A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
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Accepted Article

Title: Synthesis and Analysis of Substituted Bullvalenes

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201712157
Angew. Chem. 10.1002/ange.201712157

Link to VoR: http://dx.doi.org/10.1002/anie.201712157
http://dx.doi.org/10.1002/ange.201712157

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Synthesis and Analysis of Substituted Bullvalenes

Oussama Yahiaoui,[a] *Lukáš F. Pašteka,**[b] *Bernadette Judeel,*[a] *and Thomas Fallon**[a]

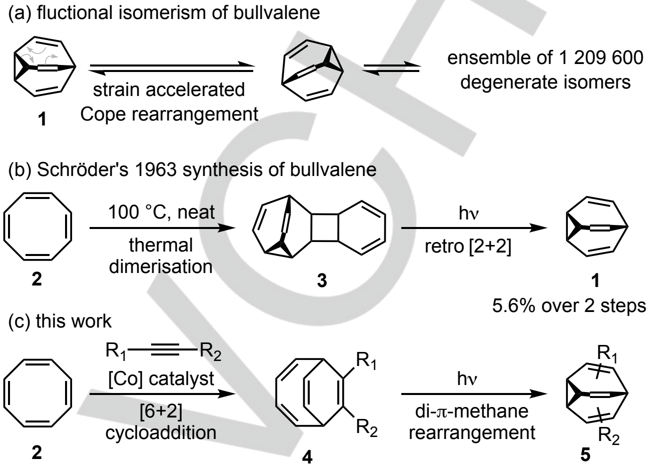
Abstract: *In this communication we detail a new, practical synthesis of bullvalene and variety of mono- and di-substituted analogues. This has been accomplished through cobalt-catalyzed [6+2] cycloaddition of cyclooctatetraene to alkynes, followed by photochemical di-π-methane rearrangement. The application of isomer network analysis, coupled with quantum chemical calculations, provides a powerful and automated tool for predicting the properties of bullvalene isomer networks.*

Bullvalene (**1**) is the archetypal fluctional molecule. By virtue of rapid Cope rearrangements it exists within an ensemble of >1.2 million degenerate isomers (Scheme 1a). With the exception of the barbaralyl cations,[1] this property of *total degeneracy* is unique. Substituents bound to this core structure will explore all possible structural isomers. This geometrically rich fluctional behaviour gives substituted bullvalenes a potentially significant place within the rapidly developing context of dynamic covalent chemistry.[2]

Doering and Roth first predicted Bullvalene in 1963.[3] Later that year, Schröder serendipitously encountered the structure while studying the photochemistry of cyclooctatetraene (COT) dimers (Scheme 1b).[4] Despite the low overall yield (5.6%), this first synthesis has remained the best, and the basis of Schröder's extensive studies into bullvalene chemistry, and the preparation of many substituted examples.[5] Rational synthetic strategies to bullvalene have also been devised by Doering[6] and Serratosa,[7] both employing a transannular cyclopropanation as a key step. Recently, Echavarren has introduced a new approach achieved through gold-catalatysed synthesis of barbaralones.[8]

Bode and co-workers have developed a syntheses of tetra-substituted bullvalenes and demonstrated supramolecular opportunities including adaptive binding and sensing.[9] This exciting new work is, however, limited by the lengthy synthetic access to these heavily substituted bullvalenes.

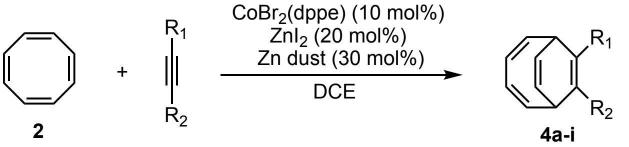
The photochemical di-*π*-methane rearrangement[10] of bicyclo[4.2.2]deca-2,4,7,9-tetraene (BDT) systems is a rare class of transformation. The parent hydrocarbon **4a** was first prepared by Jones and Scott via a low-yielding photoisomerisation of bullvalene.[11] It was found however, that **4a** slowly but cleanly photoisomerises back to bullvalene when irradiated with a medium pressure mercury lamp behind a Pyrex filter. This type of di-*π*-methane rearrangement was instrumental in Paquette's classic synthesis of substituted aza-bullvalenes,[12] as well as an attempted synthesis of diaza-bullvalene.[13]



Scheme 1. (a) Fluctional isomerism of bullvalene, (b) Schröder's original synthesis of bullvalene, (c) this work.

