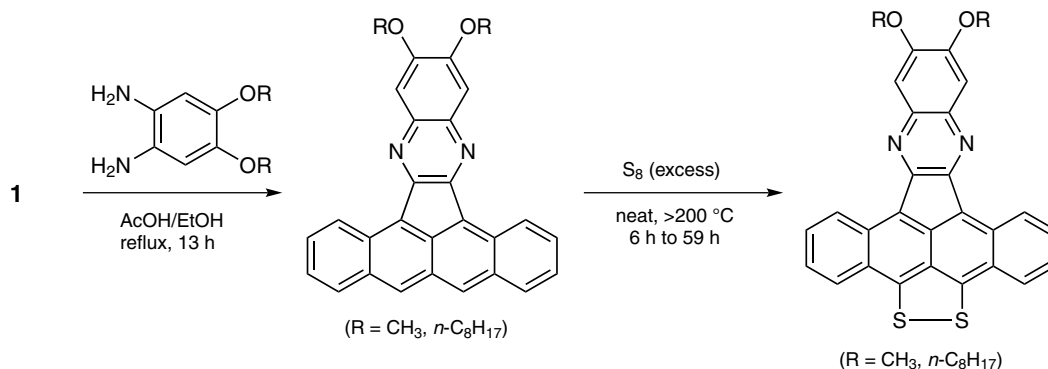


Aceanthrylene-1,2-dione



Packing structure of **1** viewed along the *c* axis

Synthesis of π -extended tetracene derivative from **1**



References

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T. Okamoto, T. Suzuki, S. Kojima, Y. Matsuo, *Chem. Lett.* **2011**, *40*, 739.
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S. Kojima, T. Okamoto, K. Miwa, H. Sato, J. Takeya, Y. Matsuo, *Org. Electron.* **2013**, *14*, 437.

An Ambipolar Organic Semiconductor with Well-Balanced High Hole and Electron Mobility

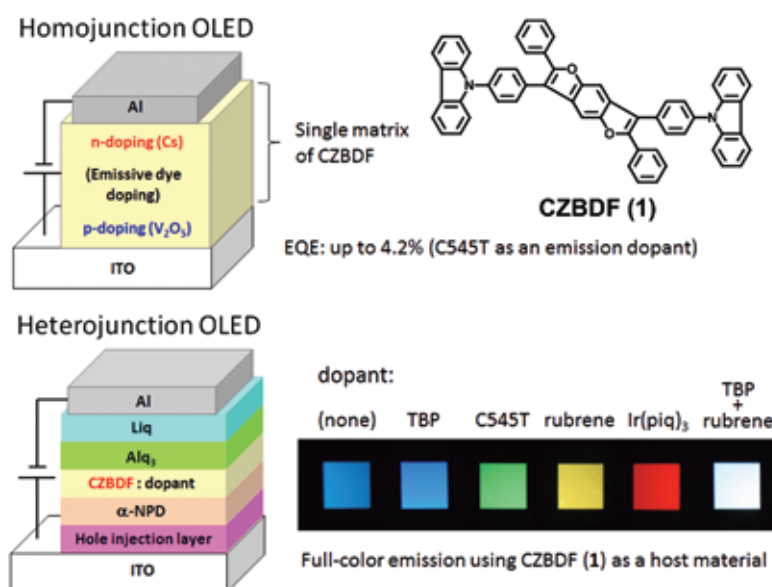
C2780 CZBDF (1)

200mg

Organic light-emitting diode (OLED) devices have received much attention because they provide a next-generation organic display and light source. Simplification of the device component is necessary in order to reduce production costs, since the OLED device usually consists of more than five layers including emissive host material, hole transporter, and electron transporter.¹⁾ The research group of Nakamura and Tsuji developed a dibenzofuran-based organic semiconductor, the so-called CZBDF (1).²⁾ Several characteristic features of **1** were reported: (1) ambipolar organic semiconductor with well-balanced high hole and electron mobility (hole: $3.7 \times 10^{-3} \text{ cm}^2/\text{Vs}$, electron: $4.4 \times 10^{-3} \text{ cm}^2/\text{Vs}$), (2) wide-gap material with HOMO-LUMO gap of 3.3 eV, (3) high glass-transition temperature ($T_g = 162 \text{ }^\circ\text{C}$), and (4) effectively storing a generated charge for an emissive dopant.

