Notizen / Notes

Synthesis and Spectroscopic Characterization of ^{15}N-Labeled Hexaaminobenzene Derivatives[1)]

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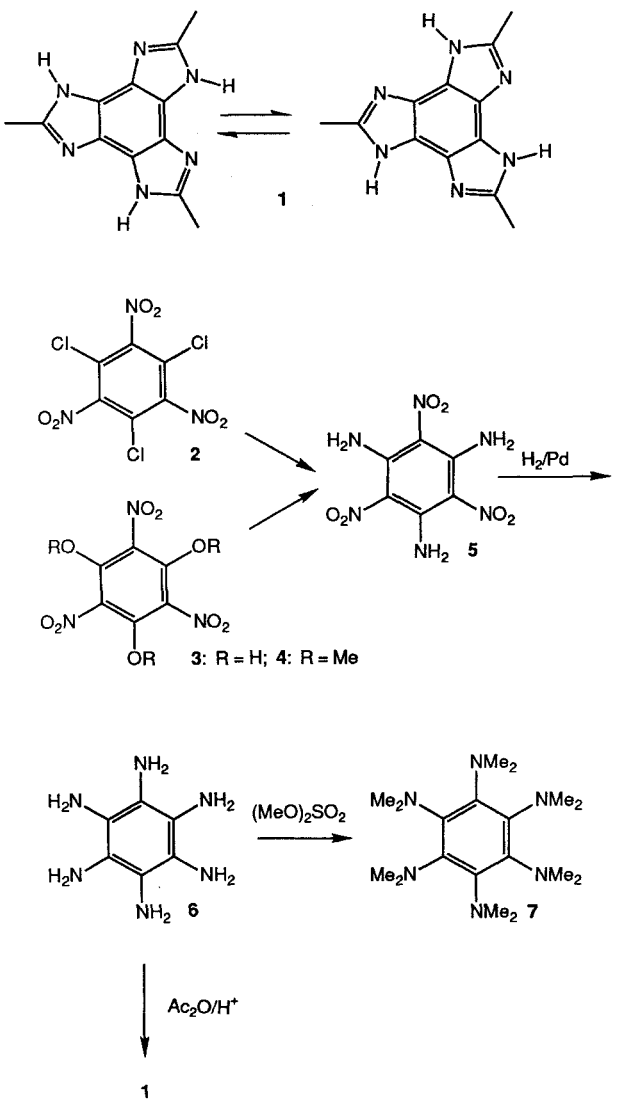
Efficient syntheses of [$^{15}N_6$]-labeled hexaaminobenzene (**6**), hexakis(dimethylamino)benzene (**7**) and 2,2′,2″-trimethylbenzotris(imidazol) (**1**) are described. The compounds are characterized by ^{15}N CPMAS NMR spectroscopy.

Recent interest in hexa(nitrogen)-substituted benzenes[2a–h)] prompts us to report our results on the synthesis of [$^{15}N_6$]-hexaaminobenzene and compounds derived therefrom[3)]. Initially, we were intrigued by the possibility of observing an intramolecular triple proton transfer in the benzotris(imidazol) **1** (Scheme 1) which has been synthesized recently[2c)]. In solution, proton transfers in NH···N hydrogen bonds can be monitored by liquid state ^1H-NMR spectroscopy[4)], provided the molecule is labeled with ^{15}N which has the spin of 1/2. Complications arising from the nuclear quadrupole moment of the naturally abundant nitrogen isotope ^{14}N (spin = 1) can thereby be avoided. In addition, ^{15}N labeling makes it also possible to study proton transfers between nitrogen atoms in the solid state by high resolution ^{15}N CPMAS NMR spectroscopy[5)], a technique combining cross polarization (CP) and magic angle spinning (MAS). Furthermore, other molecular properties may be monitored in the solid state by this method[6)]. Thus, we felt a convenient synthesis of [$^{15}N_6$]hexaaminobenzene could lead to interesting results.

As a consequence of the high costs for ^{15}N-labeled compounds, syntheses which work well with unlabeled material become excessively expensive with labeled compounds. With hexaaminobenzene, this proved to be the case: the published syntheses[2,7)] all employ 1,3,5-trichloro-2,4,6-trinitrobenzene (**2**) (Scheme 1) as intermediate which is obtained by nitration under drastic conditions with large excesses of nitrate[8)]. We thought that the crucial intermediate **5**, 1,3,5-trinitro-2,4,6-triaminobenzene, might be accessible by a more economic route.

