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# A 1,3,5-Triaxial-Triamino-Cyclohexane: The Triamine Corresponding to Kemp's Triacid[**]

Fredric M. Menger*, Jianwei Bian, and Vladimir A. Azov

[*] Prof. F. M. Menger, J.Bian, Dr. V. A. Azov
Department of Chemistry
Emory University
Atlanta, GA 30322 (USA)
Fax: (1) 404-727-6586
E-mail: menger@emory.edu

## Experimental Section

**General:** Melting points were determined on a Thomas-Hooover capillary melting point apparatus and uncorrected. Analytical TLC analyses were performed on glass plates coated with K6F silica gel 60A. $^1$H and $^{13}$C NMR spectra were recorded with Varian INOVA 400 or Mercury 300 spectrometers working at 400 or 300 MHz and 100 or 75 MHz respectively. Samples for IR spectra were prepared by pressing tablets from compound/KBr mixture and recorded on Perkin-Elmer IR-983 IR spectrometer. UV spectra were recorded with Varian DMS 200 and DMS 300 spectrophotometer. MS was performed by the Mass Spectrometry Center of Emory University. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.

***p*K Determination.** A solution (22mL) containing $3.7 \cdot 10^{-2}$ M **1**·3HCl in 1M KCl was adjusted to 25°. Base (0.5073N KOH) was added in increments of 0.1 mL with a syringe. A pH electrode with a built-in reference was used, which was calibrated with standard pH solutions (pH=7 and pH=10).

***Kinetic studies.*** All runs were carried out in chlorobenzene at 25.0° C. [ester] = $0.9 \times 10^{-4}$ M with **1**, and 4 - 6 x $10^{-4}$ M with other amines. [triamine **1**] = 2.l – 18 x $10^{-3}$ M. Reactions, monitored spectrophotometrically at 360 or 400 nm for pNPA and 290 nm for pCyPA and pChPA, were run to infinity. Pseudo-first-order plots were linear for two half-lives. The aminolysis of pChPA with triamine was carried out at 58.5° C using the method of initial rates because of its poor solubility in chlorobenzene.

***Single crystals' growth.*** Triazide single crystal was obtained by slow evaporation of its diluted solution in MeOH or $CHCl_3$; Triisocynate single crystal was grown by slow evaporation of its methanolic solution; Triamine single crystal was obtained by slow evaporation its solution in $CHCl_3$; Monosalt single crystal was achieved by slow evaporation of its solution in $CH_2Cl_2$ in NMR tube, and trisalt single crystal was grown by diffusing $CHCl_3$ into the methanolic solution; The single crystals of Ni(II), Cu(II), Zn(II), Co(III) complexes were grown by slow evaporation of their diluted aqueous solution; Both di- and triacetyl derivative were recrystallized from the diffusion of hexane to $CHCl_3$ solution; Urea single crystal was achieved by diffusing $CHCl_3$ to its methanolic solution; Single crystal of Kemp's triacid and Menger's triamine complex (1:1) was grown by slow evaporation of MeOH or diffusing $CHCl_3$ into the methanolic solution.

**5-(Chloroformyl)-*cis,cis*-1,3,5-trimethylcyclohexane-1,3-dicarboxylic Anhydride (1).** With an ice bath, thionyl chloride (9.2g, 77.3mmol) was added to a 100mL flask containing Kemp's triacid (1g, 3.87mmol) and 50mL anhydrous ethyl ether. The mixture was stirred at R.T. for 12h. Evaporation and crystallization from dry toluene gave 98% of **1**: mp 255-256 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.24-1.404 (m, 12H), 1.999-2.045 (d, 1H), 2.718-2.768 (d, 2H); $^{13}$C NMR $\delta$ 25.2, 30.6, 40.3, 42.0, 42.6, 44.2, 171.3.

***cis,cis*-1,3,5-Tris(chloroformyl)-1,3,5-trimethylcyclohexane (2).** With an ice bath, $\alpha,\alpha$-Dichloromethyl methyl ether (8g, 70mmol) was added to a 100mL flask containing **1** (0.9g, 3.5mmol), zinc chloride (20mg) and 50mL $CHCl_3$. The mixture was refluxed for 6h. Evaporation and crystallization from $CHCl_3$ gave 92% of **2**: mp 196 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.29-1.34 (d, 3H), 1.44 (s, 9H), 2.85-2.91 (d, 3H); $^{13}$C NMR $\delta$ 31.3, 43.2, 51.3, 179.7.

***cis,cis*-1,3,5-Tris(azidoformyl)-1,3,5-trimethylcyclohexane (3).** To a 100 mL ice bath cooled flask, $NaN_3$ (1.04g, 16mmoL) and 12 mg $^tBu_4NBr$ were added. Adding $H_2O$ until all the $NaN_3$ was dissolved. 20mL $CH_2Cl_2$ was added. **2** (0.5g, 1.6mmoL) was dissolved in $CH_2Cl_2$ and slowly transferred to the flask. The mixture solution was stirred at 0 °C for 1h and then washed with $H_2O$ (15 mL x 2, back-extracted with 20 mL $CH_2Cl_2$), brine (15 mL x 2). The organic layer was dried over anhydrous $MgSO_4$ for 30 minutes. Evaporation and purification by chromatography with $CHCl_3$ gave crystalline **3** (0.44g, 82%) : decomposes at 115-118 °C and explodes at 120-122 °C in the melting point tube;

