Synthesis of a Tetraazido-Substituted 2-Tetrazene from 1,5-Cyclooctadiene and Iodine Azide

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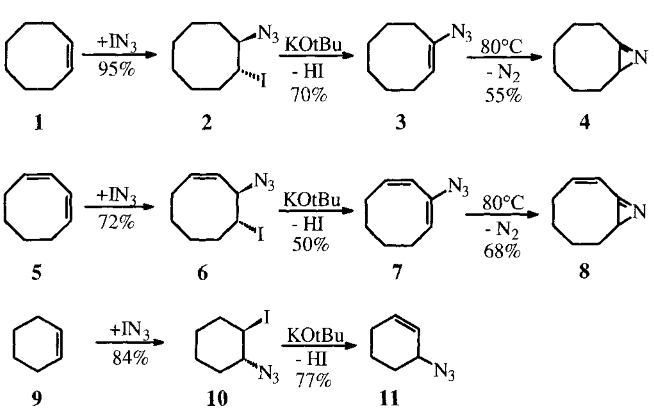
In contrast to the addition of iodine azide to cyclooctene (**1**) or 1,3-cyclooctadiene (**5**), its reaction with 1,5-cyclooctadiene (**12**) leads mainly to the surprisingly stable tetraazido-substituted 2-tetrazene **14**. The structure of this was established by ^{15}N-NMR studies and an X-ray structural analysis. Treatment of **14** with hydrochloric acid yields the diazido-substituted 9-azabicyclo[3.3.1]nonane **20**.

In the course of our studies concerning the formation of bis(2*H*-azirines) for possible use in repetitive 1,3-dipolar cycloaddition reactions[1], we reinvestigated a synthetic route developed by Hassner and Fowler in the 1960s[2]. They described the generation of 2*H*-azirines starting from olefins, by the initial *trans*-addition of iodine azide generated in situ[3]. The adducts can easily be transformed to vinyl azides by treatment with bases. The vinyl azides lose nitrogen at elevated temperatures or on irradiation and cyclize to form the desired products[4]. Starting from cyclooctene (**1**) the synthetic sequence led, via the azides **2** and **3**, to the bicyclic azirine **4**. An analogous process applied to 1,3-cyclooctadiene (**5**) yielded, via **6** and **7**, the related azirine **8**. A remarkable selectivity can be observed for the addition of iodine azide to the conjugated diene **5** as well as for the dehydroiodination. The originally assumed *trans* [(*Z*)] configuration of the azidocycloalkenes[2] could not be established, but the tendency to undergo *anti* elimination is undoubtedly present and in the 6-membered ring series this leads to the reaction sequence **9**→**10**→**11**. Of course, the resulting allyl azide (**11**) (Scheme 1) is not suitable for the formation of an azirine. The addition of iodine azide to bicyclic olefins can also lead to rearrangement products that are not capable of azirine formation[3,4].

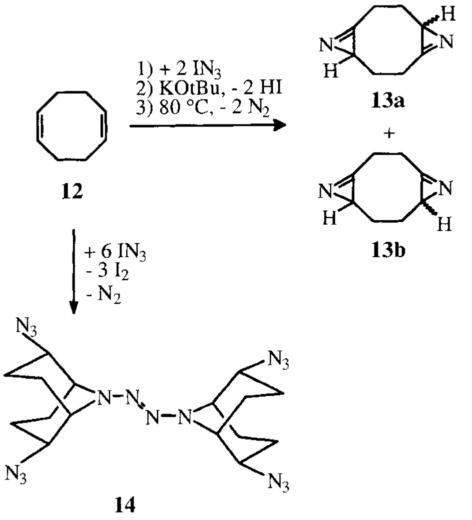
We characterized the structures **2**–**4**, **6**–**8**, **10** and **11** by ^{1}H- and ^{13}C-NMR spectroscopy. In 1992 Mattay and Müller[5] reported the synthesis of the isomeric bisazirines **13a,b** from 1,5-cyclooctadiene (COD) **12** by the reaction sequence shown in Scheme 2. The attractive bifunctional molecules **13a,b** were then used as "krypto-1,3-dipoles" in [3 + 2] cycloadditions under photoinduced electron-transfer (PET) conditions, yielding pyrrolophanes[5].