Initial attempts to nitrate 1,3,5-tris(acetylamino)benzene[9)] have failed to produce **5** or its tris(*N*-acetyl) derivative. Only mono- or bis-nitration could be effected in fair yields[3)]. However, we anticipated that 1,3,5-trimethoxy-2,4,6-trinitrobenzene (**4**), like **2**[2)], would easily exchange its methoxy groups with ammonia. **4** has been obtained by stoichiometric nitration of 1,3,5-tris(acetoxy)benzene[3,10)] to yield trinitrophloroglucinol (**3**), which in turn has been quantitatively methylated by diazomethane. **4** indeed produces **5** in ex-

Scheme 1



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cellent yield on treatment with ammonia. Catalytic hydrogenation[2a-d] of **5** gives hexaaminobenzene which has been characterized as its hydrochloride salt by ^{15}N CPMAS NMR spectroscopy. Two peaks are observed at $\delta = 21.8$ and 44.5 (solid $^{15}NH_4Cl$: $\delta \equiv 0$) which can be assigned to the NH_3^+ and NH_2 units, respectively. For comparison, $Ph^{15}NH_3^+$ and $Ph^{15}NH_2$ absorb in solution at $\delta \approx 20$ and 33–38, respectively[11].

Acetylation and subsequent heating at reflux with hydrochloric acid (the Phillips synthesis[12]) yielded **1**, displaying two singlets at $\delta = 128$ and 201 which are assigned to protonated and to non-protonated nitrogen atoms. Unfortunately, no signs of a possible solid-state proton tautomerism according to Scheme 1 were observed between 150 and 400 K. We attribute this result to the formation of intermolecular hydrogen bonds in the solid state[2c] which block the intramolecular proton tautomerism. As a consequence, **1** is practically insoluble in apolar solvents which precluded an intramolecular proton transfer to be observed by liquid state ^1H-NMR spectroscopy. So far, we have been unable to synthesize higher homologs of **1** carrying longer alkyl chains instead of the methyl groups of **1**. These compounds should be less likely to form intermolecular hydrogen bonds as can be inferred from their lower melting points and higher solubilities[2c].

We have also prepared ^{15}N-labeled hexakis(dimethylamino)benzene (**7**) and its hydrochloride salt. Results on the spectroscopic behavior of **7** · 3 HCl and **6** · 4 HCl will be reported in due course.

Experimental

General Comments: Routine ^1H and ^{13}C NMR spectra: Bruker WP 250 or AM 300 working at 250 and 300 MHz for ^1H. – ^{15}N CPMAS spectra: Bruker CXP 100 equipped with a Doty CPMAS probe, working at 9.12 MHz for ^{15}N; reference: solid $^{15}NH_4Cl$ ($\delta \equiv 0$ ppm). As a consequence of the complete labeling with ^{15}N, the ^{15}N signals of the compounds studied were found to be subject to magnetization transfer by spin diffusion[13]. If this process is completed, the peak integrals correspond to the proper mole fractions of the different environments monitored. – Mass spectra: MAT 44 S, Finnigan MAT, 70 eV for EI. We thank Dr. Wörth, Freiburg, for recording the mass spectra. – $^{15}NH_4Cl$ (96% ^{15}N-enriched) and $H^{15}NO_3$ (95% ^{15}N-enriched): IRE Diagnostik, Düsseldorf. $H^{15}NO_3$ was converted into the potassium salt by neutralization with KOH. – *Unless stated otherwise, spectroscopic and analytical data refer to the non-labeled compounds synthesized under otherwise identical conditions.*

[$^{15}N_3$]Trinitrophloroglucinol (**3**): To an ice-cooled, stirred solution of $K^{15}NO_3$ [1023.0 mg (10.019 mmol)] in concentrated sulfuric acid (6 ml), phloroglucinol triacetate[10] [830.3 mg (3.292 mmol)] was added slowly. The cooling bath was removed and the slightly brownish suspension was stirred at room temperature for 2.5 h. The mixture was cooled again to 0 °C and ice/water (ca. 15 ml) was slowly added; it was then extracted with ether (4 × 25 ml). The combined extracts were washed with satd. brine (10 ml); the aqueous phase was back-extracted (20 ml ether). The organic phases were dried with sodium sulfate and the solvent was evaporated in vacuo to give crude [$^{15}N_3$]-**3** (ca. 906 mg) which was sublimed at 130 to 140 °C/0.05 Torr to give the pure anhydrous compound [821.1 mg (3.109 mmol, calcd. for $K^{15}NO_3$: 93%)] as a yellow powder, mp 167–168 °C (dec.), ref.[14] 167 °C.