Cobalt(I)-catalysed formal cycloaddition reactions have recently emerged as a powerful method in organic synthesis.[14,15] In 2006, Buono reported that cyclooctatetraene undergoes [6+2] cycloadditions with alkynes to give substituted BDTs, using a CoI_2(dppe)/ZnI_2/Zn catalyst system.[16] This reaction has recently been re-evaluated, revealing that a variety of Co(II) salts are viable precatalysts.[17]

With access to substituted BDTs, we foresaw a rapid two-step synthetic path to mono- and di-substituted bullvalenes. A range of BDTs were prepared by adaptation of the reported protocols (Scheme 2). Interestingly, acetylene gas also participates in this reaction to give the parent hydrocarbon (84% yield, 12 g scale).[18]



4a: R_1, R_2 = H, H, 84%
4b: R_1, R_2 = Me, H, 70%
4c: R_1, R_2 = *n*-hex, H, 90%
4d: R_1, R_2 = CH_2OH, H, 86%
4e: R_1, R_2 = Bn, H, 91%
4f: R_1, R_2 = $SiMe_3$, H, quant.
4g: R_1, R_2 = CH_2OH, CH_2OH, 80%
4h: R_1, R_2 = Me, *n*-pent, 87%
4i: R_1, R_2 = Ph, H, 63%

Scheme 2. Cobalt catalysed synthesis of bicyclo[4.2.2]deca-2,4,7,9-tetraenes.

With BDT precursors in hand, photoisomerisation to the corresponding bullvalenes was investigated. Irradiation of solutions of **4a-h** in acetone (150 W medium pressure mercury lamp, Pyrex glassware) led to the corresponding bullvalenes in fair to very good yield (Scheme 3). In some cases long reaction times were needed. The synthesis of bullvalene itself proceeds in 71% yield (8 g isolated, 60% yield from COT). This procedure avoids the low yielding thermal dimerization of COT, and provides practical access to the parent hydrocarbon. A variety of mono-substituted bullvalenes were prepared (**5b-f**), as well as

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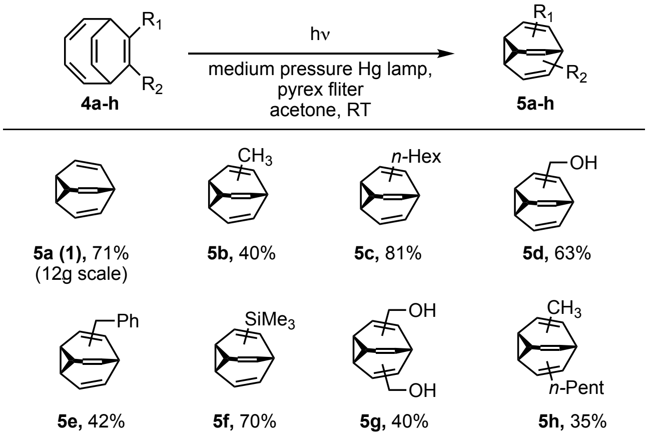
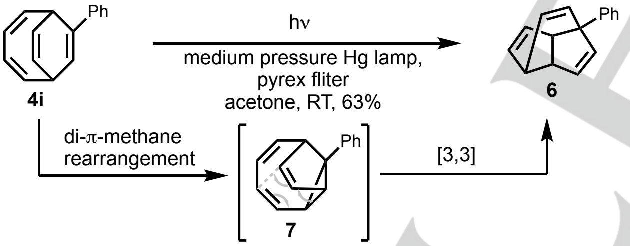
the bis(methylenehydroxy) bullvallene **5g** and methyl(*n*-pentyl)bullvalene **5h**.



Scheme 3. Photochemical synthesis of bullvalenes.