Applying the Hassner-Fowler method to **12** we found that the main product of the reaction was the tetraazido-substituted 2-tetrazene **14**, which was already formed in the first step. The yield could be raised to 68% by using a high excess of iodine azide (see the Experimental Section).

Scheme 1



Scheme 2



Elemental analysis of this unexpected product with the empirical formula $C_{16}H_{24}N_{16}$ revealed a nitrogen content of

51%. In spite of the four azido groups the substance shows an exceptional thermal stability and melts at 110 °C. A slow decomposition with evolution of nitrogen starts above 168 °C. The C_2 symmetry of the total structure and the "local symmetry" of the bicycles are evidenced by the simplicity of the NMR spectrum. The four signals in the ^{13}C-NMR spectrum were assigned to the CH_2 groups ($\delta = 21.1$, 26.4) and the CH groups ($\delta = 58.6$, $C-N_3$ and $\delta = 52.3$, $C-N$) on the basis of selective frequency decoupling (SFD) experiments. Some of these signals are slightly split into two peaks (at 100 MHz) because there is a local symmetry operation of the bicycles, which involves a fast nitrogen inversion and a fast rotation around the C_2 axis through the nitrogen and the centre of the bicycle (see the Experimental Section). The IR spectra are dominated by the characteristic strong absorption band of the azido group at 2100 cm^{-1}. The unsubstituted compound was synthesized by oxidation of 9-amino-9-azabicyclo[3.3.1]nonane[6].

2-Tetrazenes were first obtained by E. Fischer in 1877[7]. They are usually prepared by oxidation of 1,1-disubstituted hydrazines with lead tetraacetate or by thermal decomposition of the sodium salts of dialkyl benzenesulfonylhydrazides[8]. In the present case, the generation of **14** should start with the addition of iodine azide to the olefinic double bonds of COD **12**, giving the four possible isomers **15a–d**. Under the conditions applied these adducts seem to be unstable and split off hydrogen iodide, which can form hydrazoic acid with excess iodine azide present in acetonitrile solution. After addition of HN_3 to the vinylazides **16a,b**, an intermediate triazide **17** with a configuration similar to that found in the product has to be assumed. (Instead of the elimination-addition process **15**→**17** one can also assume substitution of the iodo by an azido group[9].) Nevertheless, the stereoselectivity in the formation of **17** and **14** has to be recognized. We suppose that the intermediate **17** undergoes a transannular reaction typical for medium-sized rings, with homolytic cleavage of the weak C–I bond to form the radical **18**, which loses a nitrogen atom to give the radical **19**. Combination of **18** and **19** leads to the 2-tetrazene **14** (Scheme 3).

An X-ray analysis[10] was performed on a single crystal of **14** isolated from a DMSO solution that was slowly enriched with light petroleum ether. The crystal structure clearly shows the (*E*) configuration of the NN double bond as well as the C_2 symmetry of the molecule with equatorial azido substituents. In the crystal the molecules are found in layers. The azido groups possess a slight distortion of 5–10° from the 180° angle (Figure 1). The distances for the single and double NN bonds of the tetrazene unit are in the range expected for aliphatic substituted 2-tetrazenes[11]. Selected bond lengths and angles are summarized in the text of Figure 1.

