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Theoretical design of tetra(arenediyl)bis(allyl) derivatives as model compounds for Cope rearrangement transition states†‡

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Several systems formed by two allyl fragments linked by four arenediyl tethers have been studied through DFT calculations. A delocalised bis(allyl) system, similar to Cope rearrangement transition states, is preferred for derivatives bearing 5-membered ring tethers, as a result of the large strain in the related localised geometry.

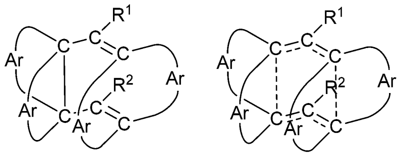
Despite the key role of transition states (TS's) in reaction mechanisms, very little data can be experimentally obtained for such structures. However, relevant structural information can instead be obtained from geometrically-constrained model compounds keeping the major features of the TS's for a number of reactions (such as proton[1] and hydride[2] transfer, S_N2,[3] 1,2-alkyl shift—by using non-classical carbocations—,[4] or phosphate transfer).[5] As an application, drugs can be designed on the basis of their similitude to the convenient TS geometries.[6]

Some Cope rearrangement TS model compounds (showing two allyl fragments bound through two partial C⋯C bonds) have been designed by annelation of semibullvalene,[7–10] barbaralane[7] and bis-allyl[11] frameworks through methylene,[8,11] ethylene[8,9] or oxydicarbonyl[7] tethering. Although some of such model compounds have been characterised through UV-vis[7,12] and IR[10] spectroscopies, no X-ray diffraction data have been reported for such species up to now. In this work I report the theoretical results on a bis(allyl) system tethered through four arenediyl fragments as a new strategy to design delocalised compounds as models for typical Cope rearrangement TS's.

All calculations were carried out by using the Gaussian09 suit[13] (see details in ESI‡). Geometries of all structures were obtained by using the restricted B3LYP (RB3LYP) method[14] with the 6-311+G(d) basis set because of the excellent results of this technique on the Cope rearrangement activation barriers of hexa-1,5-diene (theoretical: 33.7 kcal mol^{-1}; experimental: 33.3 kcal mol^{-1})[15] and semibullvalene (theoretical: 3.8 kcal mol^{-1}; experimental: 4.8 kcal mol^{-1}).[5] Unrestricted B3LYP (UB3LYP) calculations were not used for geometry optimisations because of the artifactual occurrence of an intermediate in the Cope rearrangement reaction of 2,5-dimethylidenehexanedinitrile at this level.[16] Nevertheless, broken-symmetry UB3LYP energies were calculated on RB3LYP/6-311+G(d) geometries to take into account the possible diradicaloid character of the studied structures.[17]

Calculations on tetra(benzene-1,2-diyl)bis(allyl) (Ar = benzene-1,2-diyl; $R^1 = R^2 = H$, Scheme 1) showed the occurrence of energy minima for a C_s-symmetric localised structure as well as a C_{2v}-symmetric delocalised framework, as a consequence of the destabilisation of the localised structure due to the large ring strain of two fused benzocyclobutane systems.[18] Interestingly, the delocalised structure is slightly preferred (by 1.9 kcal mol^{-1} in Gibbs free energy).

With the aim of designing a more stable delocalised structure, the introduction of different substituents on the central carbon atom on one or two allyl systems was considered (Table 1). Interestingly, relative Gibbs free energies show that delocalised structures are destabilised by all kinds of substituents, similarly to experimental results on activation barriers for Cope rearrangement reactions.[19] Delocalised structures are also destabilised by further tethers. For several systems, both localised and delocalised structures were identified as energy minima linked through a TS (see ESI‡), whereas delocalised structures showing relative Gibbs free energies larger than 1.0 kcal mol^{-1} were characterised as TS's.



Scheme 1 Localised (left) and delocalised (right) structures for bis(allyl) derivatives.

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‡ Electronic supplementary information (ESI) available: Gaussian09 full reference, theoretical procedure as well as selected properties of all studied structures. See DOI: 10.1039/c4ra16381h

Table 1 Relative Gibbs free energies for delocalised structures of substituted bis(allyl) derivatives (Ar = benzene-1,2-diyl) (kcal mol^{-1}, at 25 °C) as well as allyl–allyl distances (Å) for localised (bonded C–C and non-bonded terminal C/C) and delocalised (both C⋯C bond lengths) structures

R^1	R^2	ΔG^a	C–C distance	C/C distance	C⋯C distance
H	H	−1.9	1.788	2.447	2.294
F	H	−1.3	1.765	2.453	2.287
Me	H	−0.9	1.766	2.453	2.285
NO_2	H	−0.5	1.765	2.438	2.276
Cl	H	−0.5	1.761	2.446	2.277
F	F	−0.5	1.744	2.453	2.288
CN	H	−0.2	1.758	2.436	2.269
C≡CH	H	−0.2	1.730	2.446	2.273
Me	Me	0.7	1.750	2.453	2.293
NH_2	H	1.2^b	1.737	2.481	2.292
Cl	Cl	1.9^b	1.761	2.446	2.269
CN	CN	2.8^b	1.735	2.436	2.247
C≡CH	C≡CH	3.3^b	1.730	2.449	2.256
–COCH═CHCO–	—	0.7	1.745	2.433	2.252
–NHCONH–	—	1.4^b	1.747	2.418	2.237
Naphthalene-1,8-diyl	—	2.1^b	1.734	2.431	2.237
–COOCO–	—	2.2^b	1.733	2.410	2.217
Benzene-1,2-diyl	—	2.8^b	1.713	2.410	2.207
Phenanthrene-4,5-diyl	—	3.0^b	1.717	2.432	2.235

