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A Facile, General Route to Adamantanophanes. Synthesis and Conformational Behavior of [4.4](1,3)Adamantanophan-*trans,trans*-1,8-diene

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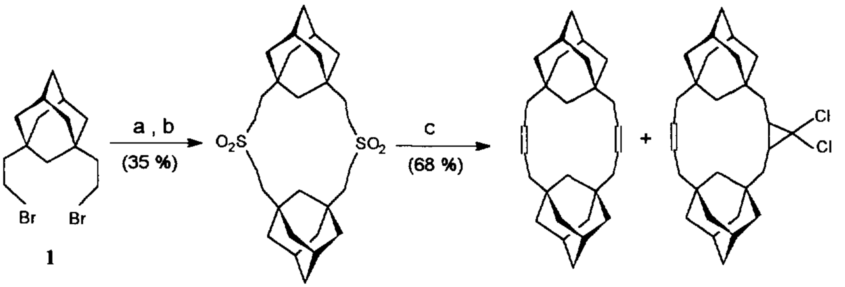
Abstract: Ramber-Bäcklund rearrangement of disulfone **2** leads to the ring-contracted 4,6:11,13-di(1,3-adamantano)cyclotetradeca-*trans,trans*-1,8-diene (**3a**) along with 4,6:11,13-di(1,3-adamantano)cyclotetradeca-*cis,trans*-1,8-diene (**3b**) and 4,6:12,14-di(1,3-adamantano)-8,10-dehydro-9,9-dichlorocyclopentadeca-1-diene (**4**) as a minor products. The ring inversion of **3a** can most reasonably be interpreted in terms of equilibrium process between two conformers with effective C_{2h} symmetry. Copyright © 1996 Elsevier Science Ltd

The syntheses and chemistry of cyclophanes has attracted considerable attention in recent years because of their unusual structures, conformational properties, and ability to act as host to both neutral molecules and ionic species.[1]

Over the years, many methods have evolved for the conversion of dithiacyclophanes to cyclophanes with unsaturated bridges. In general, ring contraction of dithiacyclophanes can be achieved conveniently *via* the Stevens rearrangement,[2] or the Wittig rearrangement[3] followed by Hofmann elimination. Conversion of variety of disulfides to the corresponding cyclophane-dienes proceeds very well (90% yield) by Hofmann elimination in the metacyclophane series but often less well in the case of other cyclophane.[4] Alternative is a modified Stevens rearrangement which uses benzyne generated *in situ* to give phenyl sulfides, oxidation of which followed by pyrolytic elimination of phenylsulfinic acid then provides the cyclophane-dienes.[5] On the other hand, synthetic methodologies leading to completely aliphatic adamantane-containing phane molecules[6] are rather scarce. To the best of our knowledge the only example published to date includes Vögtle's recent synthesis of [2.2.2](1,3)adamantanophane.[7]

As part of our continuing interest in effective metodology applicable for the syntheses of various types of aliphanes, we wish to report a new approach to [m.n]adamantanophanes as demonstrated by the synthesis of [4.4](1,3)adamantanophandienes (**3a** and **3b**). Our strategy, summarized in **Scheme 1,** makes use of intermolecular sulfur-based cyclocoupling[8] in conjunction with Meyer's modification[9] of Ramberg-Bäcklund reaction as the main reaction. Intermolecular cyclization of 1,3-bis(2-bromoethyl)adamantane (**1**) with thioacetamide under previously developed conditions gave a macrocyclic thioether[10] which was subsequently oxidized with 2.5 equiv. of *m*-CPBA to give disulfone **2** in 95 % yield.[11] Ramberg-Bäcklund rearrangement of disulfone **2** afforded a mixture of ring-contracted products **3a**, **3b** and **4** , from which **3a** was isolated as the major product.[12] Minor products **3b** and **4** were isolated in 10 % and 8 % yield, respectively, and characterized by spectroscopic means.[14] Confirmation of the overall C_{2h} molecular symmetry possessed by structure **3a** was provided by the observation of (i) 9 resonances in the broadband-decoupled ^{13}C NMR spectrum (-50^{0}C), and (ii) separate, well-resolved signals in the ^{1}H NMR spectrum for 9 sets of heterotopic hydrogen atoms. Final unambigous identification of **3a** was achieved by its x-ray crystallographic analysis.[15]

Scheme 1.



1 2 3a + 3b 4

Reagents and conditions: a) thioacetamide, KOH, EtOH/C_6H_6, reflux; b) *m*-CPBA, CH_2Cl_2, rt; c) KOH, CCl_4,, t-BuOH, 50^{0}C

In the solid state, **3a** displays an approximately rectangular shape with antiplanar torsions along its sides and with gauche and anticlinal torsions at each corner. The crystal structure of **3a** has a center of symmetry and hence at least C_i symmetry. As a consequence, it shows a slightly distorted chair-like conformation. This chair-like conformation is calculated, by means of molecular mechanics,[16] to have the lowest energy (**Figure 1.**). Moreover, these results confirm the identification of **3a** as 4,6:11,13-di(1,3-adamantano)cyclotetradeca-*trans,trans*-1,8-diene and, in particular, rule out the possibility of *trans,trans*-conformer with crossed double bonds.