When a solution of the 2-tetrazene **14** in chloroform was treated with concentrated hydrochloric acid, evolution of nitrogen was observed. After stirring for 5 h at ambient temperature the reaction was complete. Separation of the layers and workup of the chloroform phase led to 2,8-diazido-9-azabicyclo[3.3.1]nonane (**20**). The azido groups re-

Scheme 3

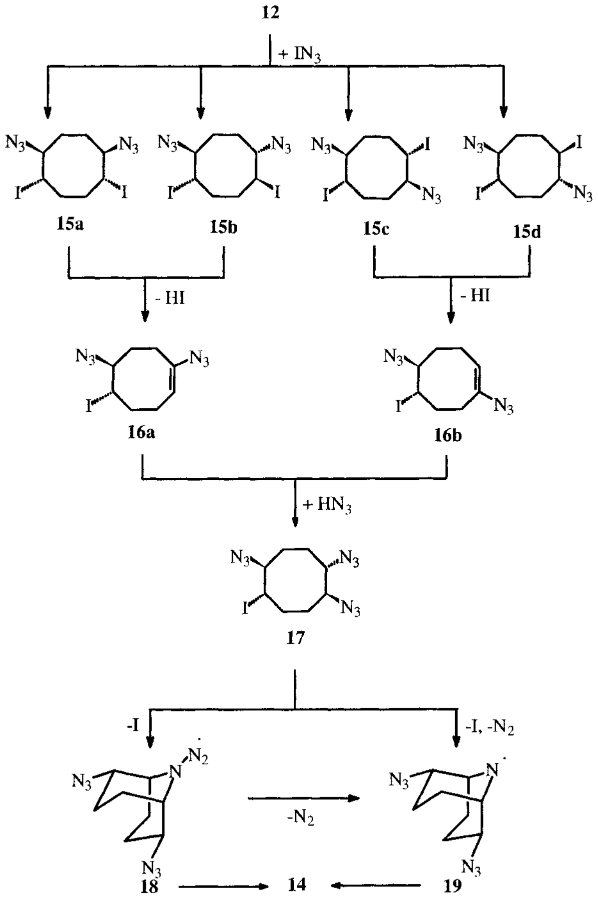
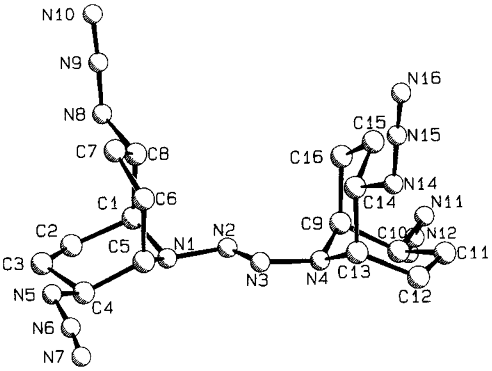


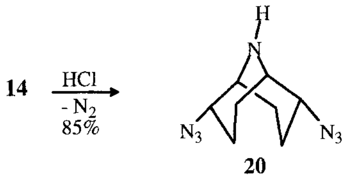
Figure 1. Crystal structure (PLUTO 78 plot) of the 2-tetrazene **14**[a]



[a] Bond lengths and bond angles are in the expected range. The central tetrazene unit has the following values: N(1)–N(2) 1.390(3) Å, N(2)–N(3) 1.248(3) Å, N(1)–N(2)–N(3) 114.4(2)°; the azido groups are slightly bent: N(5)–N(6)–N(7) 170.8(3)°, N(8)–N(9)–N(10) 175.2(5)°, and have the following bond lengths: N(5)–N(6) 1.216(4) Å, N(6)–N(7) 1.127(4) Å, N(8)–N(9) 1.210(4) Å, N(9)–N(10) 1.138(4) Å.

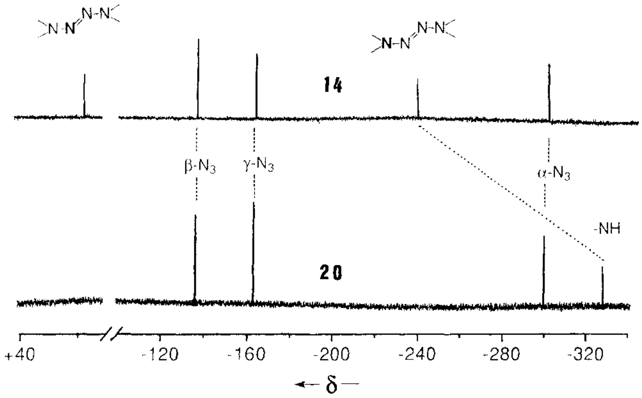
mained untouched whereas the tetrazene function was cleaved.