Interestingly, when phenyl-substituted BDT **4i** was irradiated under the standard conditions, phenyl "lumibullvalene" **6** was isolated in 62% yield (Scheme 4). None of the expected phenylbullvalene could be detected in the reaction mixture. Presumably, the di-π-methane rearrangement proceeds, but through an alternate path to give phenyl substituted "isolumibullvalene" **7**, which would rapidly undergo a cyclopropane accelerated Cope rearrangement to give phenyl lumibullvalene.[19] This switch in reactivity is not yet understood, and may preclude the use of our strategy for the synthesis of aryl-substituted bullvalenes. However, access to substituted lumibullvalene frameworks may prove useful.



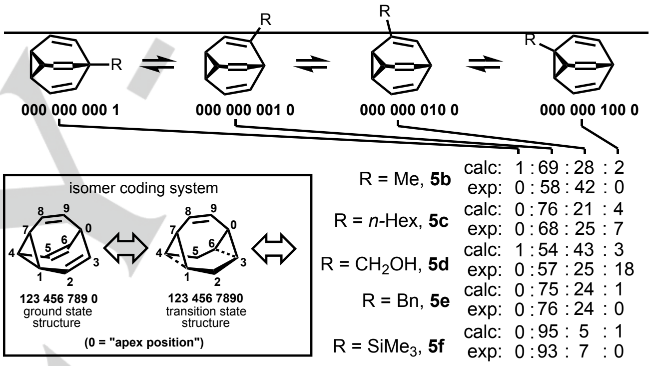
Scheme 4. Synthesis of phenyl-lumibullvalene **6**.

As dynamic ensembles of exchanging isomers, bullvalenes represent a conceptually intriguing, and challenging analytical problem. Mono-substituted bullvalenes have four possible isomers, di-substituted networks have either 15 isomers (identical substituents) or 30 isomers (unique substituents). With further substitution the level of complexity rapidly escalates.[20]

Substituted bullvalenes represent closed reaction graphs.[21] Bode introduced a convenient isomer coding system (Figure 1) and algorithm that enumerates the interconnections of any bullvalene substitution pattern.[22] Building on this method, we've developed a program that evaluates any possible substituted bullvalene network and performs quantum chemical energy calculations on all objects within the reaction graph.

Using the required substituent geometries as input, our newly developed algorithm generates the full rearrangement network with corresponding codes for all isomers and interconnecting transition states. Further, enantiomeric pairs are identified and starting geometries for all nondegenerate species are produced. These are subsequently optimized in two steps with an increasing level of theory via the interface to the program package ORCA 4.0.[23] In the first step, large-scale screening of rotamers is performed and the lowest energy rotamer is chosen for each isomer employing the combination of inexpensive semiempirical and density functional theory (DFT) methods. In the second step, geometries of all isomers are fully optimized using DFT. Finally, for the optimized structures, single point energies are calculated using the highest level of theory with or without a solvation model. Detailed account of the computational methods used to obtain the presented results can be found in SI.

Experimental isomer ratios were determined using low temperature NMR measurements. For mono-substituted bullvalenes **5b-f** the analysis is routine (Figure 2). In all cases, the computationally predicted ratios are consistent with the experiment.[24]



R = Me, **5b** calc: 1 : 69 : 28 : 2
exp: 0 : 58 : 42 : 0
R = *n*-Hex, **5c** calc: 0 : 76 : 21 : 4
exp: 0 : 68 : 25 : 7
R = CH_2OH, **5d** calc: 1 : 54 : 43 : 3
exp: 0 : 57 : 25 : 18
R = Bn, **5e** calc: 0 : 75 : 24 : 1
exp: 0 : 76 : 24 : 0
R = $SiMe_3$, **5f** calc: 0 : 95 : 5 : 1
exp: 0 : 93 : 7 : 0

Figure 1. Monosubstituted bullvalene network analysis and populated isomers.