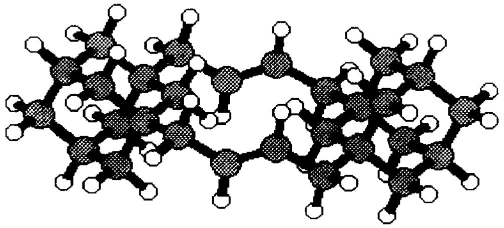


Figure 1. MM2-optimized geometry of lowest energy conformation of **3a**

The conformational behavior of diene **3a** in solution was analyzed by means of dynamic NMR spectroscopy, which indicates that **3a** is conformationally mobile. At low temperatures, ring inversion in **3a** becomes slow on the NMR time scale, whereas at room temperature the molecule rapidly equilibrates between two conformers with effective C_{2h} symmetry (**Figure 2**). In order to determine the Gibbs energy of activation ($\Delta G_c^{\neq}$) at the coalescence temperature (T_c), a series of variable temperature ^{13}C and ^{1}H NMR measurements were carried out. ^{13}C NMR spectra of **3a** were obtained over the temperature range of -50 to 55^{0}C. At room temperature, the spectrum showed six carbon resonances. Substantial line broading[17] of the C-7/8 and C-5/6 was already visible at room temperature (22^{0}C). As the temperature was lowered, changes appeared mainly in the aliphatic region (**Table 1**.). The olefinic resonance remained practicaly unchanged with only little broadening, which could be due to a decrease in resolution as gradual precipitation of **3a** was observed at the low-temperature limit. On the other hand, the broad peaks assigned to the methyne and methylene carbons (C-7/8 and C-5/6, respectively) become well-resolved doublets of equal intensity, indicating a slow rate of exchange between the conformers. Analyses of the temperature-dependent ^{13}C NMR spectra afforded the kinetic and termodynamic data listed in **Table 2.**[18]

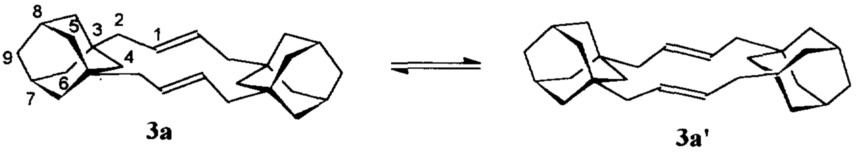


Figure 2. Equilbrium between two conformers of diene **3a**

Table 1. ^{13}C NMR Spectroscopic Data of **3a** at Different Temperatures[a]

TEMP (°C)	**C-1** (d, 4C)	**C-2** (t, 4C)	**C-3** (s, 4C)	**C-4** (t, 2C)	**C-5/6** (t, 4C; t, 4C)	**C-7/8** (d, 2C; d, 2C)	**C-9** (t , 2C)
-50	128.68	47.16	33.33	45.51	44.26 ; 40.01	29.26 ; 28.49	36.66
-10	128.71	47.34	33.49	45.78	44.55 ; 40.29	29.52;28.78	36.89
0	128.67	47.34	33.49	45.81	-	-	36.92
22	128.75	47.46	33.62	45.98	-	29.36	37.07
55	128.79	47.55	33.75	46.15	42.82	29.59	37.22

[a] All spectra were recorded on a Varian Gemini 300 spectrometer with Me_4Si as internal standard. The spectra of **3a** were obtained in $CDCl_3$. Chemical shifts are reported in parts per million (δ).

Table 2. Temperature Dependent ^{13}C NMR Data and Kinetic and Thermodinamic Parameters for **3a**

Carbon atoms	T_c / °C[a]	$\Delta\nu$ / Hz[b]	k_c / s^{-1}[c]	$\Delta G_c^{\neq}$[d]
C-5/6	35	320.6	712.2	14.0
C-7/8	22	58.0	128.8	14.4

[a] Temperatures are accurate to within 1°C. [b] Chemical shift difference between magnetically uneqivalent carbon atoms was determined at -50 °C. [c] Exchange rate constant at coalescence temperature. [d] $\Delta\Delta G_c^{\neq} = \pm 1$ kcal mol^{-1}.

The process detected in the dynamic ^{13}C NMR spectra also causes line-shape changes in the ^{1}H NMR spectra. At room temperature and above, only four different types of methylene protons and two types of methyne protons are observed. Below 10 °C the spectrum undergoes continuous and complex changes down to about -30 °C. The most noteworty feature of the spectrum below -30 °C is the presence of an unusually high-field doublet at $\delta = 0.61$ ppm which we assigned to two of the four protons at C-4 which are strongly shielded as a result of being situated within the field region of a double bond.[13,20]

Although NMR data have provided quantitative data on these conformations, the possible pathways for the conformational transitions as well as transition state for the ring inversion are unknown. We suspect that there is a complex sequence of several conformers. Work along these lines is in progress.