[a] Gibbs free energies calculated from UB3LYP/6-311+G(d)//RB3LYP/6-311+G(d) electronic energies and RB3LYP/6-311+G(d) thermal corrections. [b] Delocalised structure is a TS (showing one imaginary frequency).

The localised structure for the non-substituted compound shows a very long C_{sp^3}–C_{sp^3} bond (1.788 Å), significantly longer than that experimentally found for 9-*tert*-butyl-9,10-dewar anthracene (1.623 Å),[18] also bearing two fused benzocyclobutane systems. Such an increased bond length can be attributed to an incipient σ-aromaticity. Accordingly, the C_{sp^3}–C_{sp^3} bond shortening induced by all studied substituents on the localised framework can be attributed to a σ-aromaticity decrease due to the relative destabilisation of the delocalised structure.

All localised structures show similar non-bonded terminal allyl C/C distances (2.433–2.453 Å), excepting those bearing a further tether (2.410–2.453 Å) and the amino-derived framework (2.481 Å, due to the larger pyramidalisation of the terminal allyl carbon through NH_2-vinyl conjugation). On the other hand, C⋯C bond lengths of delocalised energy minima (2.252–2.294 Å range) are similar to that calculated for the boat Cope rearrangement TS for hexa-1,5-diene (2.249 Å, at the same theoretical level).

As a second tactic to find a stable delocalised structure, replacement of benzene-1,2-diyl radicals by other tethers was considered (Table 2).

A significant dependence of the delocalised structure stability on the arenediyl tether was found. Thus, the localised structure is preferred for the naphthalene-1,8-diyl derivative, whereas the delocalised structure is predilected for naphthalene-2,3-diyl and thiophene-3,4-diyl derivatives (localised and delocalised structures being linked through a TS in all cases, see ESI‡). Finally, the delocalised structure was the only energy minimum for pyrrole-3,4-diyl and furan-3,4-diyl derivatives.

The preference for the delocalised structure in 5-membered cycle derivatives can be attributed to the high strain introduced by the cyclobutane-heterocycle fusion in localised structures. Thus, junction C_{sp^2} bond angles (97.4° in the non-substituted benzene-1,2-diyl derivative) are significantly deformed relative to conventional sp^2 bond angles (120°), and even more in comparison with typical angles in non-strained 5-membered rings (C3–C4–H angles: thiophene, 124.3°; furan, 126.1°; pyrrole, 127.1°).[20]

A significant dependence of the S^2 expectation value was found for the UB3LYP wavefunction on the relative stability of the delocalised structure can be remarked: a pure singlet wavefunction for the napthalene-1,8-diyl derivative, a significant spin contamination (*ca.* 30% triplet contribution) for 6-membered ring tethered structures and a mixed spin-state (*ca.* 50 : 50 singlet–triplet) for 5-membered ring derived frameworks. Although the spin contamination in the singlet wavefunction is likely exaggerated by UB3LYP calculations (as inferred from singlet–triplet gap computations on acenes),[21] a further stabilisation for all delocalised structures (excepting those lacking spin-contamination) was found by considering the "pure singlet" UB3LYP wavefunction (calculated from $\langle S^2 \rangle$ values and energies for singlet and triplet states through the Kraka formula, see ESI‡).[22]

The decreasing trend of the singlet–triplet gap by increasing the structure strain (0.1 kcal mol^{-1} differences for pyrrole-3,4-diyl and furan-3,4-diyl derivatives) is analogous to that predicted for increasingly large acenes.[23] Continuing this analogy, the predicted low singlet–triplet gap on higher acenes has not prevented the experimental synthesis of nonacene.[24]

Allyl–allyl C–C bond length in localised structures is dependent on the strain involved in the cycloalkane–(het)arene fusion. Thus, the relatively short bond for the naphthalene-1,8-diyl

Table 2 Selected properties for delocalised structures of bis(allyl) derivatives ($R^1 = R^2 = H$) as well as allyl–allyl distances for localised (bonded C–C and non-bonded terminal C/C) and delocalised (both C···C bond lengths) structures

Ar	ΔG^a	$\langle S^2 \rangle^b$	Singlet–triplet gap[c]	C–C distance[d]	C/C distance[d]	C···C distance[d]
Naphthalene-1,8-diyl	6.5[e]	0.000	61.2	1.740	2.650	2.333
Benzene-1,2-diyl	−1.9	0.539	11.4	1.788	2.447	2.294
Naphthalene-2,3-diyl	−3.3	0.613	9.6	1.819	2.454	2.326
Thiophene-3,4-diyl	−14.0	0.988	1.6	1.876	2.526	2.441
Pyrrole-3,4-diyl	—	1.063	0.1	—[f]	—[f]	2.500
Furan-3,4-diyl	—	1.070	0.1	—[f]	—[f]	2.545

[a] UB3LYP/6-311+G(d)//RB3LYP/6-311+G(d) calculations. Relative Gibbs free energies (at 25 °C, kcal mol^{-1}). [b] Singlet-state wavefunction. [c] Relative electronic energies (kcal mol^{-1}). [d] In Å. [e] Delocalised structure is a TS. [f] Localised structure could not be obtained.