For disubstituted bullvalenes **5g** and **5h**, the complexity of the mixtures and signal overlap necessitated the careful interpretation of 2D NMR experiments. The bis(methylene-hydroxy)bullvalene **5g** proved to be the most challenging analysis, which revealed a dynamic ensemble of six populated isomers (Figure 2a).[25] For this system, the isomer distribution is remarkably flat.[5f] In fact, all possible isomers that do not have a vicinal arrangement of substituents, or a substituent at the apex position, are found to be populated.

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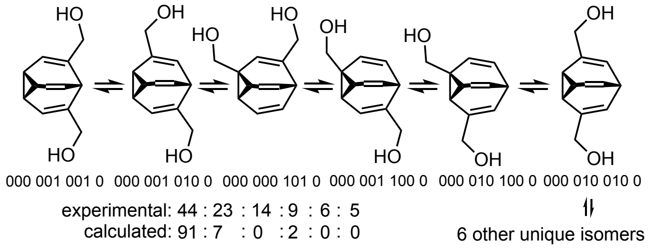
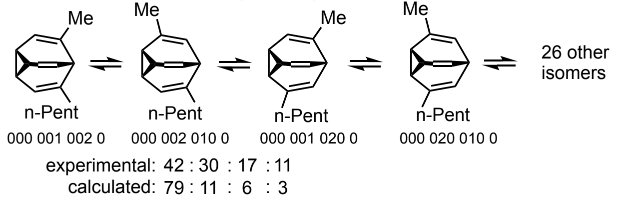
(a) populated isomers of bis(methylenehydroxy)bullvalene **5g**



(b) populated isomers of methyl(n-pentyl)bullvalene **5h**



(c) Reaction graph of methyl(n-pentyl)bullvalene **5h**

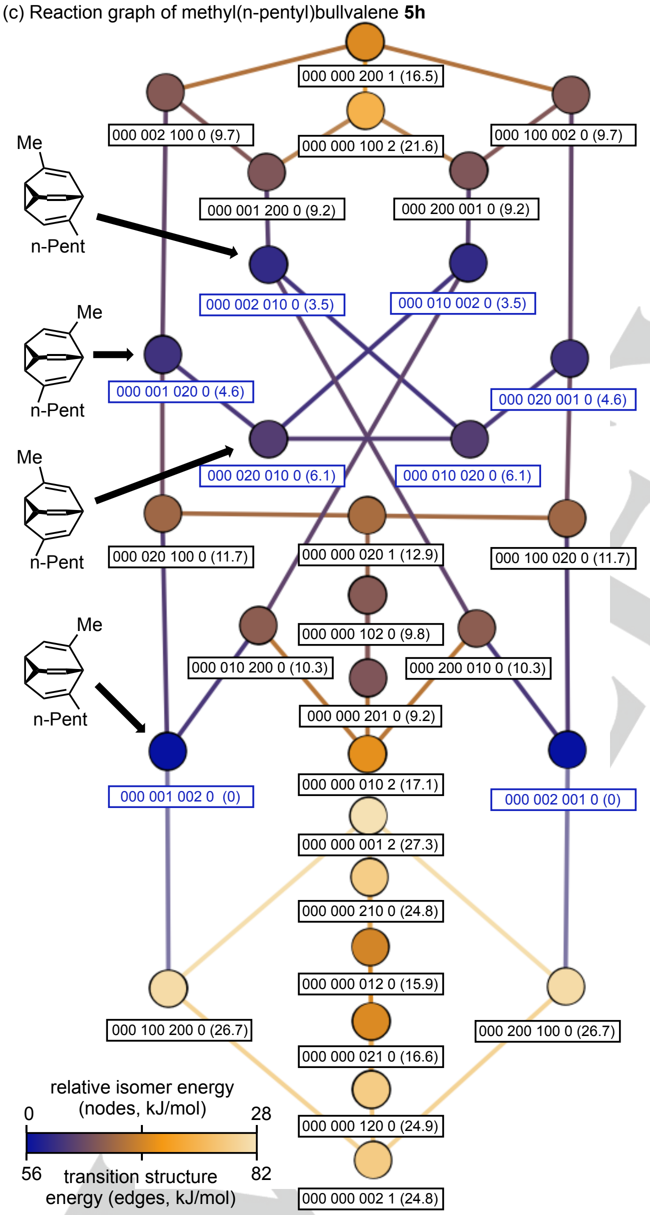


Figure 2. (a) experimental and computationally predicted populated isomers of bis(methylenehydroxy)bullvalene **5g**. (b) experimental and computationally predicted populated isomers of methyl(*n*-pentyl)bullvalene **5h**. (c) Reaction graph of **5h**. The nodes shaded blue comprises the populated isomers. A mirror plane of symmetry bisects the graph vertically, and relates the enantiomer pairs.