Scheme 4



Because ^{1}H- and ^{13}C-NMR spectra of **20** are similar to those found for the 2-tetrazene **14**, we also performed ^{15}N-NMR measurements to determine the structure of compound **20**. The signals for the α-, β- and γ-nitrogen atoms of the azido groups have typical δ values in **14** as well as in **20**. In the case of the 2-tetrazene **14** two additional signals can be assigned to the N_4 unit, one with $\delta = 15.1$, belonging to the azo group, and the other one at $\delta = -236.8$, belonging to the amine nitrogen. Due to the elimination of molecular nitrogen in the reaction **14**→**20** only the amine nitrogen is preserved in **20**; however its signal is strongly shifted to high field, at $\delta = -329.4$ (Figure 2). The fast nitrogen inversion provokes a C_2 symmetry. In contrast to **14** this is a symmetry element for the whole molecule **20**.

Figure 2. ^{15}N-NMR spectra of the tetrazene **14** and its cleavage product **20** (δ values in $CDCl_3$ related to nitromethane as internal standard)



The bicyclus **20** belongs to a very interesting class of compounds applicable in photoaffinity labeling experiments[12]. Due to the spherical shape of the small molecule combined with the presence of *two* photolabile azido groups, **20** could be a very useful reagent for this purpose. The prospect of creating model compounds for the bonding of substrate molecules to **20** is under current investigation.

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Experimental Section

Solvents were purified in the usual way. The light petroleum ether used had a boiling range of 40–70°C. – IR: Beckman Acculab 4, KBr pellets or films between NaCl plates. – ^{1}H-, ^{13}C- and ^{15}N-NMR: Bruker AC 200 or AM 400, $CDCl_3$ as solvent (the ^{13}C signals were assigned on the basis of spin-echo and DEPT spectra, and the ^{15}N signals by inverse-gated SFD experiments). – MS: Varian MAT CH 7A (EI, ionization energy 70 eV) and Finnigan MAT 95 (FD, accelerating voltage 5 kV, heating rate 10 mA/min). – M.p.: Büchi melting point apparatus, uncorrected values. – Elemental analyses were performed in the microanalytical laboratory of the Chemical Institute of the Johannes-Gutenberg University, Mainz, Germany.

X-ray Crystal Structure Analysis of **14**: Performed with an Enraf Nonius Turbo-Cad4 equipped with rotating anode on a transparent colourless single crystal of size 0.34 × 0.23 × 0.12 mm. Empirical formula: $C_{16}H_{24}N_{16}$, $M = 440.51$ g mol^{-1}, orthorhombic, space group $P2_12_12_1$ (No. 19), wavelength used: Cu-K_α with graphite monochromation: 1.54180 Å, $T = 298(2)$ K, unit cell dimensions: $a = 7.2604(3)$, $b = 13.4352(6)$, $c = 21.9289(3)$, $V = 2139.05(13)$ Å^3, $Z = 4$, d (calcd.): 1.368 g/cm^3, absorption $\mu = 0.790$ mm^{-1} (no correction): Θ range for data collection: 3.86–69.78°; index ranges: $-8 \leqslant h \leqslant 8$, $-16 \leqslant k \leqslant 16$, $-26 \leqslant l \leqslant 26$. No. of reflections collected: 4492; independent reflections 3897 [R(int) = 0.0444]. The structure was solved by direct methods. Structure refinement by full-matrix least-squares on F^2[13] with anisotropic temperature factors for all non-hydrogen atoms. Goodness-of-fit on F^2: 1.062, final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0619$, w$R_2 = 0.1710$, R indices (all data): $R_1 = 0.0626$, w$R_2 = 0.1725$. The final difference Fourier map showed minimum and maximum values of -0.237 and 0.374 eÅ^{-3}. The absolute configuration could not be determined. The Flack absolute structure parameter is $-0.2(5)$.

