September, 1993] © *1993 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***66***, *2665—2667(1993)* 2665

Preparation and Structure of a Tetrasubstituted Derivative of *N″*-Cyanoguanidine, *N*,*N*,*N′*,*N′*-Tetrabenzyl-*N″*-cyanoguanidine

Ryuichi SHIBA,* Miyuki TAKAHASHI, Hiraku SHINOZAKI, Toichi EBISUNO,† and Michiaki TAKIMOTO††
Department of Materials Science and Engineering, Faculty of Technology, Tokyo Denki University,
Kanda 2-2, Chiyoda-ku, Tokyo 101
†Department of Chemistry, Faculty of Science, Toho University, Miyama 2-2-1, Funabashi, Chiba 274
††Fukui Institute of Technology, Gakuen 3-6-1, Fukui 910

(Received March 3, 1993)

A tetrasubstituted derivative of *N″*-cyanoguanidine (CG), *N*,*N*,*N′*,*N′*-tetrabenzyl-*N″*-cyanoguanidine (TBCG), was prepared by a phase-transfer reaction of CG with benzyl chloride in a 25% (w/w) NaOH aq soln–dichloromethane using tetrabutylammonium hydrogensulfate as a catalyst. TBCG was identified by means of an elemental analysis, ^{1}H- and ^{13}C NMR spectroscopy, FD mass spectrometry and an X-ray crystal analysis. The crystal is monoclinic, space group $P2_1/n$, $a=10.231$ (2), $b=14.158$ (4), $c=17.231$ (4) Å, $\beta=95.27$ (4)°, $V=2483$ (1) Å^3, $Z=4$, $D_c=1.189$ g cm^{-3}, μ (Mo $K\alpha$)$=0.66$ cm^{-1}. The final R value was 0.069 for 1196 reflections.

The maximum number of formaldehyde molecules to be added to *N″*-cyanoguanidine (CG) can be anticipated as being 4 in analogy with urea, since urea has an analogous structure to that of CG, and is known to react with formaldehyde to give 3,5-bis(methoxymethyl)tetrahydro-4*H*-1,3,5-oxadiazin-4-one, a tetrasubstituted urea derivative.$^{1)}$ However, the exhaustive hydroxymethylation of CG with a large excess of formaldehyde provided no tetrasubstituted CG, but, rather, 4-cyanoimino-3-(methoxymethyl)tetrahydro-2*H*-1,3,5-oxadiazine, a trisubstituted CG derivative as the major product.$^{2,3)}$ We speculated that a steric hindrance of the hydroxymethyl groups played an important role in the reaction of CG with formaldehyde, and that a decrease in the steric hindrance by the condensation of two hydroxymethyl groups into tetrahydro-2*H*-1,3,5-oxadiazine ring enabled the third addition of formaldehyde. However, any further addition of formaldehyde was interfered with by the cyanoimino group.$^{4)}$ T. Suyama et al.$^{5—7)}$ tried an indirect alkylation of CG in order to avoid the difficulty in the direct alkylation, and to obtain the tetrasubstituted CG derivative. They reported substitution reactions of *N′*-cyano-*S*-alkylisothiourea or *N′*-cyano-*O*-alkylisourea with amines in the presence of heavy-metal chloride into the corresponding alkyl derivatives of CG. However, none of tetrasubstituted CG derivatives could be prepared.

Because the difficulty in obtaining tetrasubstituted CG was supposed to arise from a steric hindrance of the substituent groups and/or the cyanoimino group, and the phase-transfer reaction was expected to have a different reaction mechanism$^{8)}$ from the hydroxymethylation of CG with formaldehyde and to be able to alkylate CG directly, the preparation of *N*,*N*,*N′*,*N′*-tetrabenzyl-*N″*-cyanoguanidine (TBCG) was designed by the phase-transfer reaction of CG with benzyl chloride in a 25% (w/w) NaOH aq soln–dichloromethane using tetrabutylammonium hydrogensulfate (TBAHS)$^{9)}$ as a catalyst. The reaction product was identified as being TBCG by means of an elemental analysis, ^{1}H- and ^{13}C NMR spectroscopy, FD mass spectrometry, and an X-ray crystal analysis.

