significant steric congestion and to short inter-ring Au ··· Au distances; since the Au ··· Au interaction is attractive,[12] it is naturally present. However, in **4b** the longer tetramethylene chain leads to a 25-membered ring, and the observed conformation with the tetramethylene chains passing through the ring centers naturally leads to minimum steric congestion but longer Au ··· Au distances than in **4a**. The complex could distort to give shorter Au ··· Au distances but this would cause greater steric hindrance; the steric effects are clearly dominant in this case.

In summary, it is established that gold(I) catenanes with diacetylide and diphosphane ligands can be formed easily by self-assembly, that the transition from simple ring to [2]catenane can be controlled by simple ligand design and that, in at least one case, it is possible for the simple ring and [2]catenane to interconvert. While aurophilic attractions may enhance catenane formation they are clearly not a necessary feature, and the low steric hindrance associated with the linear gold(I) acetylide units appears to be more important in allowing the easy formation of catenanes. Attractive inter-aryl forces also favor catenane formation. It follows that the principles outlined here may also be useful in the design of more complex molecular topologies, such as rotaxanes and knots with organometallic functionality, and that these systems are well suited for studies of the mechanisms and energetics of catenane formation.

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[9] Synthetic procedures are similar to those described in ref. [8], with gold complexes protected from light by using darkened flasks throughout. Selected data: **2:** Yield: 94 % from [AuCl(SMe$_2$)]. IR (Nujol): $\tilde{\nu} = 2000$ (w, C≡C) cm^{-1}. **3a:** Yield: 70 %. IR (Nujol): $\tilde{\nu} = 2130$ (w, C≡C) cm^{-1}; ^{1}H NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 1.65$ (s, 6H; 2CH$_3$), 2.51 (m, 4H; 2CH$_2$), 4.75 (s, 4H, 2OCH$_2$), 7.01 (m, 4H; 2C$_6$H$_4$), 7.23 (m, 4H; 2C$_6$H$_4$), 7.42 – 7.52 (m, 20H; 4C$_6$H$_5$); ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 40.26$ (s). **4a:** Yield of mixture with **3b** and third isomer: 81 %. Recrystallization from CH$_2$Cl$_2$/Et$_2$O gave pure **4a**. ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 31.67$ (s); IR (Nujol): $\tilde{\nu} = 2132$ (w, C≡C) cm^{-1}. **3b**: ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 35.61$ (s). Third isomer: ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 34.56$ (s), 34.47 (s). **4b**: Yield 68 %; IR (Nujol): $\tilde{\nu} = 2132$ (w, C≡C) cm^{-1}; ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 38.73$ (s). **4c:** Yield 70 %; IR (Nujol): $\tilde{\nu} = 2130$ (w, C≡C) cm^{-1}; ^{31}P NMR (CD$_2$Cl$_2$, 25 °C): $\delta = 37.36$ (s).

[10] The identity of the third isomer is not established at this stage. It could be a more complex catenane or an oligomer. Note that the bulky Ph$_2$P groups will act as a barrier to prevent free motion of interpenetrating rings.