IR (KBr) $\nu_{max}$ 3415, 2969, 2935, 2393, 2150, 1713, 1452, 1424, 1377, 1352, 1271, 1239, 1206, 1138, 1017; $^1$H NMR ($CDCl_3$) δ 0.98-1.03 (d, 3H), 1.22 (s, 9H), 2.64-2.69 (d, 3H); $^{13}$C NMR δ 30.7, 43.5, 43.6, 184.4; HRMS calcd. for $C_{12}H_{15}N_9O_3$ (M + Li) 340.1458, found 340.1448; Anal. calcd. for $C_{12}H_{15}N_9O_3$: C, 43.24; H, 4.50; N, 37.84; found C, 43.49; H, 4.56; N, 37.95.

***cis,cis*-1,3,5-Triisocyanato-1,3,5-trimethylcyclohexane (4).** To a 50 mL flask, **3** (0.4g, 1.2mmoL) and 20mL THF were added. After refluxing for 30 minutes, **3** was quantitatively converted to **4** by Curtius rearrangement. mp 190-192 °C; $^1$H NMR ($CDCl_3$, 400MHz) δ 1.34-1.39 (d, 3H), 1.40 (s, 9H), 2.05-2.10 (d, 3H); $^{13}$C NMR δ 33.7, 49.4, 54.7, 122.5; Anal. calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86; found C, 58.06; H, 6.14; N, 16.73.

***cis,cis*-1,3,5-Triamino-1,3,5-trimethylcyclohexane trihydrochloride (5).** To a 50 mL flask containing **4** (0.25g, 1mmoL) and 20 mL THF, 2 mL HCl (37%) was slowly added. The mixture solution was refluxed for 4h and white solids precipitated during the reaction. After filtration, the solids were washed with cold THF 3 times and dried over vacuum. No further purification was needed. mp > 275 °C; $^1$H NMR ($D_2O$) δ 1.63 (s, 9H), 1.97-2.01 (d, 3H), 2.32-2.36 (d, 3H); $^{13}$C NMR δ 24.9, 42.3, 53.8; Anal. calcd. for $C_9H_{21}N_3 \cdot 3HCl \cdot 1.5H_2O$: C, 35.13; H, 8.84; N, 13.66; Cl, 34.57; found C, 35.40; H, 8.65; N, 13.48; Cl, 35.05.

***cis,cis*-1,3,5-Triamino-1,3,5-trimethylcyclohexane (6).** **5** was converted to **6** by ion-exchanging with Dowex 550A $OH^-$ resin in MeOH. Purification by sublimation at 60 °C in vacuum gave 85% of **6**: mp 86-90 °C; $^1H$ NMR ($CHCl_3$) $\delta$ 1.10 (s, 9H), 1.33-1.38 (d, 3H), 1.54-1.58 (d, 3H); 1.92 (bs, 6H); $^{13}C$ NMR $\delta$ 35.9, 51.1, 51.3; HRMS calcd. for $C_9H_{21}N_3$ (M + Li) 178.1896, found 178.1891; Anal. calcd. for $C_9H_{21}N_3{\bullet}2H_2O$: C, 52.14; H, 12.15; N, 20.27; found C, 52.62; H, 11.78; N, 20.01.

**Urea (7).** 7 was the side product of step e. It was purified by chromatography with eluent $CHCl_3$:MeOH/$NH_3$ (0$\rightarrow$20%). mp 221-223 °C;

**Diacetyl derivative.** Triamine **1** was dissolved in pyridine. Dry crashed molecule sieves were added. Cooled it to –70 °C. AcCl was added dropwise via syringe. The mixture was stirred overnight at RT. Precipitate and sieves were filtered. Residue was evaporated to dryness and then dissolved in $CHCl_3$. Dried with $K_2CO_3$ and treated with decolorizing charcoal C. Filtered and evaporated the solvent gave the crude product which was purified by chromatography with $CHCl_3$ : MeOH/$NH_3$ (5$\rightarrow$50%). The single crystal was grown by diffusing hexane into its $CHCl_3$ solution.

**Triacetyl derivative.** Triamine **1** was dissolved in pyridine and cooled to 0°C. Then, AcCl was added quickly and precipitate formed immediately. The mixture was slowly heated to RT. After 30 minutes, evaporation of solvent gave the crude product. Dissolving it in $CHCl_3$ and washed with $Na_2CO_3$, HCl, NaCl. Evaporation of the solvent and purification by chromatography with $CHCl_3$:MeOH/$NH_3$ (0→5%). The single crystal was achieved by diffusing hexane into its $CHCl_3$ solution.

**Ni(II), Cu(II), Zn(II) and Co(III) complexes.** All metal complexes were synthesized by the following procedure: The aqueous solution of the appropriate metal salt ($Ni(NO_3)_2\cdot6H_2O$, $Cu(NO_3)_2\cdot3H_2O$, $Zn(NO_3)_2\cdot xH_2O$, $Co(II)Cl_2\cdot6H_2O$) was slowly added to a stirring aqueous solution containing 2 equivalents of triamine **1**. Precipitates formed immediately. The crude product was recrystallized from $H_2O$.