

## Notizen / Notes

Conformational Analysis of [3.3]Paracyclophane<sup>1)</sup>Katsuya Sako<sup>a</sup>, Tatsuya Meno<sup>a</sup>, Hiroyuki Takemura<sup>b</sup>, Teruo Shinmyozu<sup>\*\*a</sup>, and Takahiko Inazu<sup>\*\*a</sup>Department of Chemistry, Faculty of Science, Kyushu University<sup>a</sup>, Higashi-ku, Hakozaki 6-10-1, Fukuoka 812, JapanLaboratory of Chemistry, College of General Education, Kyushu University<sup>b</sup>, Ropponmatsu 4-2-1, Chuo-ku, Fukuoka 810, Japan

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According to a VT-NMR study, [2,2,11,11-D<sub>4</sub>][3.3]paracyclophane (**1-D<sub>4</sub>**) exists as a mixture of chair and boat conformers in the ratio of 1.0:1.3 ( $\Delta G_0 = 0.1$  kcal/mol) at  $-70^\circ\text{C}$  with an energy barrier for the chair-boat inversion of 12.0 kcal/mol (270 MHz, ca. 1% CD<sub>2</sub>Cl<sub>2</sub> solution,  $T_c = -15^\circ\text{C}$ ). The con-

former ratio (chair/boat) is dependent on the concentration of **1-D<sub>4</sub>**; it is 1:1 in ca. 1% CD<sub>2</sub>Cl<sub>2</sub> solution but 1:2 in ca. 5% CD<sub>2</sub>Cl<sub>2</sub> solution, due to preferential crystallization of the chair conformer.

[3.3]Paracyclophane (**1**) exists in the chair conformation in the crystalline state<sup>2)</sup>. In solution it is mobile at room temperature; its trimethylene bridges can undergo a chair-boat-type inversion process (Figure 1) whose energy barrier is amenable to a dynamic NMR spectroscopy study<sup>3)</sup>. There have been conflicting reports in the literature on the ratio of the chair-boat conformers in **1**. Anet et al. reported that **1** exists as a mixture of chair and boat conformers in a ratio of ca. 1:2 at  $-88^\circ\text{C}$  in CDCl<sub>3</sub>/CDCl<sub>2</sub>F (4% solution), with the energy barrier for the chair-boat inversion being 11.7 kcal/mol<sup>4)</sup>. Ziegler et al., however, found that the chair-boat ratio was 1:1 in [D<sub>8</sub>]toluene (1% solution) at  $-70^\circ\text{C}$ <sup>5)</sup>. We intended, therefore, to restudy the dynamic NMR spectroscopy of **1** using [2,2,11,11-D<sub>4</sub>]-[3.3]paracyclophane (**1-D<sub>4</sub>**). We report here its VT-<sup>1</sup>H- and <sup>13</sup>C-NMR study.

It develops two broad peaks at  $-45^\circ\text{C}$ , and finally it appears as an AB quadruplet and a pair of broad singlets as shown in Figure 3 [chair:  $\delta = 6.63$  (H<sub>A</sub>, d,  $J = 7.8$  Hz) and 6.74 (H<sub>B</sub>, d,  $J = 7.8$  Hz); boat:  $\delta = 6.62$  (H<sub>A</sub>, br. s) and 6.78 (H<sub>B</sub>, br. s)]. The isomer with a larger coupling constant [ $J_{ortho}(H_{A'c}, H_{B'c}) = 7.8$  Hz] is assigned to a chair conformer, and the other isomer [ $J_{meta}(H_{A'b}, H_{B'b}) < 1.5$  Hz] to a boat one. Our assignments of the aromatic protons of both conformers, as opposed to those reported by Ziegler et al.<sup>5)</sup>, are based on the fact that an aromatic proton (H<sub>B</sub>) to which a central methylene proton of the trimethylene bridge is spatially directed, suffers steric deshielding<sup>1)</sup>.

