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Clear Cut Example of Preference for a 6-Membered Ring Radical Cyclisation over the Homologous 5-Membered Ring Radical Cyclisation. The Reaction of 5-[Bromoalkyl]-5H-Dibenzo[*a,d*]cycloheptenes with Bu_3SnH

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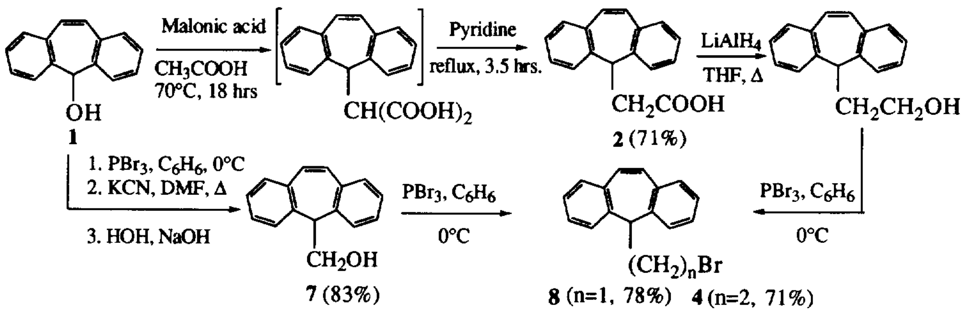
Abstract: The radical cyclisation reaction of the 5-[2-bromo-ethyl]-5H-dibenzo[*a,d*]cycloheptene **4** with Bu_3SnH and AIBN led to the cyclised hydrocarbon **5** as major product, whereas the bromo-derivative **8** with Bu_3SnH and AIBN gave only the straight chain product **9**. An explanation based on the conformational rigidity of dibenzo[*a,d*]cycloheptene system calculated by AM1 method is proposed.

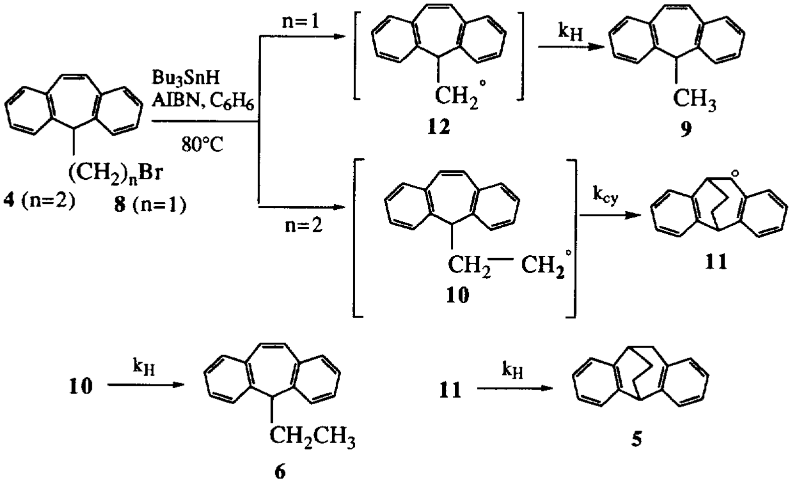
Radical cyclisations leading to 6-membered rings are less general than cyclizations affording 5-membered rings: 5-hexenyl radicals generally lead to the 5-exo cyclisation products.[1] Important exceptions however exist and the 6-endo cyclisation can be the major pathway.[1a,2] With the 6-heptenyl radicals, the formation of the methylcycloalkanes (6-exo mode) is promoted, but such radicals are subject to intramolecular 1,5 hydrogen atom transfer.[1,3] Although both 5- and 6-exo trig cyclisations are predicted by Baldwin's rules,[4] it is well-established that the 6-exo trig cyclisation is significantly slower than its lower homologue.[5] As a consequence, the 5-hexenyl radical is probably the most popular radical clock used as mechanistic tool or kinetic standard.[6] Nevertheless, Srikrishna and Hemamalini pointed out that the 6-exo cyclisation could compete effectively the 5-exo reaction when it yields bridged systems: they obtained a regioselective construction of chiral bicyclo [2.2.2] octanes via 6-exo trig radical cyclisation reactions.[7] No data are available in the field of dibenzocyclic compounds. The rigidity of dibenzocyclic system, generally prevents their involvement in intramolecular radical cyclisations.[8] We therefore studied the dibenzo[*a,d*]cycloheptene suitably substituted to yield, through radical cyclisations either 5- or 6-exo ring closures. The present results suggest that one of these molecules can be used as a "radical clock" leading to a 6-membered ring.