[11] X-ray data; Enraf-Nonius diffractometer equipped with a CCD detector; refinement used SHELX software; crystals were small and of only adequate quality but the structures are well-defined; partial occupation of lattice vacancies by solvent molecules is responsible for the unusual stoichiometries: Complex **3a** · 0.75 CH$_2$Cl$_2$: C$_{47.75}$H$_{43}$Au$_2$Cl$_{1.50}$O$_2$P$_2$, $M_r = 1157.87$, $T = 293$ K, monoclinic, $P2_1/n$, $a = 17.9418(7)$, $b = 14.4752(6)$, $c = 20.1253(6)$ Å, $\beta = 111.736(2)°$, $V = 4855.1(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.584$ Mg m^{-3}, $\mu = 6.218$ mm^{-1}, 33078 reflections, 9880 independent reflections, $\theta_{max} = 26.41°$, refinement by full-matrix least-squares on F^2, 505 parameters, $R1 = 0.0817$, $wR2 = 0.1091$. Complex **4a** · 0.125 C$_2$H$_4$Cl$_2$: C$_{48.25}$H$_{44.5}$Au$_2$Cl$_{0.25}$O$_2$P$_2$, $M_r = 1121.07$, $T = 150(2)$ K, $\lambda = 0.71073$ Å, monoclinic, $P2_1/n$, $a = 12.4526(3)$, $b = 45.006(2)$, $c = 30.538(1)$ Å, $\beta = 98.570(2)°$, $V = 16924(1)$ Å^3, $Z = 16$, $\rho_{calcd} = 1.760$ Mg m^{-3}, $\mu = 7.056$ mm^{-1}, 27409 reflections, 18686 independent reflections, $\theta_{max} = 26.38°$, refinement by full-matrix least-squares on F^2, 1450 parameters, $R1 = 0.0889$, $wR2 = 0.1726$. Complex **4b** · 2.5 CHCl$_3$: C$_{50.25}$H$_{47.25}$Au$_2$Cl$_{3.75}$O$_2$P$_2$, $M_r = 1271.94$, $T = 200(2)$ K, $\lambda = 0.71073$ Å, triclinic, $P\bar{1}$, $a = 15.7561(4)$, $b = 16.1929(5)$, $c = 21.2826(7)$ Å, $\alpha = 106.545(1)$, $\beta = 97.842(1)$, $\gamma = 102.660(1)°$, $V = 4962.5(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.702$ Mg m^{-3}, $\mu = 6.209$ mm^{-1}, 70232 reflections, 34852 independent reflections, $\theta_{max} = 32.70°$, 1103 parameters, $R1 = 0.0957$, $wR2 = 0.2390$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-120855 – 120857. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Specific Alkylation of Guanine Opposite to a Single Nucleotide Bulge: A Chemical Probe for the Bulged Structure of DNA

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Drug interactions at nucleotide bulges have been intensively studied because the stabilization of the bulged structure by intercalators is thought to enhance frameshift mutation of DNA.[1] Furthermore, the drugs bound to RNA bulges has

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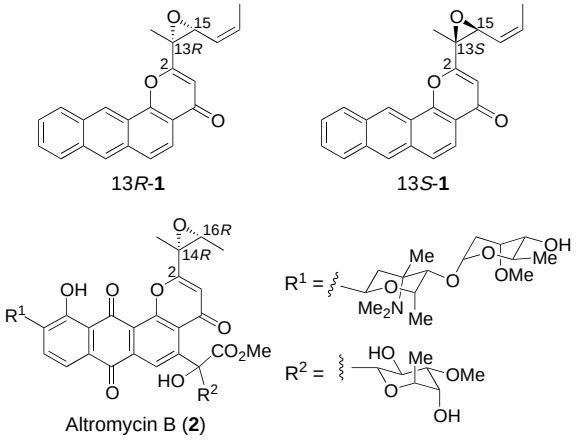
recently been shown to prevent binding of the Tat protein to the *trans*-activating region (TAR).[2] Chemical modifications of DNA and RNA bulges by intercalating and cleaving drugs occurred primarily near the bulge as a result of the much more efficient formation of an intercalated complex at the bulge than at an intrinsic site for the drug.[3, 4] Herein we report that the chiral DNA-alkylating intercalator 13*R*-**1** is a remarkable drug that specifically alkylates guanine (G) opposite a bulge and can be used as a chemical probe for the detection of a bulged structure.



The DNA-alkylating agent **1**[5, 6] was designed as an aglycon model for altromycin B (**2**),[7] a pluramycin antibiotic[8] that intercalates into the DNA base pairs by a threading mode and alkylates guanine at the N7 position by an electrophilic attack by the epoxide.[9] We recently demonstrated that one enantiomer 13*S*-**1**, which possesses a 13*S* epoxide, alkylates guanine of 5′-GG-3′ sequences with high 5′-G selectivity, whereas the other enantiomer 13*R*-**1** exhibited only a very low reactivity.[5] On the basis of molecular modeling and ab initio calculation experiments we have established that the alkylation of guanine by 13*S*-**1** proceeds by a threading intercalation at the 3′-side of the alkylated guanine residue, and the preferential intercalation into the GG step is the origin of the high GG sequence selectivity. The poor reactivity of 13*R*-**1** was rationalized by assuming that the orientation of the epoxide in the intercalated complex is not well suited for the S_N2-type ring opening by 5′- or 3′-guanine residues.[10] To gain further insight into the significance of the precovalent intercalation in DNA alkylation we investigated the alkylation of guanine residues in oligodeoxynucleotides (ODNs) containing a single nucleotide bulge.