One can fabricate a homojunction OLED device of the ambipolar material **1** by vapor deposition. For instance, V_2O_5 (oxidant) or Cs (reductant) was simultaneously deposited with **1** on ITO (anode) or Al (cathode) for the purpose of p-doping or n-doping, however, **1** was used as a sole host material. The doping of blue (TBP), green fluorophore (C545T) and red phosphorophore ($\text{Ir}(\text{piq})_3$) to the non-charged layer of **1** enabled us to show three primary-colored emissions. In particular, the doping of the green fluorophore (C545T) indicated a high external quantum efficiency of 4.2%.²⁾

In addition, Nakamura and Tsuji *et al.* also reported a heterojunction OLED using **1** as a host material. They successfully fabricated a multi-colored OLED device by doping TBP, C545T, rubrene and $\text{Ir}(\text{piq})_3$. A device using the dual dopants (TBP and rubrene) showed a white-colored emission with an external quantum efficiency of 1.8%.³⁾



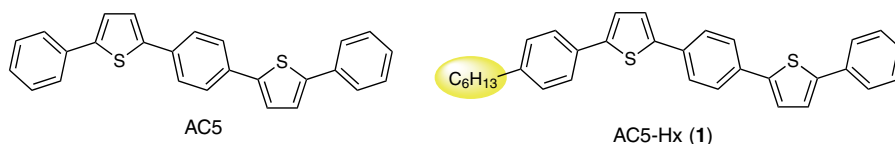
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Y. Shirota, H. Kageyama, *Chem. Rev.* **2007**, *107*, 953.
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H. Tsuji, C. Mitsui, Y. Sato, E. Nakamura, *Adv. Mater.* **2009**, *21*, 3776.
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C. Mitsui, H. Tsuji, Y. Sato, E. Nakamura, *Chem. Asian J.* **2012**, *7*, 1443.

Solubility-improved Organic Semiconductor, Thiophene/Phenylene Co-oligomer (TPCO)

H1448 4"-Hexyl-1,4-bis(5-phenyl-2-thienyl)benzene (purified by sublimation)
(= AC5-Hx) (1)

50mg



Organic electronics are electronics using organic semiconductors. A large number of next-generation organic devices are well developed because they are alternatives to inorganic materials. Such organic materials are promising for an electronic paper and a flexible display because they are lightweight and flexible in the processing.

Hotta *et al.* developed thiophene/phenylene co-oligomers (TPCOs) with several types of a thiophene-phenylene combination.¹⁾ The TPCOs are important semiconductor materials for organic electronics. One TPCO material has excellent carrier mobility comparable with that of amorphous silicon, and many of them are thermally stable and heat-resistant.

The AC5-Hx (1) has an *n*-hexyl group on one side of the molecule, thus it is a monoalkylated TPCO. **1** can be dissolved in THF in the amount of 0.41 g/L, suggesting more than 10 times the solubility over that of the non-alkylated AC5. A field-effect transistor (FET) measurement of **1** fabricated by a vapor deposition gave carrier mobility of $\mu = 5.9 \times 10^{-3} \text{ cm}^2/\text{Vs}$ (bottom-contact configuration) and $\mu = 2.4 \times 10^{-2} \text{ cm}^2/\text{Vs}$ (top-contact configuration). The resulting carrier mobility of **1** was higher than that of the non-alkylated AC5.²⁾