We prepared the alkyl bromo-derivatives **4** and **8**[9,10] (Scheme 1) and tested these compounds as free radical probes, in the reaction with tri-n-butyltin hydride and 2-2'-azobisisobutyronitrile.[11]



Scheme 1

The bromo derivatives **4** and **8** were treated with tri-n-butyltin hydride and a free-radical initiator such as AIBN (Scheme 2).



Scheme 2.

A typical procedure is exemplified by the reaction of **4**: to a benzene solution (33.4 ml) of bromo derivative **4** (100 mg, 3.34 10^{-4} mol), AIBN (5 mg) and Bu_3SnH (0.194 g, 6.67 10^{-4} mol) were added successively at 65°C; the reaction mixture was kept at 80°C for 18-24 hrs. A saturated aqueous solution KF (10 ml) was added to the mixture and stirred a few minutes.[12] After filtration, the mixture was extracted with ether and washed with water and brine, dried, and concentrated. The obtained crude oil was investigated by ^1H and ^{13}C-NMR and GC chromatography. The studies pointed out the presence of two compounds **5** and **6**, in different distribution depending on reaction conditions. The pure majoritary **5** was obtained by crystallisation of crude oil from ethanol. The procedure applied to **8** led only to the uncyclised hydrocarbon **9**.[13]

The radical chain mechanism to obtain **5** is presented in Scheme 2. The radical **10**, generated in the first propagation step, undergoes unimolecular ring-closure by the 6-exo mode (**4** -- **5**), to give **11**, in competition with intermolecular hydrogen transfer from Bu_3SnH (**4** -- **6**).The high rate of cyclisation of **10** may be due both to benzylic radical stabilisation and to favorable conformational factors. In order to explain these results, we attempted to determine the distance between reaction sites for both radicals (**10** and **12**) obtained from bromine derivatives **4** and **8**, using the semi-empirical method AM1.[14,15] Interatomic distances between reaction sites determinated by AM1 method were respectively 2.97 Å and 4.08 Å for radical **10** and **12**. Thus, only the radical **10** displays a distance similar to that required in the transition state of cyclisation (2.4 Å).[5d,e]

Application of the usual steady-state theory shows that when tri-n-butyltin hydride is present in large excess, $k_{cy} = k_H [Bu_3SnH]_o[RC]/[RH]$ (eq. 1), where [RC] and [RH] hold for the final concentrations of cyclised and uncyclised products respectively, $[Bu_3SnH]_o$ is the initial concentration in Bu_3SnH and k_{cy} the rate constant for cyclisation.[6b] Thus, using increasing amounts of Bu_3SnH it was possible to estimate the rate constant for cyclisation of **4** (Table 1). Rate constant for the ring-closure ($k^{80^\circ C}_{cy}$) was obtained using eq. 1, $k^{80^\circ C}_{cy} = 5\ 10^6\ s^{-1}$, where $k^{80^\circ C}_H$ was estimated at $6.1\ 10^6\ M^{-1}s^{-1}$. This value was obtained from Arrhenius parameters previously reported by Ingold and co-workers,[16] for the reaction of ethyl radical with Bu_3SnH, with the reasonable assumption that the relevant part of the structure of our radical is similar enough with an ethyl radical. [12]

Table 1. Data for the Cyclisation of Dibenzo[*a,d*]cycloheptene Radical

Exps	$[Bu_3SnH]_o/[\mathbf{4}]$ ($[Bu_3SnH]_o$)	**5***	**6***
1	2 (0.01 Ml^{-1})	94	6
2	5 (0.05)	87	13
3	10 (0.098)	84	16
4	15 (0.30)	80	20
5	20 (0.39)	75	25

* Percent yields of hydrocarbons determined by capillary GC and by ^{1}H-NMR spectroscopy.

Thus, the dibenzo[*a,d*]cycloheptene system **4** cyclises in a 6-exo mode with a larger rate constant than the value reported for the 5-exo cyclisation reactions.[6c]

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