trans-1-Azido-2-iodocyclooctane **2**: Yield 95% (ref.[2] 95%), yellowish liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20–2.25 (m, 12H, CH_2), 3.88 (m, 1H, 2-H, assignment by single frequency decoupling, SFD), 4.23 (dq, ^3J = 9.5 Hz, 1H, 1-H, SFD). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.7, 25.1, 25.5, 26.6, 31.0, 33.8 (C-3,4,5,6,7,8), 39.2 (C-2), 71.0 (C-1). – ^{15}N NMR ($CDCl_3$, 41.5 MHz): δ = –289.6 (α-N), –163.0 (γ-N), –133.5 (β-N, SFD, ^3J(N,H) = 3.7 Hz).

1-Azidocyclooctene **3**: Yield 72% (ref.[2] 70%) yellow liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30–2.25 (m, 12H, CH_2), 5.24 (t, ^3J = 5.3 Hz, 1H, 2-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.7, 26.0, 26.9, 28.1, 29.6, 30.3 (C-3,4,5,6,7,8), 114.2 (C-2), 137.6 (C-1).

9-Azabicyclo[6.1.0]non-1(9)-ene **4**: Thermal yield 55% (ref.[2] 93%, photolytically), colourless liquid, b.p. 23°C/0.02 Torr. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.70–2.10 (m, 11H, 3,4,5,6,7,8-H), 2.50–2.90 (m, 2H, 2-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.1, 23.8, 24.7, 28.3, 29.0 (C-2,3,4,5,6,7), 30.1 (C-8), 175.3 (C-1).

trans-3-Azido-4-iodocyclooctene **6**: Yield 72% (ref.[2] 72%), yellow liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30–2.28 (m, 8H, CH_2), 4.11 (dt, ^3J = 11.4 Hz, 1H, 4-HC), 4.53 (m, 1H, 3-H), 5.41 (m, 1H, 2-H), 5.97 (m, 1H, 1-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.3, 27.1, 28.4, 36.1, (C-5,6,7,8), 40.1 (C-4), 66.6 (C-3), 126.9 (C-1), 135.2 (C-2).

2-Azido-1,3-cyclooctadiene **7**: Yield 50% (ref.[2] 50%), yellow liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31–2.32 (m, 8H, CH_2), 5.26 (t, 1H, 1-H), 5.69 (d, 1H, 3-H), 5.81 (m, 1H, 4-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 24.0, 26.3, 28.6 (CH_2), 116.3, 120.3, 136.8 (C-1,3,4), 134.4 (C-2).

9-Azabicyclo[6.1.0]nona-1(9),2-diene **8**: Thermal yield 68% (ref.[2] 100% photolytically in pentane), colourless liquid, b.p. 30°C/0.02 Torr. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.71–2.28 (m, 8H, 4,5,6,7,8-H), 2.83–3.03 (m, 1H, 4-H), 6.59 (m, 2H, 2-H, 3-H). –

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.6, 24.9, 27.8, 30.3 (C-4,5,6,7), 28.7 (C-8), 117.7 (C-2), 147.5 (C-3), 166.7 (C-1).

trans-1-Azido-2-iodocyclohexane **10**: Yield 84% (ref.[2] 83%), yellowish liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16–2.49 (m, 8H, 3,4,5,6-H), 3.49 (m, 1H, 2-H), 3.93 (td, ^3J = 4.2 Hz, 1H, 1-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9, 27.0, 32.0, 38.4 (C-3,4,5,6), 33.3 (C-2), 67.2 (C-1).