$C_6H_3N_3O_9$ (261.1) Calcd. C 27.60 H 1.16 N 16.09
Found C 27.53 H 1.21 N 15.99

[$^{15}N_3$]1,3,5-Trimethoxy-2,4,6-trinitrobenzene (**4**): Diazomethane[15] [obtained from 21.42 g (100 mmol) *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide] was distilled with ether into a solution of [$^{15}N_3$]-**3** [602.0 mg (2.280 mmol)] in methanol (10 ml) which was cooled to –15 °C with stirring. The excess diazomethane was destroyed with acetic acid and the solvent was evaporated; the residue was dried at 0.05 Torr. The resulting slightly yellow [$^{15}N_3$]-**4** [704.5 mg (101%)] was used without further purification, mp 72–74 °C. Pure material, nearly colorless, could be obtained by chromatography on silica gel, eluting with light petroleum ether/ethyl acetate, 95:5; mp 74–76 °C, ref.[16] 75 °C (corr.). – ^1H NMR ($CDCl_3$): $\delta = 4.06$ (s). – ^{13}C NMR ($CDCl_3$): $\delta = 64.41$, 135.72, 147.26.

[$^{15}N_6$]2,4,6-Triamino-1,3,5-trinitrobenzene (**5**): [^{15}N]ammonia was obtained from $^{15}NH_4Cl$ [448.8 mg (8.237 mmol)] in an apparatus modeled after a literature report[17]. It was condensed into a cooled (–78 °C) solution of the ether [$^{15}N_3$]-**4** [312.3 mg (1.020 mmol)] in dry toluene (7 ml) contained in a vessel which was equipped with a high-vacuum teflon stopcock. The cooling bath was removed and the vessel closed. The reaction mixture was stirred at room temperature and a bright yellow precipitate formed after several minutes; stirring was continued for 12 h at this temperature and then for 3 h at 65–70 °C. The suspension was then cooled with liquid nitrogen and HCl (5 ml of a 5% solution) was added; the closed vessel was warmed to room temperature. The mixture was vigorously shaken and the precipitate was removed by centrifugation (5000 min^{-1}). The toluene was discarded and the aqueous phase collected. The precipitate was washed three times with water and then dried at 110 °C to afford [$^{15}N_6$]-**5** [260.1 mg (97%)] as a bright yellow powder, mp > 300 °C, ref.[2i] > 360 °C (dec.). – MS (EI): *m/z* (%) = 259 [M + H$^+$] (14), 258 [M$^+$] (100), 228 [M$^+$ – NO] (40). – IR (KBr): $\tilde{\nu} = 3600-2920$ cm^{-1} (NH, polymeric) 3320, 3220 (NH) 1610 (C=C).

The aqueous phases were freed from water and dried at 0.05 Torr over KOH to yield $^{15}NH_4Cl$ (290.2 mg, amounting to quantitative recovery of ^{15}N).

[$^{15}N_6$]2,2',2''-Trimethylbenzotris(imidazol) (**1**) (modified procedure from ref.[2c]): [$^{15}N_6$]-**5** [120.3 mg (0.4555 mmol)] was suspended in ethyl acetate (10 ml) with vigorous stirring and hydrogenated at 60 °C under normal pressure with 10% Pd/C (31 mg) as catalyst. Hydrogen uptake stopped after 4–5 h (ca. 90 ml being absorbed) and the suspension had become colorless. The solvent was evaporated with exclusion of oxygen and degassed acetic anhydride (1 ml) was added to the residue. Heating to 60–70 °C under nitrogen resulted in a gel-like suspension of acetylated hexaaminobenzene to which HCl (4 ml of a 33% solution + 6 ml water) was added. The mixture was heated at reflux for 10 h under nitrogen. It was then transferred to a vessel equipped with a high-vacuum quality teflon stopcock and was heated under nitrogen to 185–190 °C for 6 h, whereupon colorless, fine needles separated from the solution, which was then cooled. The catalyst was filtered off and washed with water. The filtrate was made alkaline with concd. aqueous NH_3 and heated to reflux for a short time. Reddish needles separated on slow cooling. These needles were filtered and dried at 110 °C. They were dissolved in methanol, filtered again and chromatographed on silica gel (45 g) by eluting with chloroform/methanol/ammonia = 100/15/1. [$^{15}N_6$]-**1** was obtained as a colorless powder [62.5 mg (56%)], mp > 300 °C, ref.[2c] > 350 °C. – ^1H NMR ([D$_6$]DMSO) in agreement with ref.[2c]. – MS (EI, for [$^{15}N_6$]-**6**): *m/z* (%) = 247 [M + H$^+$] (12), 246 [M$^+$] (100), 245 [M$^+$ – H] (11), 231 [M$^+$ – CH_3] (5), 216 [M$^+$ – CH_3NH] (5), 204 [M$^+$ – CH_3CN] (9). – By comparison with a spectrum obtained from unlabeled **1** under identical conditions, the labeled sample was shown to be ca. 96% enriched in ^{15}N. – ^{15}N CPMAS NMR: $\delta = 128.2$ (protonated nitrogen atoms), 201.3 (non-protonated nitrogen atoms), integration approximately 1:1. No significant spectral