In summary, this synthetic approach provides a straightforward entry to various [m.n.]adamantanophanes with the readily available 1,3-bis(2-bromoethyl)adamantane as the starting material. The reactions involve neither expensive reagents nor complicated operations. Several variations on this basic idea to produce conceptually similar [m.n.]aliphane molecules are under intensive exploration.

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11. All new compounds gave spectroscopic data in agreement with the assigned structures. Spectroscopic data of **2**: m. p. > 350°C; IR (KBr) ν 2895, 2840, 1295, 1160, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.04-2.68 (m, 8H), 2.14-1.89 (m, 4H), 1.66-1.17 (m, 28H), 0.97(s, 4H); ^{13}C NMR ($CDCl_3$) δ 44.60 (t, 4C), 44.38 (t, 2C), 41.47 (t, 8C), 37.59 (t, 4C), 35,73 (t, 2C), 32.51 (s, 4C), 28.26 (d, 4C); Anal. Calcd. for $C_{28}H_{44}S_2O_4$ (508.76): C, 66.09; H, 8.72 % ; Found: C, 66.16; H, 8.75 %.
12. The major product **3a** was isolated from the mixture by column chromatography on silica gel using 0 → 40% of CH_2Cl_2 in pentane, followed by column chromatography on Al_2O_3 (activity I) treated with 10% of $AgNO_3$ using pentane as the eluent.[13]
13. Spectroscopic data of **3a** (numbering shown in formula): m. p. 212-214°C; IR (KBr) ν 3020, 1630, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$, -50°C) δ 5.45-5.30 (m, 4H, H-1), 2.04-1.96 (m, 4H, H-5a), 1.95-1.87 (AB, 4H, H-2a), 1.69-1.63 (AB, 4H, H-2b), 1.62-1.57 (m, 4H, H-9), 1.60-1.54 (m, 4H, H-7/8), 1.49-1.40 (AB, 4H, H-6a and 2H, H-4a) 1.34-1.21 (AB, 4H, H-5b and 4H, H-6b), 0.61 (d, J=12Hz, 2H, H-4b); Anal. calcd. for $C_{28}H_{40}$ (376.60): C, 89.29; H, 10.71 %, Found: C, 89.09, H, 10.88 %.
14. Spectroscopic data of **3b**: IR (KBr) ν 3010, 1630, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.60-5.47 (m, 2H), 5.40-5.25 (m, 2H), 2.12-1.16 (m, 34H),1.07-0.94 (m, 1H), 0.70-0.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ129.19, 129.05, 127.48, 127.12, 48.05, 47.97, 47.50, 47.19, 45.21, 45.13, 45.02, 44.97, 44.62, 44.46, 41.58, 41.21(2C), 40.08, 39.61, 37.27, 34.85, 34.51, 33.95, 33.70, 30.03, 29.91, 29.79, 29.29. (**4**): IR (KBr) ν 3020, 1625, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.50-5.35 (m, 2H), 2.66 (d, 2H), 2.21-1.20 (m, 32H), 0.98-0,80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 128.72 (d), 58.12 (d), 47.43 (t), 46.79 (t), 46.23 (t), 44.63 (t), 44.54 (t), 40,61 (t), 40.51 (t), 36.79 (t), 33.52 (s), 32.61 (s), 29.59 (s), 29.28 (d), 28.74 (d).
15. Crystals of diene **3a** are monoclinic and belong to the space group C2/c: a = 14.119 (3) Å, b = 12.022 (1) Å, c = 12.826 (1) Å, β = 97.72 (1) °, z = 4. The details of the X-ray structure of **3a** will be published separately : Mlinarić-Majerski, K., Pavlović, D.; Milinković, V.; Kojić-Prodić, B., in preparation..
16. Molecular mechanics calculations (MM2) gave a strain energy of 23.90 kcal/mol for **3a** and 27.24 kcal/mol for **3b**. The program used was written and parametrized by N. L. Allinger and Y. H. Yuh (University of Georgia, Athens, GA, (1980). For strain energies of other cyclophanes see Bickelhaupt, F. *Pur. Appl. Chem.* **1990**, *62*, 373.
17. Carefull examination of spectra reveals the presence of two very broad peaks (C-5/6), which are hardly discernible from the base line.
18. In the ^{13}C NMR studies rate constant (k_c) of the observed conformational interconversion at T_c was calculated using approximate Gutowsky-Holm equation, whereas the Gibbs free energy of activation ($\Delta G_c^{\neq}$) at coalescence was estimated using the Eyring equation.[19]
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