The oligonucleotides used in this study were designed to contain a single nucleotide bulge just opposite the GG step, which is the most efficiently alkylated site for **1**.[5] A 35-mer ODN 5′-d(TTT TTG TTA TT**G**$_{12}$ **G**$_{13}$**G**$_{14}$T T**G**$_{17}$**G**$_{18}$ TT**G**$_{21}$ **G**$_{22}$**G**$_{23}$T T**G**$_{26}$**G**$_{27}$ TTG TTT TT) (ODNP) contains two GG doublets and two GGG triplets (shown in bold face), and a single nucleotide bulge was created on the complementary strand opposite the $G_{17}G_{18}$, $G_{21}G_{22}$, and $G_{22}G_{23}$ steps by annealing it with bulge-forming oligomers ODN2, ODN3, and ODN4, respectively (Figure 1). These ODNs possess a 5′-CTC-3′ sequence instead of the 5′-CC-3′ sequence in fully complementary ODN1. ODNP in which the 5′-end was labeled with ^{32}P was annealed with ODN1-ODN4 and the duplex was treated with 13*S*- or 13*R*-**1**. Alkylated guanine residues were detected as cleavage bands by treatment with hot piperidine followed by polyacrylamide gel electrophoresis (PAGE) analysis. Autoradiograms of the gel are shown in Figure 2.

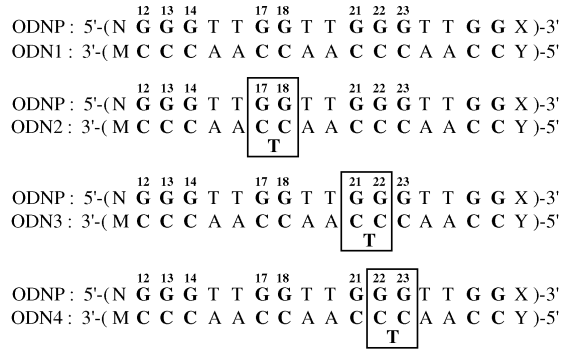


Figure 1. Sequences of ODNP and ODN1 – ODN4. GC base pairs at normal and bulged sites are shown in bold face. Bulged sites are also boxed. N = TTTTTGTTATT, M = AAAAACAATAA, X = TTGTTTTT, Y = AACAAAAA.