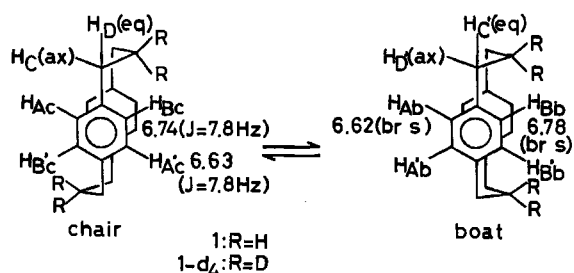
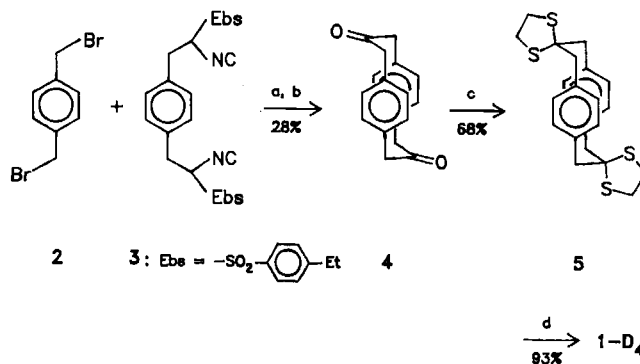


Figure 1. Trimethylene bridge inversion process in [3.3]paracyclophane (**1**)

**1-D<sub>4</sub>** was prepared by reductive desulfurization of 2,11-bis(1,4-dithiabutane-1,4-diyl)[3.3]paracyclophane (**5**) with tri-*n*-butyltin deuteride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in refluxing xylene for 14 hours in 93% yield<sup>1,6,7)</sup>.

At  $27^\circ\text{C}$  **1-D<sub>4</sub>** (270 MHz, ca. 1% in CD<sub>2</sub>Cl<sub>2</sub> solution) shows benzylic and aromatic protons as sharp singlets at  $\delta = 2.68$  and 6.67, respectively. Both protons exhibit strong temperature-dependent phenomena, as shown in Figures 2–4. The singlet of the aromatic protons at  $27^\circ\text{C}$  broadens as the temperature is lowered (Figure 2).

Scheme 1. Synthetic route to **1-D<sub>4</sub>**. a: *n*-Bu<sub>4</sub>NI, NaOH, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, b: concd. HCl, c: HSCH<sub>2</sub>CH<sub>2</sub>SH, Et<sub>2</sub>O–BF<sub>3</sub>, AcOH, d: *n*-Bu<sub>3</sub>SnD, AIBN, xylene



An NOE experiment with **1-D<sub>4</sub>** at  $-70^\circ\text{C}$  supports our assignments; irradiating the axial benzylic protons (chair: H<sub>C</sub>; boat: H<sub>D</sub>) gave a small enhancement (4%) of the aromatic protons at higher field (chair: H<sub>Aa</sub>, H<sub>A'a</sub>; boat: H<sub>Ab</sub>, H<sub>A'b</sub>), but no effect was observed when irradiating the equatorial benzylic protons (chair: H<sub>D</sub>; boat: H<sub>C</sub>). On the other hand, irradiation of the higher field aromatic protons generated a small enhancement (3%) of the benzylic pro-

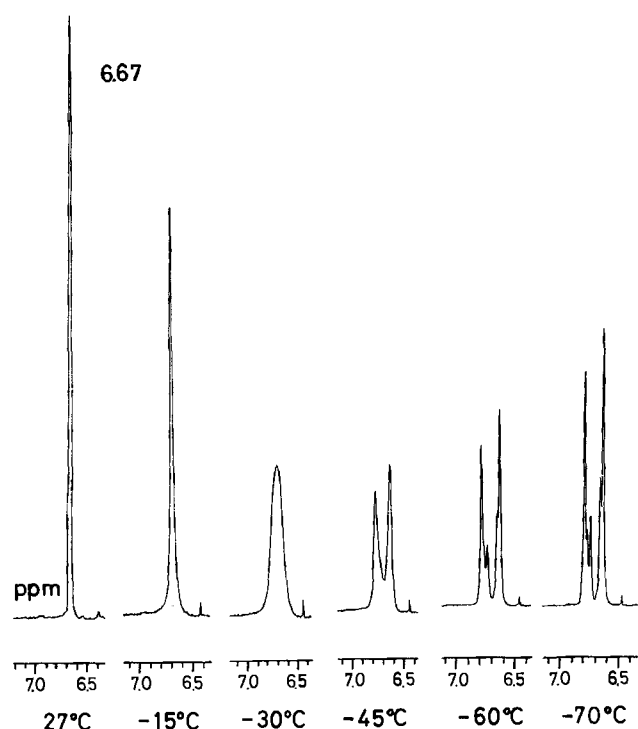


Figure 2.  $^1\text{H-NMR}$  spectra (270 MHz,  $\text{CD}_2\text{Cl}_2$ ) of the aromatic protons of  $1\text{-D}_4$  at various temperatures