Results and Discussion

TBCG was obtained in a 64% yield by a phase-transfer reaction of CG with benzyl chloride at room temperature for 24 h. The reaction product was identified as being TBCG by means of an elemental analysis, FD mass spectrometry, and ^{1}H- and ^{13}C NMR spectroscopy in a $CDCl_3$ solution. The yields of TBCG could not exceed 70%, probably because a part of CG was converted into *N*,*N*-(diaminomethylene)urea$^{10)}$ (DU) and/or cyanourea.$^{11)}$ DU was detected in the aquous phase by UV spectrometry.

A colorless prismatic crystal of TBCG was obtained by slowly cooling a MeOH solution. The X-ray crystallographic analysis on this sample finally confirmed the structure of TBCG. The final atomic and equivalent isotropic thermal parameters are listed in Table 1.$^{12)}$ The selected bond lengths and angles are shown in Table 2. The molecular structure of TBCG is shown by an ORTEP drawing in Fig. 1. The structure agrees with that deduced from the elemental analysis and spectroscopic data. A tetrasubstituted CG derivative, TBCG, was prepared for the first time by the phase-transfer reaction. Other tetraalkyl derivatives of CG, such as tetra-*n*-butyl-CG and tetraethyl-CG, could be prepared by similar procedures.

The least-square planes (plane 1—4) comprising of each 6 carbon atoms in the benzene ring (C(4)—C(9) : R-1, C(11)—C(16) : R-2, C(18)—C(23) : R-3, and C(25)—C(30) : R-4, respectively) listed in Table 3 show their planary nature. The dihedral angles between each two planes are also listed in Table 3. Plane 1 is approximately antipararell to plane 4.

Experimental

Preparation of TBCG. After dissolving 0.42 g (5.0

Table 1. Final Atomic Parameters (Positional, $\times 10^4$) and Thermal Parameter (B_{eq}, $\times 10$) for *N*,*N*,*N*′,*N*′-Tetrabenzyl-*N*″-cyanoguanidine ($C_{30}N_4H_{28}$)

Atom	x	y	z	$B_{eq}/\text{Å}^2$	Atom	x	y	z	$B_{eq}/\text{Å}^2$
N(1)	1812	−1510	8381	57	C(14)	6575	3395	9722	61
N(2)	2904	62	8405	33	C(15)	6579	2435	9766	63
N(3)	3790	1323	7842	35	C(16)	6074	1919	9126	52
N(4)	4426	−173	7436	38	C(17)	4739	126	6652	47
C(1)	2351	−784	8368	41	C(18)	4236	−578	6038	35
C(2)	3706	363	7904	37	C(19)	2904	−753	5894	47
C(3)	2744	1912	8143	41	C(20)	2445	−1384	5297	56
C(4)	1363	1673	7782	33	C(21)	3285	−1823	4866	62
C(5)	323	1617	8249	48	C(22)	4582	−1646	5011	59
C(6)	−944	1483	7920	67	C(23)	5066	−1033	5584	49
C(7)	−1176	1378	7136	68	C(24)	4987	−1078	7748	39
C(8)	−182	1410	6662	57	C(25)	6145	−931	8345	30
C(9)	1117	1567	6983	43	C(26)	6000	−831	9136	61
C(10)	5043	1829	7740	43	C(27)	7138	−678	9660	40
C(11)	5561	2390	8463	37	C(28)	8315	−655	9398	40
C(12)	5574	3353	8441	48	C(29)	8443	−735	8658	40
C(13)	6062	3872	9076	63	C(30)	7383	−891	8134	65