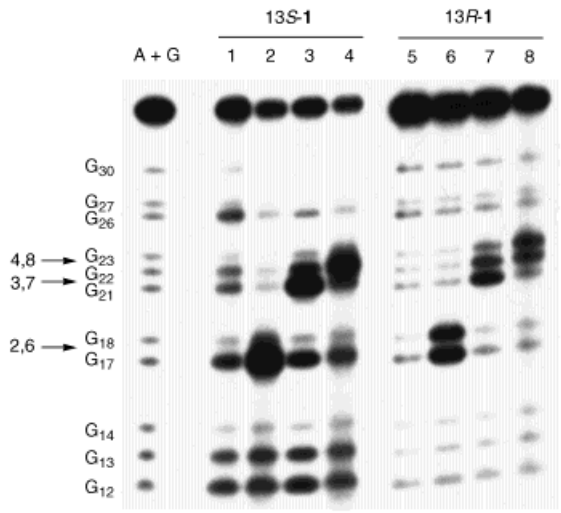


Figure 2. Guanine alkylation in the duplex DNAs containing a single bulge by 13*S*- and 13*R*-**1**. ODNP in which the 5′-end was labeled with ^{32}P was annealed with ODN1 – ODN4. The duplexes were treated with 13*S*- and 13*R*-**1** (50 μM) for 5 h at 37 °C in Tris-HCl buffer (pH 7.6, 50 mM) in the presence of calf thymus DNA (10 μM). Alkylated ODNs were separated by precipitation with ethanol. Alkylated G residues were detected as cleavage bands by heating with piperidine (90 °C, 30 min) followed by electrophoresis on the denaturing sequencing gel (15 % polyacrylamide and 7 M urea) and autoradiography. Lanes 1 and 5: ODN1; lanes 2 and 6: ODN2; lanes 3 and 7: ODN3; lanes 4 and 8: ODN4; A + G, Maxam – Gilbert A + G sequencing reactions. Lanes 1 – 4: 13*S*-**1** and lanes 5 – 8: 13*R*-**1**. For clarity the bulged sites are shown by arrows with the lane numbers.

Guanine alkylation of the fully complementary duplex ODNP – ODN1 by 13*S*-**1** selectively occurred at the 5′-G of the 5′-GG-3′ sequence (lane 1). The 5′-G (G_{12} and G_{21}) and middle G (G_{13} and G_{22}) were selectively alkylated in the 5′-GGG-3′ sequence, which indicates that 13*S*-**1** preferentially intercalates into the GG step and alkylates 5′-G at the

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intercalated site. Guanine alkylation occurred more readily at bulged sites than at normal GG sites in the duplexes containing a single nucleotide bulge (lanes 2–4). Alkylation at $G_{17}G_{18}$ in ODNP–ODN2 (lane 2) and $G_{21}G_{22}$ in ODNP–ODN3 (lane 3) in a bulged structure was enhanced 2.5- and 3.6-fold, respectively, relative to the cleavage of the normal strand (lane 1).[11] Almost same 5′-G selectivity as observed for the normal GG doublets was detected. Enhanced alkylation susceptibility of guanine residues opposite the bulge is well rationalized in terms of the increased stability of the intercalated complex of 13*S*-**1**.[4]

In sharp contrast to the nearly negligible guanine alkylation of the fully complementary duplex ODNP–ODN1 by 13*R*-**1** (lane 5), strong cleavage bands at guanine residues opposite a bulge were observed (lanes 6–8). Alkylation at $G_{17}G_{18}$ in ODNP–ODN2 (lane 6) and $G_{21}G_{22}$ in ODNP–ODN3 (lane 7) was enhanced 13- and 25-fold, respectively.[12] Both the 5′- and 3′-side guanine residues of the 5′-GG-3′ sequence in the bulge are almost equally alkylated, in sharp contrast to the high 5′-G selectivity observed for 13*S*-**1** (lanes 6 and 2, respectively). Since the alkylation at the normal G and GG sites by 13*R*-**1** is quite inefficient (lane 5), the marked enhancement of the reactivity of guanine alkylation should be ascribable to the formation of a unique intercalated complex of 13*R*-**1** that is only attainable in the bulged structure.

Having established that 13*R*-**1** selectively alkylates guanine opposite a bulge, we carried out molecular modeling studies for the complex of bulge-containing simplified model oligomer d(CATG$_4$_G$_5$TAC/GTAC$_{12}$T$_{13}$C$_{14}$ATG) with 13*R*-**1**.[13] These simulations showed that the alkylation at G_4 seems to proceed smoothly only when 13*R*-**1** intercalates into the G_4G_5 step through a threading mode and the intercalated complex is stabilized by stacking with G_5 and with T_{13} of the complementary strand (Figure 3a). The average nonbonding distance between C15 of 13*R*-**1** and N7 of G_4 in the molecular dynamic simulation for 100 ps at 300 K was 3.37 Å. An alternative intercalated complex for G_5 alkylation where 13*R*-**1** strongly stacks with both G_4 and T_{13} was also feasible (Figure 3b).