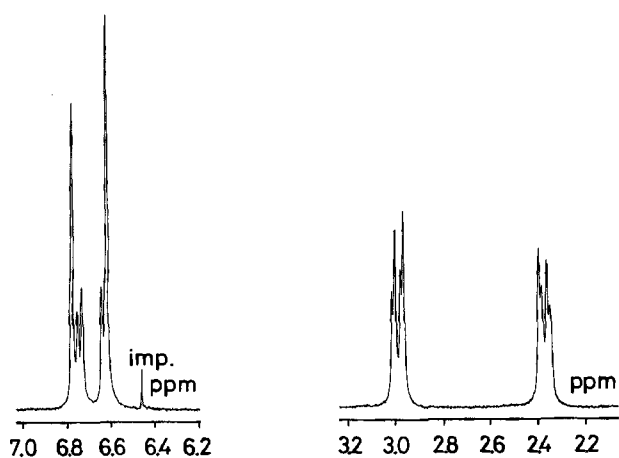


Figure 3. Expanded  $^1\text{H-NMR}$  spectrum of the aromatic (left) and benzylic protons (right) of  $1\text{-D}_4$  at  $-70^\circ\text{C}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ )

tons at higher field, while irradiation of the lower field aromatic protons (chair:  $\text{H}_{\text{Bc}}$ ,  $\text{H}_{\text{B'c}}$ ; boat:  $\text{H}_{\text{Bb}}$ ,  $\text{H}_{\text{B'b}}$ ) had no effect. These results indicate that the axial benzylic protons (chair:  $\text{H}_{\text{C}}$ ; boat:  $\text{H}_{\text{D}}$ ) are closer to  $\text{H}_{\text{A}}$  than to  $\text{H}_{\text{B}}$ .

The sharp singlet of the benzylic protons at  $27^\circ\text{C}$  broadens as the temperature is lowered, and begins to resolve into two broad signals at  $-30^\circ\text{C}$ . Each signal becomes a doublet at still lower temperatures and finally splits into two sets of doublets as shown in Figures 3 and 4 [chair:  $\text{H}_{\text{C}}(\text{ax})$   $\delta = 2.36$  (d,  $J = 14.2$  Hz) and  $\text{H}_{\text{D}}(\text{eq})$  2.99 (d,  $J = 14.2$  Hz); boat:  $\text{H}_{\text{D}}(\text{ax})$  2.38 (d,  $J = 13.9$  Hz) and  $\text{H}_{\text{C}}(\text{eq})$  2.98 (d,  $J = 13.9$  Hz)]. Populations of the isomers are estimated to be chair:boat = 1.0:1.3 ( $-70^\circ\text{C}$ ) on the basis of the integral of aromatic signals:  $\delta = 6.74$  (chair,  $\text{H}_{\text{Bc}}$ , d) and 6.78 (boat,  $\text{H}_{\text{Bb}}$ , br. s). The energy barrier for the chair-boat inversion ( $\Delta G^\ddagger$ ) is calculated to be 12.0 kcal/mol with  $T_c = -15^\circ\text{C}$ <sup>8)</sup>. In the experi-

ment described above no crystals were observed even at  $-70^\circ\text{C}$ .  $^1\text{H-NMR}$  data of the chair and boat conformers are summarized in Table 1.