changes could be observed in the temperature range between 153 and 363 K.

[^{15}N]Hexaaminobenzene Trihydrochloride (**6** · 3 HCl) (cf. ref.[7,18]): [$^{15}N_6$]-**5** was obtained from [$^{15}N_6$]-**4** [29.2 mg (0.111 mmol)] as described for the synthesis of [$^{15}N_6$].-**1**. The mixture was freed from the solvent and degassed, then water (2.5 ml) was added under nitrogen. The catalyst was filtered off and washed twice with water. The filtrate was concentrated to a volume of ca. 1–2 ml and was saturated with HCl gas at −15°C whereupon slightly brownish needles separated which were filtered off and dried in vacuo at 50°C. – ^{15}N CPMAS NMR: δ = 21.8, 44.5, integration: 2:1.

$C_6H_{12}N_6 \cdot 3$ HCl (277.6)
Calcd. C 25.95 H 5.45 N 30.28 Cl 38.32
Found C 25.88 H 5.46 N 30.08 Cl 38.36

[$^{15}N_6$]Hexakis(dimethylamino)benzene (**7**): [$^{15}N_6$]-**5** was obtained from [$^{15}N_6$]-**4** [44.3 mg (0.168 mmol)] as described for the synthesis of [$^{15}N_6$]-**1**. The mixture was freed from the solvent, then degassed water (2.5 ml), potassium hydroxide [400 mg (14.3 mmol)] and degassed dimethyl sulfate [0.50 ml (5.3 mmol)] were added. After 12 h of vigorous stirring at room temperature, the same amounts of base and alkylation agent were added again and this repeated after further 24 h of stirring. After a final 12 h of stirring, the mixture was diluted with water (5 ml) and extracted with light petroleum ether (4 × 20 ml). The combined organic phases were dried with sodium sulfate and the solvent was evaporated in vacuo. The yellow residue was dissolved in anhydrous acetone (10 ml) and potassium carbonate [400 mg (2.89 mmol)] and dimethyl sulfate [0.50 ml (5.3 mmol)] were added. After 18 h of stirring the same amounts of reagents were added and this was repeated twice. By then, no partially methylated product was detectable by TLC. The solvent was removed in vacuo and the residue was taken up in water. Subsequent extraction with light petroleum ether (4 × 20 ml each), drying with sodium sulfate and chromatography on alumina (10 g, act. III) yielded the permethylated amine [$^{15}N_6$]-**7** as colorless shiny prisms [31.2 mg (54%)] which were sublimed without residue at 70°C/0.1 Torr, mp 230°C (dec.), ref.[19] 236°C. – ^{1}H NMR ($CDCl_3$): δ = 2.66 (s). – ^{13}H NMR ($CDCl_3$): δ = 44.81, 152.02.

$C_{18}H_{36}N_6$ (336.5) Calcd. C 64.24 H 10.78 N 24.97
Found C 64.20 H 10.91 N 24.83

*Trihydrochloride Salt of [$^{15}N_6$]-**7*** (cf. ref.[19]): The amine [$^{15}N_6$]-**7** [31.0 mg (0.0905 mmol)] was treated with concd. HCl (1 ml). The slightly turbid solution was dried over potassium hydroxide in a desiccator at 15 Torr to constant weight. The trihydrochloride remained as a yellowish powder [39.7 mg (97%)].

$C_{18}H_{36}N_6 \cdot 3$ HCl Calcd. C 48.48 H 8.82 N 18.85
Found C 48.38 H 9.01 N 18.69

CAS Registry Numbers

1: 133649-22-6 / **3**: 133649-23-7 / **4**: 133649-24-8 / **5**: 133649-25-9 / **6** · 3 HCl: 133649-26-0 / **7**: 133649-27-1 / **7** · 3 HCl: 133649-28-2 / phloroglucinol triacetate: 2999-40-8

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