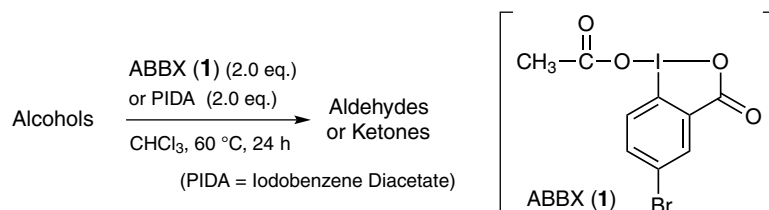
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R. Hirase, M. Ishihara, T. Katagiri, Y. Tanaka, H. Yanagi, S. Hotta, *Org. Electron.* **2014**, *15*, 1481.

ABBX, A Highly Active Trivalent Iodine Compound for Oxidation Reactions

A2678 1-Acetoxy-5-bromo-1,2-benziodoxol-3(1*H*)-one (1)

1g



Alcohols	Aldehydes or Ketones	Yield [Purity]
		ABBX : 90% [90%] PIDA : 32%
		ABBX : 74% [73%] (TBDPSO = <i>t</i> -Butyldiphenylsilyloxy)

1-Acetoxy-5-bromo-1,2-benziodoxol-3(1*H*)-one (**1**, ABBX) is a highly active trivalent iodine compound developed by Togo *et al.*¹⁾ **1** oxidizes aliphatic primary and secondary alcohols to the corresponding aldehydes and ketones in good yields. 5-Bromo-2-iodobenzoic acid, formed as a co-product of this reaction, can be recovered by acidification of the aqueous layer. **1** has chemically similar activity to "Super DIB" (ANBX) which was introduced in *TCIMAIL* number 157 p.8, and has more solubility in organic solvents than Super DIB.^{1,2)}

Typical Procedure: Oxidation of 4-methylbenzyl alcohol to 4-methylbenzaldehyde

To a solution of 4-methylbenzyl alcohol (1.0 mmol, 122.1 mg) in CHCl₃ (4 mL) is added ABBX (2.0 mmol, 767.7 mg). The mixture is stirred at 60 °C for 24 h. After the reaction is completed, the reaction mixture is added to aq. NaHCO₃ (10 mL). The aqueous layer is extracted with CHCl₃ (3 × 10 mL), and the organic layer is dried over Na₂SO₄. The filtrate is concentrated under reduced pressure to give 4-methylbenzaldehyde (108.0 mg, 90% yield) with 90% purity. The aqueous layer is acidified (pH ca. 2) with 1 M aq. HCl (15 mL) and the obtained mixture is filtered to afford 2-iodo-5-bromobenzoic acid (593 mg, 91%).

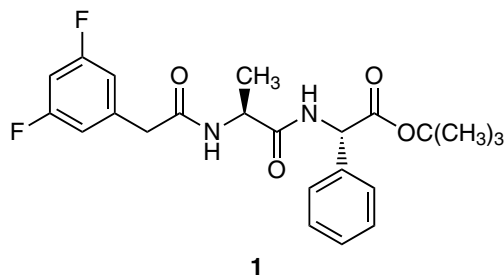
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γ -Secretase Inhibitor

D4257 DAPT (1)

25mg



DAPT (**1**) is a γ -secretase inhibitor and a dose-dependent reducer of brain amyloid β -peptide ($A\beta$) levels.¹⁾ It was also demonstrated that **1** disrupts Notch signaling indirectly.²⁾

Notch pathway functions during diverse developmental and physiological processes and is highly conserved throughout the animal kingdom.³⁾ It was reported that inhibition of the Notch response by **1** resulted in enhanced neuronal differentiation in embryonic stem cell-derived embryoid bodies and the enhancement is independent on Sonic Hedgehog signaling.⁴⁾