Table 2. Selected Bond Lengths and Bond Angles

Bond length	l/Å	Bond length	l/Å
N(1)-C(1)	1.168		
C(1)-N(2)	1.324		
N(2)-C(2)	1.315		
C(2)-N(3)	1.367	C(2)-N(4)	1.370
N(3)-C(3)	1.487	N(4)-C(17)	1.479
C(3)-C(4)	1.529	C(17)-C(18)	1.509
C(4)-C(5)	1.395	C(18)-C(19)	1.374
C(5)-C(6)	1.379	C(19)-C(20)	1.408
C(6)-C(7)	1.363	C(20)-C(21)	1.339
C(7)-C(8)	1.362	C(21)-C(22)	1.351
C(8)-C(9)	1.408	C(22)-C(23)	1.373
C(9)-C(4)	1.385	C(23)-C(18)	1.368
N(3)-C(10)	1.493	N(4)-C(24)	1.484
C(10)-C(11)	1.531	C(24)-C(25)	1.510
C(11)-C(12)	1.364	C(25)-C(26)	1.392
C(12)-C(13)	1.373	C(26)-C(27)	1.423
C(13)-C(14)	1.363	C(27)-C(28)	1.326
C(14)-C(15)	1.361	C(28)-C(29)	1.301
C(15)-C(16)	1.383	C(29)-C(30)	1.364
C(16)-C(11)	1.384	C(30)-C(25)	1.351
Bond angle	**ϕ/°**	**Bond angle**	**ϕ/°**
N(1)-C(1)-N(2)	175.0	C(2)-N(4)-C(17)	123.7
C(1)-N(2)-C(2)	123.1	C(2)-N(4)-C(24)	118.6
N(2)-C(2)-N(3)	115.1	C(17)-N(4)-C(24)	117.6
N(2)-C(2)-N(4)	127.6	N(3)-C(3)-C(4)	113.9
N(3)-C(2)-N(4)	117.3	N(3)-C(10)-C(11)	91.1
C(2)-N(3)-C(3)	118.1	N(4)-C(17)-C(18)	111.7
C(2)-N(3)-C(10)	123.7	N(4)-C(24)-C(25)	120.2
C(3)-N(3)-C(10)	115.1		

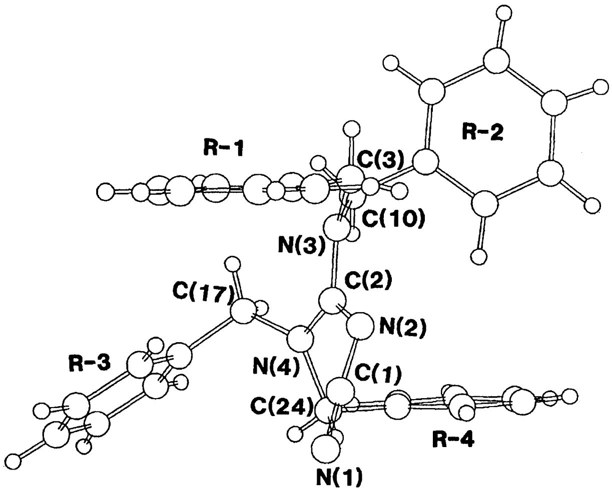

Fig. 1. Molecular structure of *N*,*N*,*N*′,*N*′-tetrabenzyl-*N*″-cyanoguanidine with atomic numbering. The atomic numbering is identical with Table 1 and R-1—R-4 represent the benzene rings comprising of C(4)—C(9), C(11)—C(16), C(18)—C(23), and C(25)—C(30), respectively.

mmol) of CG and 0.39 g (1.2 mmol) of TBAHS in 8 ml of a 25% (w/w) aquous NaOH soln at room temperature or below, 3.16 g (25 mmol) of benzyl chloride and 4 ml of dichloromethane were added. While keeping this solution at room temperature, it was stirred for 24 h. The solution was allowed to stand until it separated into two layers; the dichloromethane layer was then separated. After elimination of solvent and residual amounts of benzyl chloride under reduced pressure, the deposited crystals (TBCG) were recrystallized from MeOH to give TBCG (1.42 g:64%). Mp. 159—160 °C.