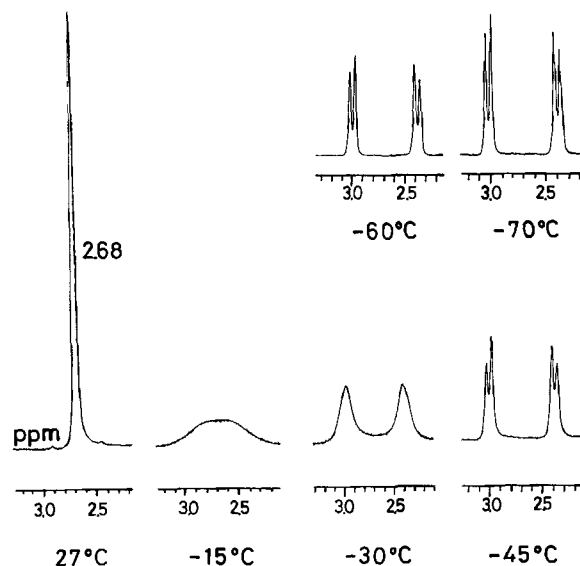


Figure 4.  $^1\text{H-NMR}$  spectra (270 MHz,  $\text{CD}_2\text{Cl}_2$ ) of the benzylic protons of  $1\text{-D}_4$  at various temperatures

Table 1. Proton chemical shifts ( $\delta$ ) and coupling constants (Hz) of chair and boat conformers of  $1\text{-D}_4$  (400 MHz, ca. 1%  $\text{CD}_2\text{Cl}_2$  solution,  $-70^\circ\text{C}$ )

	chair	boat
$\text{H}_{\text{ax}}$	2.36 ( $\text{H}_{\text{C}}$ )	2.38 ( $\text{H}_{\text{D}}$ )
$\text{H}_{\text{eq}}$	2.99 ( $\text{H}_{\text{D}}$ )	2.98 ( $\text{H}_{\text{C}}$ )
$J_{\text{CD}}$	14.2 Hz	13.9 Hz
$\text{H}_{\text{A}}$	6.63	6.62
$\text{H}_{\text{B}}$	6.74	6.78
$J_{\text{AB'}}$	7.8 Hz	—
$J_{\text{AB}}$	—	<1.5 Hz

A similar VT-NMR study of  $1\text{-D}_4$  in  $[\text{D}_8]\text{toluene}$  (ca. 1% solution, 400 MHz) showed that both the chair-boat ratio (1.0:1.3) and the chemical shifts of the aromatic protons at  $-70^\circ\text{C}$  are in complete agreement with those reported by Ziegler et al., except for the assignment of the aromatic protons<sup>5)</sup> [chair:  $\delta = 6.51$  ( $\text{H}_{\text{Ac}}$ ,  $\text{H}_{\text{A'c}}$ ,  $J = 7.6$  Hz) and 6.58 ( $\text{H}_{\text{Bc}}$ ,  $\text{H}_{\text{B'c}}$ ,  $J = 8.1$  Hz); boat: 6.48 ( $\text{H}_{\text{Ab}}$ ,  $\text{H}_{\text{A'b}}$ , br. s) and 6.62 ( $\text{H}_{\text{Bb}}$ ,  $\text{H}_{\text{B'b}}$ , br. s)]. In this case, however, the fact that crystals appeared at low temperatures as reported by Ziegler et al. makes the data for the population of the isomers unreliable.

The proton-decoupled  $^{13}\text{C-NMR}$  data for  $1\text{-D}_4$  (ca. 5%  $\text{CD}_2\text{Cl}_2$  solution, 68 MHz) at  $25^\circ\text{C}$  are shown in Table 2<sup>9)</sup>. The completely averaged aromatic and benzylic carbon signals suggest the presence of a rapid isomerization process. At  $-90^\circ\text{C}$ , each signal splits into two peaks with unequal intensities, except for the C-2,11 signal, in which the original quintuplet broadens due to the overlap of two sets of quintuplets as shown in Figure 5. The more intense signal of each pair may be assigned to a boat conformer, while the less intense ones are ascribed to the chair forms, based on the chair-boat ratio observed in the  $^1\text{H-NMR}$  spectrum. Chemical shifts for the chair and boat conformers at  $-90^\circ\text{C}$  in  $\text{CD}_2\text{Cl}_2$  are summarized in Table 2. C-5 and -8 in the chair form, and C-8 and -9 in the boat