In the case of methyl(*n*-pentyl)bullvalene **5h**, the four possible isomers which retain the substituents connected to alkenes were found to be populated (Figure 2b). These experimental ratios are all consistent with a computational survey of isomer stability.

Our computational toolbox also allows for the generation of reaction graph diagrams. This is a convenient method to visualise the interconnectivity, and energy profile, of any given bullvalene network. An example is shown for bullvalene **5h** showing the 30 possible isomers (Figure 2c). Nodes represent isomers and edges transition structures. A vertical plane of symmetry bisects the diagram and relates enantiomers. This technique aids in highlighting the non-populated but low-lying isomers, as well as giving an overview of the kinetic parameters of rearrangement. In future, these features will become valuable in the analysis of bullvalene ensembles in response to external stimuli.

To conclude, this work provides a two-step synthesis of bullvalene itself, and substituted derivatives. This represents the shortest synthesis of any substituted bullvalenes, and the most practical preparation of the parent structure. Our network analysis algorithm allows for rapid assessment of the energy landscape and interconnections of any bullvalene isomer ensemble. DFT calculations predict the ratios of populated isomers in good agreement with experiment.

Acknowledgements

We gratefully acknowledge the New Zealand Royal Society (Marsden Fund No. 15-MAU-154). We gratefully thank Mr. Chris Blake and Ms. Eliza Tarcoveanu (Australian National University, Canberra) for assistance with NMR measurements. We acknowledge support from the project NESI00302 of NeSI high-performance computing facilities (NZ eScience Infrastructure) funded jointly by NeSI's collaborator institutions and the Ministry of Business, Innovation & Employment's Research Infrastructure programme.

Keywords: Valence isomerization • Sigmatropic rearrangement • Photochemistry • Cycloaddition • Density functional calculations

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[20] In fact, for 2 or more unique substituents, N_{sub}, the total numbers of isomers, N_{iso}, and interconnecting transition states, N_{TS}, follow the relations:

$$N_{iso} = \frac{1}{3}\frac{10!}{(10-N_{sub})!}\ ,\quad N_{TS} = \frac{1}{2}\frac{10!}{(10-N_{sub})!}.$$

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[24] For the disubstituted bullvalenes **5g** and **5h** our ratio of isomers was determined by a comparison of like ^{13}C signals and should be regarded as indicative rather than quantitative.

[25] This analysis included a range of high-resolution heteronuclear correlation experiments including HSQC-TOCSY, H2BC and HMBC, as well as a very high-resolution HSQC spectrum from which high-quality carbon-resolved 1D proton spectra of each isomer could be extracted and reconstructed. See the Supporting Information for details.

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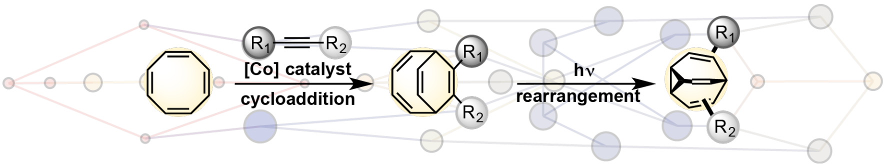

Shape-Shifters. A rapid two-step synthesis of substituted bullvalenes is reported. The method involves cobalt-catalysed [6+2] cycloaddition of alkynes to cyclooctatetraene, followed by photochemical rearrangement. The fluxional nature of these shape-shifting molecules is supported by DFT calculations and network analysis.

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Page No. – Page No.

Synthesis and Analysis of Substituted Bullvalenes

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