Elemental Analysis: Found: C, 80.92; N, 12.54; H, 6.34%. Calcd for $C_{30}N_4H_{28}$: C, 81.08; N, 12.61; H, 6.31%. FD-MS (m/z)=444 (M^+). ^{1}H NMR (90 MHz, $CDCl_3$) δ=4.39 (s, 8H, $-CH_2-$), 7.18—7.46 (m, 20H, $-C_6H_5$); ^{13}C NMR (90 MHz, $CDCl_3$) δ=52.95 ($-CH_2-$), 116.61 (-CN), 127.96, 128.80, 135.55 ($-C_6H_5$), 166.88 ($=C\langle$).

Tetra-*n*-butyl-CG: Yield 40%, viscous liquid; elemental analysis: Found: C, 70.08; N, 18.12; H, 11.75%. Calcd for $C_{18}N_4H_{36}$: C, 70.13; N, 18.18; H, 11.69%. FD-MS (m/z)=308 (M^+). ^{1}H NMR (90 MHz, DMSO-d_6) δ=3.23 (t, J=5 Hz, 12H, $-CH_3$), 1.39 (m, 16H, $-CH_2-$), 0.88 (t, J=5

Table 3. The Least-Square Planes Composed of 6 Carbon Atoms of Benzene Rings with Their Heights from the Plane and Dihedral Angles between the Planes

Plane 1		Plane 2		Plane 3		Plane 4	
Atom	Shift/Å	Atom	Shift/Å	Atom	Shift/Å	Atom	Shift/Å
C(4)	−0.006	C(11)	−0.003	C(18)	−0.002	C(25)	+0.003
C(5)	+0.010	C(12)	+0.008	C(19)	−0.001	C(26)	−0.003
C(6)	−0.007	C(13)	−0.010	C(20)	+0.002	C(27)	+0.007
C(7)	−0.002	C(14)	+0.007	C(21)	−0.001	C(28)	−0.012
C(8)	+0.009	C(15)	−0.004	C(22)	−0.001	C(29)	+0.012
C(9)	−0.003	C(16)	+0.001	C(23)	+0.003	C(30)	−0.007

Dihedral angles between the planes

	Plane 2	Plane 3	Plane 4
Plane 1	84.62	144.20	177.35
Plane 2	—	78.41	92.87
Plane 3	—	—	33.90

Hz, 8H, $-CH_2-$); ^{13}C NMR (90 MHz, DMSO-d_6) $\delta=13.51$ ($-CH_3$), 19.35, 29.18, 43.38 ($-CH_2-$), 116.60 (–CN), 166.10 (=C<).

Tetraethyl-CG: Yield 24%, viscous liquid; elemental analysis: Found: C, 61.15; N, 28.51; H, 10.28%. Calcd for $C_{10}N_4H_{20}$: C, 61.22; N, 28.57; H, 10.20%. FD-MS (m/z)= 196 (M^+). ^{1}H NMR (90 MHz, $CDCl_3$) $\delta=3.35$ (q, $J=4$ Hz, 12H, $-CH_3$), 1.17 (t, $J=4$ Hz, 8H, $-CH_2-$); ^{13}C NMR (90 MHz, $CDCl_3$) $\delta=12.93$ ($-CH_3$), 43.38, ($-CH_2-$), 117.48 (–CN), 166.26 (=C<).