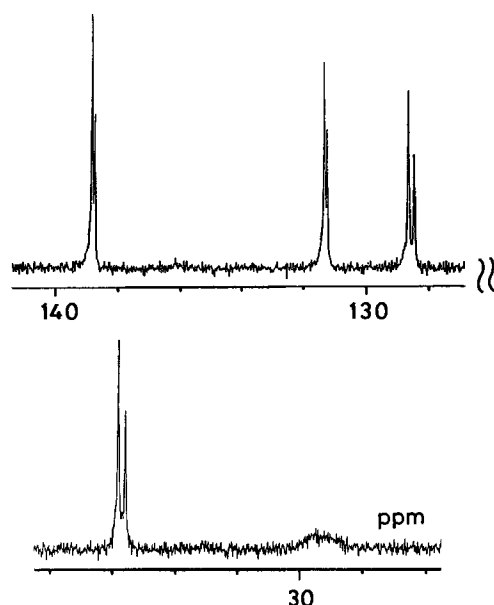


Figure 5.  $^{13}\text{C}$ -NMR spectrum of **1-D<sub>4</sub>** in  $\text{CD}_2\text{Cl}_2$  at  $-90^\circ\text{C}$  (68 MHz)

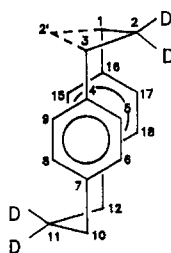


Table 2.  $^{13}\text{C}$  chemical shifts ( $\delta$ ) of chair and boat conformers of **1-D<sub>4</sub>** (68 MHz, ca. 5%  $\text{CD}_2\text{Cl}_2$  solution, 25 and  $-90^\circ\text{C}$ )

	25°C	-90°C	
	chair	chair	boat
C-2,11	29.3		
C-1,3,10,12	36.1	35.9	36.1
C-4,7,13,16	138.8	138.9	139.0
C-5,8,14,17	130.0	C-5,8,14,17 128.7	C-8,9,14,15 128.9
C-6,9,15,18	130.0	C-6,9,15,18 131.5	C-5,6,17,18 131.6

form are shielded by 2.7–2.8 ppm compared with C-6 and -9 (chair) and C-5 and -6 (boat), respectively, because of the steric effect of the trimethylene bridges. The chair-boat ratio is estimated to be ca. 1:2 by the integral of the C-5 and -8 (chair) and C-8 and -9 (boat) signals, which is in accord with the ratio reported by Anet et al.<sup>4)</sup> In this experiment, however, crystallization was observed at  $-90^\circ\text{C}$ . The increased ratio of the boat conformer suggests the preferential crystallization of the chair isomer.

In conclusion, our experiments clearly indicate that the conformer ratio depends on the solubility of the isomers; when both isomers are soluble (ca. 1%  $\text{CD}_2\text{Cl}_2$  solution), the chair:boat ratio is ca. 1:1 ( $-70^\circ\text{C}$ ), while it is ca. 1:2 ( $-90^\circ\text{C}$ ) at higher concentration (ca. 5%  $\text{CD}_2\text{Cl}_2$  solution) because of the preferential crystallization of the less soluble chair isomer. In solution, the boat isomer is slightly more stable than the chair conformation ( $\Delta G_0 = 0.1$  kcal/mol); the latter is the exclusive isomer found in the crystalline state<sup>2)</sup>. The energy barrier for the trimethylene bridge inversion in

**1-D<sub>4</sub>** (12.0 kcal/mol) is comparable to but slightly higher than that of [3.3]metacyclophane (11.6<sup>1)</sup>, 11.5<sup>10)</sup> kcal/mol).

We thank Miss *K. Ogi* for 400-MHz NMR-spectral measurements.

## Experimental

IR: Jasco IR-700. —  $^1\text{H}$  NMR: Jeol FX-90Q, JNM-GSX 270, and JNM-GX 400; chemical shifts ( $\delta$  values) relative to TMS for protons and carbons. —  $^{13}\text{C}$  NMR: Jeol JNM-GSX 270 (68 MHz). — Mass spectra: Jeol JMS-DX 300 (ionization energy 70 eV). — Column chromatography: Daiso gel IR-60 (40–63  $\mu\text{m}$ ). — TLC: silica gel 60 F<sub>254</sub> Merck (aluminium sheets) for analytical purposes, silica gel 60 PF<sub>254</sub> Merck for preparative purposes. — Elemental analyses: Service Centre of the Elementary Analysis of Organic Compounds affiliated to the Faculty of Science, Kyushu University. — 4-Ethylbenzenesulfonylmethyl isocyanide (EbsMIC) adduct **3** was prepared according to literature procedures<sup>9)</sup>.