3-Azidocyclohexene **11**: Yield 77% (ref.[2] 77%), colourless liquid. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15–2.20 (m, 6H, CH_2), 3.84 (m, 1H, 3-H), 5.68 (m, 1H, 2-H), 5.94 (m, 1H, 1-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.2, 24.7, 28.6 (C-4,5,6), 55.9 (C-3), 124.7 (C-1), 132.7 (C-2).

(E)-1,2-Bis(2,6-diazido-9-azabicyclo[3.3.1]nonan-9-yl)diazene **14**: Following the general procedure of Hassner and Fowler[2] for the preparation of iodine azide adducts to olefins, the generation of **14** as the main product was observed. In order to optimize the yield, the conditions were modified as follows. A suspension of 30 g (0.5 mol) of sodium azide and 36.6 g (0.23 mol) of iodine monochloride in 200 ml of dry acetonitrile was cooled under stirring to −30°C. A solution of 5.4 g (50 mmol) of 1,5-cyclooctadiene (**12**) in 40 ml of CH_3CN was added carefully within 30 min to the brownish-red slurry, which was stirred at temperatures below −15°C. After 3 h at −30°C and an additional 12 h at room temp., the solvent was evaporated at room temp. and the remaining oil extracted first with a mixture of petroleum ether/ethyl acetate (15:1) and then with methanol. The crude solid product was recrystallized from chloroform at −18°C and yielded 7.5 g (68%) of colourless crystals, m.p. 110°C ($CHCl_3$), 165°C dec. (gas evolution). – IR (KBr): $\tilde{\nu}$ = 2910 cm^{-1}, 2095 (N_3), 1475, 1425, 1340, 1250, 1100, 900. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.75–2.01 (m, 16H, 3-H, 4-H, 7-H, 8-H), 3.82 (m, 4H, 2-H, 6-H), 4.04 [m, 4H, 1-H, 5-H (SFD)]. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.09, 21.11, 26.40, 26.40 (C-3,4,7,8), 52.30, 52.35 (C-1,5), 58.61, 58.66 (C-2,6). – ^{15}N NMR ($CDCl_3$, 41.5 MHz): δ = −300.4 (α-N), −236.8 (N-9), −166.9 (γ-N), −134.0 (β-N), 15.1 (N=N). – MS (EI, 70 eV): *m/z* (%) = 440 (30) [M$^+$], 412 (5), 137 (9), 123 (7), 107 (15), 95 (23), 83 (92), 68 (100). – $C_{16}H_{24}N_{16}$ (440.4): calcd. C 43.63, H 5.49, N 50.87; found C 43.47, H 5.45, N 50.64.

2,6-Diazido-9-azabicyclo[3.3.1]nonane **20**: Tetrazene **14** (1.0 g, 2.4 mmol) was dissolved in 30 ml of chloroform and 15 ml of concentrated hydrochloric acid was added. The two-phase mixture was stirred vigorously under argon for 5 h at room temperature. After neutralization with a saturated $NaHCO_3$ solution the organic layer was washed with equal amounts of water and brine before being dried ($MgSO_4$). The solvent was removed by evaporation at room temperature, yielding 420 mg (85%) of an oil. Repeated chromatography on silica gel did not lead to a crystalline substance. – IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N–H), 2900, 2080 (N_3), 1250, 945. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.6–2.1 (m, 8H, 3-H, 4-H, 7-H, 8-H), 3.04 (m, 2H, 1-H, 5-H), 3.28 (br. s, 1H, NH), 3.80 (m, 2H, 2-H, 6-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.6 (C-3,7), 26.1 (C-4,8), 48.2 (C-1,5), 60.8 (C-2,6). – ^{15}N NMR (41.5 MHz, $CDCl_3$): δ = −329.4 (N-9), −299.5 (α-N), −167.2 (γ-N), −134.1 (β-N). – MS (FD, 5 kV): *m/z* (%) = 207 (100) [M$^+$]. – $C_8H_{13}N_7$ (207.1): calcd. C 46.34, H 6.33, N 47.32; found C 46.61, H 6.25, N 46.99.

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