X-Ray Crystal Analysis of TBCG. A noncolour prismatic crystal obtained from MeOH with dimensions of ca. 0.5×0.35×0.3 mm^3 was mounted on a Rigaku-6S automated four-circle diffractometer. Based on systematic absences of ($h0l$) reflections for $h+l$ odd and ($0k0$) k odd, the space group was determined to be $P2_1/n$. Intensity data were measured by means of the ω–2θ scan mode up to 2θ of 55.0° by using Mo $K\alpha$ radiation ($\lambda=0.7107$ Å).

Crystal data, $C_{30}N_4H_{28}$, M.W.$=444.58$, monoclinic, space group $P2_1/n$, $a=10.231$ (2), $b=14.158$ (4), $c=17.231$ (4) Å, $\beta=95.27$ (4)°, $V=2483$ (1) Å^3, $Z=4$, $D_c=1.189$ g cm^{-3}, μ (Mo $K\alpha$)$=0.66$ cm^{-1}. The structure of TBCG was solved by direct methods and refined anisotropically for Non-H atoms and isotropically for H atoms. The final cycle of full-matrix least-squares refinement was based on 1196 observed reflections ($|F_o|>3.00\sigma|F_o|$) and converged (the largest parameter shift was 1.99 times its esd) with unweighted and weighted agreement factors of 0.069 (R) and 0.064 (R_w), respectively. The standard deviation of an observation of unit weight was 2.31. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.23 and −0.25 e$^-$ Å^{-3}, respectively. Neutral-atom scattering factors were taken from Cromer and Weber.[13)] Anomalous dispersion effects were included in F_{calc};[14)] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[15)] All calculations were performed using the TEXSAN[16)] crystallographic software package of Molecular Structure Corporation.

We wish to thank Professor Hayao Kobayashi for his kind support in the data collection on the Rigaku-6S diffractometer at Toho University and in the computation.

References

1) H. Kadowaki, *Bull. Chem. Soc. Jpn.*, **11**, 268 (1936).

2) M. Takimoto, T. Ebisuno, and R. Shiba, *Bull. Chem. Soc. Jpn.*, **56**, 3319 (1983).

3) T. Ebisuno, M. Takimoto, and R. Shiba, *Bull. Chem. Soc. Jpn.*, **57**, 275 (1984).

4) R. Shiba, M. Takahashi, T. Ebisuno, and M. Takimoto, *Bull. Chem. Soc. Jpn.*, **62**, 3721 (1989).

5) T. Suyama and K. Odo, *Yuki Gosei Kagaku Kyokai Shi*, **34**, 427 (1971); *Chem. Abstr.*, **74**, 140877u (1971).

6) T. Suyama, T. Iwaoka, T. Yatsurugi, and E. Ichikawa, *Nippon Kagaku Kaishi*, **1986**, 1192; *Chem. Abstr.*, **107**, 6900t (1987).

7) T. Suyama, T. Iwaoka, and E. Ichikawa, *Nippon Kagaku Kaishi*, **1986**, 1246; *Chem. Abstr.*, **107**, 6901u (1987).

8) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).

9) A. Brandstrom and K. Gustavii, *Acta Chem. Scand.*, **23**, 195 (1969).

10) M. Takimoto and K. Koeda, *Kogyo Kagaku Zasshi*, **63**, 797 (1960); *Chem. Abstr.*, **56**, 6639c (1962).

11) A. E. A. Werner and J. Gray, *Sci. Proc. R. Dublin Soc.*, **24**, 209 (1947).

12) The coordinates and isotropic thermal parameters of H atoms, the anisotropic thermal parameters of non-H atoms, and the F_o-F_c tables have been deposited as Document No. 66037 at the Office of the Editor of Bull. Chem. Soc. Jpn.

13) D. T. Cromer and J. T. Waber, "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham, England (1974), Vol. IV, Table 2.2 A.

14) J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, **17**, 781 (1964).

15) D. T. Cromber, "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham, England (1974), Vol. IV, Table 2.3.1.

16) "TEXSAN--TEXRAY Structure Analysis Package," Molecular Strucure Corporation (1985).