[3.3]Paracyclophane-2,11-dione (**4**): A mixture of the bromide **2** (5.58 g, 21.1 mmol) and the EbsMIC adduct **3** (11.0 g, 21.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 l) was added dropwise to a refluxing mixture of *n*-Bu<sub>4</sub>NI (2.6 g), NaOH (45 g) dissolved in water (100 ml), and  $\text{CH}_2\text{Cl}_2$  (1.5 l) over a period of 6 h with vigorous stirring. After the addition, the mixture was heated at reflux for an additional 2 h. The mixture was then cooled, washed with water (2 × 2 l) and concentrated to a volume of ca. 300 ml. Conc. HCl (50 ml) was added to the concentrate, and the mixture was stirred at room temp. for 1 h. The mixture was washed with water, dried with  $\text{MgSO}_4$ , and filtered. The solvent was removed, and the residue was triturated with MeOH. The solid was collected by filtration and chromatographed on silica gel (100 g) with  $\text{CH}_2\text{Cl}_2$  [ $R_f$  (silica gel,  $\text{CH}_2\text{Cl}_2$ ) = 0.35]. Concentration of the eluate followed by trituration of the crystals with MeOH afforded the diketone **4** (1.57 g, 28%), m.p. (benzene) 267–268°C (ref.<sup>6a)</sup> 266.5–267.7°C). — IR (KBr):  $\tilde{\nu} = 1688$   $\text{cm}^{-1}$  (C=O). —  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 3.71$  (s, 8H, benzylic), 6.85 (s, 8H, aromatic).

[2,2,11,11-D<sub>4</sub>][3.3]Paracyclophane (**1-D<sub>4</sub>**): A mixture of the dione **4** (505 mg, 1.91 mmol), AcOH (45 ml), Et<sub>2</sub>O–BF<sub>3</sub> (0.1 ml), and 1,2-ethanedithiol (3.0 ml, 36 mmol) was stirred at room temp. for 12 h. Water (10 ml) was then added, and the mixture was extracted with  $\text{CHCl}_3$ . The combined  $\text{CHCl}_3$  solutions were washed successively with satd.  $\text{NaHCO}_3$  solution and brine, dried with  $\text{MgSO}_4$ , filtered, and evaporated. The resulting powdery crystals of **5** were washed successively with MeOH and acetone, and dried in vacuo (540 mg, 68%), m.p. ( $\text{CHCl}_3/\text{AcOEt}$ ) 282.5°C (dec.). —  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 3.49$  (s, 8H, benzylic), 3.50 (s, 8H,  $-\text{SCH}_2\text{CH}_2\text{S}-$ ), 7.04 (s, 8H, aromatic). — MS:  $m/z = 416$  [ $\text{M}^+$ ].

$\text{C}_{22}\text{H}_{24}\text{S}_4$  (416.7) Calcd. C 63.41 H 5.81  
Found C 63.65 H 5.74

A mixture of the thioacetal **5** (104 mg, 0.25 mmol), *n*-Bu<sub>3</sub>SnD (1.15 ml, 4.28 mmol), AIBN (43 mg), and xylene (14 ml) was heated at reflux for 14 h with stirring under  $\text{N}_2$ . After cooling, the mixture was subjected to preparative TLC (silica gel) with hexane [ $R_f$  (silica gel, hexane) = 0.37] to give **1-D<sub>4</sub>** as colorless crystals (56 mg, 93%), m.p. (sublimed at 60–80°C/0.3 Torr) 105–105.5°C. — IR (KBr):  $\tilde{\nu} = 2090, 2136, 2188$   $\text{cm}^{-1}$  (C–D). — MS:  $m/z = 240$  [ $\text{M}^+$ ].

$\text{C}_{18}\text{H}_{16}\text{D}_4$  (240.4) Calcd. C 89.94 H + 1/2D 8.38  
Found C 89.77 H + 1/2D 8.37

## CAS Registry Numbers

1: 125077-62-5 / 2: 623-24-5 / 3: 124077-63-6 / 4: 7568-20-9 / 5: 125077-64-7

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