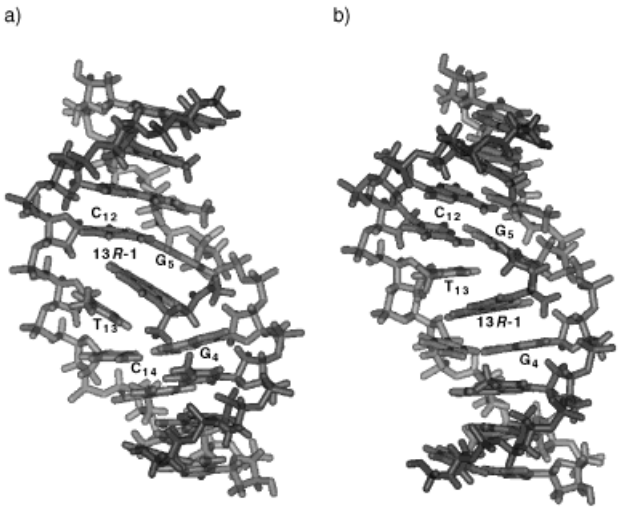

Figure 3. Energy-minimized structures for the complex of d(CATG$_4$_G$_5$TAC/GTAC$_{12}$T$_{13}$C$_{14}$ATG) with 13*R*-**1**. The complexes viewed from a major groove are shown. a) 13*R*-**1** intercalates into the G_4G_5 step by a threading mode and stacks with G_5 and with T_{13} of the complementary strand. The epoxide carbon atom C15 is close to N7 of G_4 (3.44 Å). b) 13*R*-**1** intercalates into the G_4G_5 step; but this time it stacks with G_4 and with T_{13} of the complementary strand. The epoxide carbon atom is close to N7 of G_5 (3.51 Å).

In general, DNA-cleaving intercalators are known to exhibit enhanced reactivity in cleaving DNA at bulges as a result of the increased stability of the intercalated complex. In contrast, 13*R*-**1** specifically alkylates guanine opposite a T bulge, not only because of the increased complex stability as is generally observed for most intercalating drugs, but also because of the formation of the uniquely oriented complex in which the S_N2-type ring opening of the epoxide is highly facilitated by the neighboring guanine residue. Such designed DNA-cleaving drugs that possess extremely high bulge selectivity can be used as a chemical probe for bulged structure in DNA and RNA.

Experimental Section

Molecular modeling of a bulge-containing oligomer with 13*R*-**1** was carried out as follows. An oligomer containing a single T-bulge d(CAT G_G TAC/GTA CTC ATG) was produced from a fully complementary B-form duplex d(CAT GAG TAC/GTA CTC ATG) by removing dA monophosphate form the GAG sequence. The sugar–phosphate backbone between the two guanine residues was connected manually. The structure of this oligomer was stored as a nonminimized bulge. Compound 13*R*-**1** was manually inserted into the hole of the bulged site by a threading mode, and the complex was energy minimized.[13] Manual docking of 13*R*-**1** into the nonminimized bulge was repeated with various geometries of 13*R*-**1** relative to the bulge. With these operations two complexes were obtained with a reasonable nonbonding distance between the epoxide carbon atom (C15) and the guanine N7 (Figures 3a and b). Molecular dynamic simulation was carried out with these complexes as a starting geometry for 100 ps at 300 K.

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[10] It should be noted that altromycin B (**2**) possesses an epoxide with the same absolute configuration as that of 13*R*-**1** and alkylates the 3′-G at the intercalated site. DNA–sugar interactions that would change the orientation of the epoxide relative to the 3′-G have a crucial effect on the efficiency of the epoxide ring opening.

[11] The relative intensity of the cleavage bands at G_nG_m and at $G_{12}G_{13}G_{14}$ in the same strand for the normal ODNs and for those with a bulge, $I_{normal(n,m)}$ and $I_{bulge(n,m)}$, respectively, was measured by densitometric analysis: $I_{normal(17,18)}$ (lane 1) 0.87; $I_{normal(21,22)}$ (lane 1) 0.59; $I_{bulge(17,18)}$ (lane 2) 2.2; $I_{bulge(21,22)}$ (lane 3) 2.1. The enhanced alkylation susceptibility at the bulge $I_{bulge(n,m)}/I_{normal(n,m)}$ was thus calculated as 2.5 (2.2/0.87) at the $G_{17}G_{18}$ step and 3.6 (2.1/0.59) at the $G_{21}G_{22}$ step.