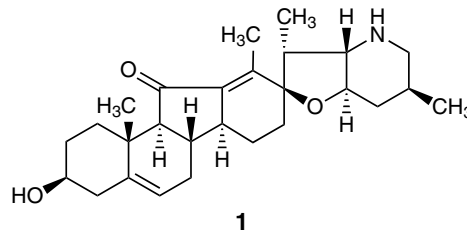
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Sonic Hedgehog Inhibitor

J0009 Jervine (1)

10mg



Hedgehog (Hh) proteins control cell growth, survival, and fate, and play important roles in vertebrate body plans.¹⁾ Mutations in the *Hh* gene were identified by Nüsslein-Volhard and Wieschaus.²⁾ The origin of the name "Hedgehog" derives from the short and "spiked" cuticle phenotype of the *Hh* mutant *Drosophila larvae*.¹⁾ Three types of subgroups of *Hh* genes, *Desert Hedgehog (Dhh)*, *Indian Hedgehog (Ihh)*, and *Sonic Hedgehog (Shh)* have been identified.³⁾

Control of the Hh signal is required for conversion of ES cells to pancreatic hormone-releasing endocrine cells.⁴⁾ Activation of Shh signaling, in combination with Oct4, reprograms mouse embryonic and adult fibroblasts into IPS cells.⁵⁾

It has been reported that Jervine (1) blocks Shh signal pathway and exposure of chick embryos to 1 results in cyclopia.⁶⁾

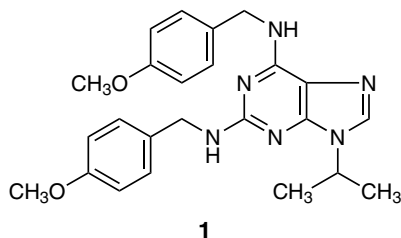
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Cell Differentiation Research Reagent

M2373 Myoseverin (1)

10mg



Myoseverin (1), one of the 2,6,9-trisubstituted purine derivatives, is a microtubule-binding molecule and inhibits tubulin polymerization.¹⁾ 1 induces fragmentation of multinucleated myotubes into mononucleated cells.^{1,2)} It was reported that the derived cells retain the properties of parental myotubes,²⁾ and the capability to revert to multinucleated tubes after treatment.³⁾

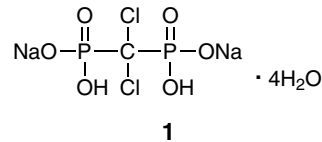
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Bone Resorption Inhibitor

D4160 Disodium Clodronate Tetrahydrate (1)

1g, 5g



Bisphosphonates (BPs) are very effective inhibitors of bone resorption *in vivo* and *in vitro*. Disodium clodronate tetrahydrate (1) is one of the BPs and is classified in the first-generation BPs.^{1,2)}

BPs are known not only as a bone resorption inhibitor but also as an anti-tumor.³⁾ Tumor-associated macrophages (TAMs) play many roles in tumor progression; tumor cell growth, migration, invasion, metastasis, and angiogenesis, *etc.*³⁾ Effects of BPs on TAMs, *i.e.*, BP-induced macrophage depletion, have been reported in detail.³⁾ In such studies, liposome-encapsulated clodronate has been applied for targeting of macrophages.⁴⁻⁷⁾

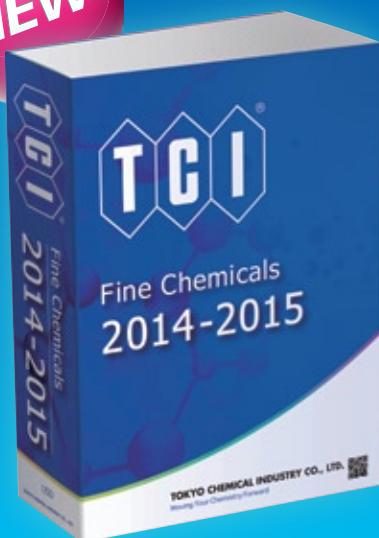
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