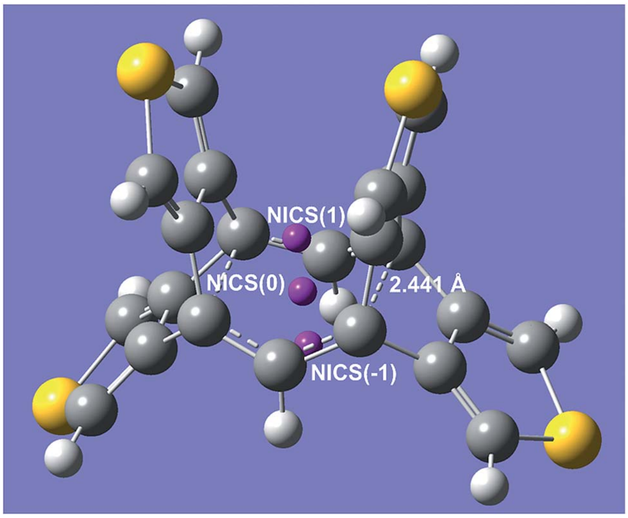

Fig. 1 RB3LYP/6-311+G(d) structure of delocalised tetra(thiophene-3,4-diyl)bis(allyl).

derivative can be attributed to the participation of a 5-membered (instead of 4-membered) ring. Instead, the ultralong C–C bond (1.876 Å) found for the thiophene derivative can be attributed to the high strain in 5-membered ring derivatives. Finally, delocalised structures could only be characterised as energy minima for pyrrole- and furan-derivatives.

Allyl–allyl terminal C/C distances of *ca.* 2.45 Å are found for benzene-1,2-diyl and naphthalene-2,3-diyl derivatives, whereas larger values are found for naphthalene-1,8-diyl (2.650 Å, due to the large separation between C1 and C8 atoms) and thiophene-3,4-diyl (2.526 Å, high ring strain) compounds.

A new family of compounds bearing ultralong C–C bonds[25] can thus be formed due to the very long allyl–allyl distances found in delocalised structures (up to 2.545 Å), close to the C···C lengths found in Cope rearrangement TS's for some substituted hexadienes (hexa-1,5-diene-1,3,4,6-tetracarbonitrile, 2.467 Å;[16] 1,3,4,6-tetraphenylhexa-1,5-diene, 2.649 Å, according to RB3LYP/6-31G(d) calculations).[26]

Aromaticity properties of σ-delocalised rings (illustrated for the thiophene-3,4-diyl derivative in Fig. 1) were confirmed by Nucleus-Independent Chemical Shifts (NICS)[27] calculations on the UB3LYP wavefunction (see ESI‡) at the corresponding ring centre [NICS(0)] (typically in the −7.8/−4.9 ppm range, though more negative values are found in structures bearing a further tether, whereas 5-membered ring derivatives show −4.7/−3.4 ppm values, presumably due to the larger size of the aromatic ring),[28] consistently with results on Cope rearrangement TS's.[29] Similar qualitative conclusions can be drawn from NICS values for points placed at 1.0 Å distances from the ring centre towards the concave [NICS(1)] or convex [NICS(−1)] ring sides (though very low negative values are obtained for the former ones). On the other hand, the erratic behaviour found for the magnetic susceptibility variations on localised/delocalised rings (see ESI‡) may be attributed to the interference of the other aromatic rings.

Replacement of one or both allyl CH groups by nitrogen atoms in such bis(allyl) systems allows obtaining aza-Cope rearrangement TS models. Thus, a preference for the delocalised structure (by 17.1 kcal mol^{-1} in Gibbs free energy) has been found for the diaza-derivative bearing four furan-3,4-diyl tethers.

Conclusions

The theoretical study on tetra(arenediyl)bis(allyl) compounds indicate that several derivatives involving 5-membered rings can occur as energy minima bearing two allyl fragments bound by two equivalent partial C···C bonds. A new theoretical Cope rearrangement-based challenge for experimental chemists, analogously to those reported for σ-polyacenes[30] or halogen-stabilised delocalised TS models,[31] is thus outlined. I encourage experimental chemists to synthesise these new models for Cope rearrangement TS's. Although some difficulties might be found in such a synthesis, some tetra(arenediyl) derivatives of other frameworks [such as bis(ethylene)[32] or bis(cyclobutane)][33] have already been characterised by X-ray diffraction analysis.

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