[12] $I_{normal(17,18)}$ (lane 5) 1.8; $I_{normal(21,22)}$ (lane 5) 1.1; $I_{bulge(17,18)}$ (lane 6) 23; $I_{bulge(21,22)}$ (lane 7) 28.

[13] Molecular mechanic calculations were carried out using the Amber* force field with the GB-SA solvation model of water implemented in the molecular modeling software MacroModel version 6.0. Molecular dynamic simulations were performed at 300 K for 100 ps. The intermediate structure during the MD simulations was sampled every 1 ps.

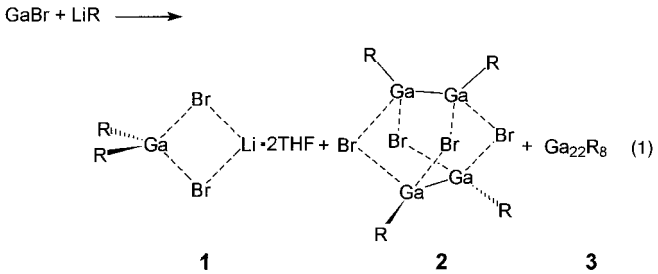
$Ga_{22}[Si(SiMe_3)_3]_8$: The Largest Atom-Centered Neutral Main Group Metal Cluster**

Andreas Schnepf, Edgar Weckert, Gerald Linti, and Hansgeorg Schnöckel*

Dedicated to Professor Reinhart Ahlrichs on the occasion of his 60th birthday

Until recently, clusters of metal atoms were limited to transition metals.[1] With the synthesis of an Al_{77} cluster,[2] which was the largest metal atom cluster hitherto that has been characterized by X-ray analysis, we have developed a new route to the synthesis of this type of compound.[3] We started from metastable AlX/GaX solutions (X = Cl, Br, I), which disproportionate, even under mild conditions, into the corresponding metal and trihalide (e.g.: $3\,GaBr \rightarrow 2\,Ga + GaBr_3$).[4] However, by substituting the halide with suitable ligands, this process can be delayed so that the compounds that contain clusters of metal atoms can be captured as intermediates before they form the metals; in some cases they can even be crystallized. Since the preparation of the necessary metastable subhalide solutions requires special apparatus,[5] this method has only been used by our research group up to now. We expect, however, that the successful synthesis of unusual species will lead to a widespread use of this technique in the future. We report here on a gallium cluster in which a central gallium atom exhibits a coordination number of 13, which is very unusual even for "real" metals.

Cocondensation of molecular GaBr, which is thermodynamically stable only at high temperatures (about 1000 °C) and low pressures (about 10^{-2} mbar), with a mixture of toluene and THF at −196 °C followed by warming to −78 °C afforded a metastable GaBr solution which already disproportionated above −20 °C into gallium and $GaBr_3$. However, treating this solution at −78 °C with tris(trimethylsilyl)silyllithium (hypersilyllithium) in toluene leads, upon slow warming, to an initially dark red solution, which later turns dark brown to almost black and is stable at room temperature [Eq. (1)].



R = $Si(SiMe_3)_3$

After removal of the solvent mixture under vacuum and extraction of the residual solid with pentane, a dark red-brown solution was obtained from which colorless crystals of **1** precipitate as a first product. In addition to this product, which is formed by oxidation of the original Ga^I species, **2** is observed as a second oxidation product under certain conditions.[6] Compound **2** is isostructural with the corresponding chloro derivative $[GaClSi(SiMe_3)_3]_4$.[7] After separation of the oxidized species **1** and **2**, a reduced, metal-rich species should therefore be present in which gallium has an oxidation number less than 1. Indeed, upon concentration of the pentane extract, such a compound, **3**, is obtained as black crystals in the form of cubes and rods. Its ESR spectrum shows that it is a diamagnetic compound. The results of the X-ray structural analysis are presented in Figure 1.

The core of the gallium cluster can be described as follows: A central gallium atom is surrounded by 13 gallium atoms at a large distance (average value 294.2 pm). This shell of thirteen atoms, within which the average distance between the gallium

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