$$(C_5Me_5)_3U^{III} \longrightarrow [(C_5Me_5)U^{IV}]^{3+} + (C_5Me_5)_2 + 3e^- \quad (4)$$

complexes can be generalized to U^{III} and can be coupled to the U^{III} redox chemistry to do multielectron reductions. This also shows that the $C_8H_8^{2-}/U^{IV}$ components of uranocene can exist in forms other than the very stable parallel ring structure of $[U(C_8H_8)_2]$. This reaction suggests a rich reductive chemistry can be accessed by coupling steric crowding and lower f-element oxidation states.

Experimental Section

All manipulations were performed under an N_2 or Ar atmosphere by glove box or Schlenk techniques.

1: In a THF-free glovebox, 1,3,5,7-C_8H_8 (24 mg, 0.23 mmol) was added to a brown solution of $[(C_5Me_5)_3U]$ (100 mg, 0.155 mmol) in toluene (10 mL). After the brown solution was stirred at room temperature for 4 d, the solvent was removed by rotary evaporation. The gummy brown solid was washed with hexanes and dried under reduced pressure to afford **1** as a dark brown powder (70 mg, 85 %). IR (KBr): $\tilde{\nu}$ 3022 m, 2903 s, 2851 m, 1435 w, 1373 w, 1020 w, 902 w, 797 w, 729 sh, 673 sh, 568 w cm^{-1}; Elemental analysis ($U_2C_{44}H_{54}$): calcd: C 49.91, H 5.14; found: C 49.64, H 4.92; ^1H NMR (400 MHz, [D_6]benzene, 25 °C): $\delta = 5.5$ (s, C_5Me_5; $\Delta\nu_{1/2} = 10$ Hz, 30 H), -41.7 (s, C_8H_8; $\Delta\nu_{1/2} = 14$ Hz,16 H), -42.2 (s, C_8H_8; $\Delta\nu_{1/2} = 20$ Hz, 8 H); ^1H NMR (400 MHz, [D_8]toluene, -100 °C): $\delta = 14.5$ (s, C_5Me_5), -80.8 (s, C_8H_8, 16 H), -87.5 (s, C_8H_8, 8 H); ^{13}C NMR (100 MHz, [D_6]benzene, 25 °C): $\delta = 395$, 280, 279, -26.

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Application of Reductive Samariation to the Synthesis of Small Unnatural Peptides**

Marina Ricci, Leire Madariaga, and Troels Skrydstrup*

Dedicated to Professor Anders Kjær on the occasion of his 80th birthday

The selective introduction of side chains to a specific glycine residue in a peptide strand represents a challenging task for the preparation of unnatural peptides. Instead of a stepwise approach where commercially available or synthetic amino acids are incorporated by a traditional peptide synthesis, application of a direct peptide modification step is justified by the numerous analogues which may be quickly synthesized from a single and intact peptide. As reactive intermediates, glycine enolates[1–4] and radicals[5–7] as well as

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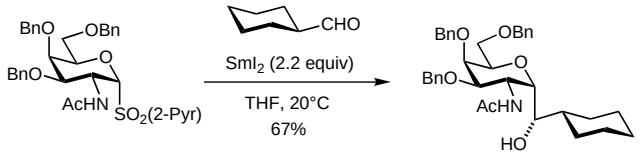
glycine cation equivalents[8, 9] have been exploited for the C–C coupling step. The seminal studies by Seebach and coworkers[1] are the most impressive in this area, demonstrating that linear and cyclic peptides up to 11 units in length can be alkylated at a glycine residue with a polylithiated peptide enolate. Such enolates are prepared by the low-temperature deprotonation of first the acidic amide protons with lithium diisopropylamide (LDA) followed by one of the α-CH protons of glycine. However, successful deprotonation and alkylation requires that the nitrogen atom of the adjacent amino acid in the C-terminus direction to the arising enolate be N-alkylated. This problem could be resolved by incorporating a removable electron-withdrawing substituent on the glycine α-carbon atom; nevertheless a subsequent reduction step is required for the removal of the activating group.[1e]

Here we show that reductive samariation of glycine pyridyl sulfides in the presence of carbonyl substrates (Barbier conditions) is a possible alternative for the selective incorporation of carbinol side chains onto glycine residues in peptides. Of particular interest is that alkylation occurs at room temperature in the presence of the amide protons and, more importantly, without the aid of an activating group.

In previous work, we have demonstrated that C-glycosides can be stereoselectively obtained by a samarium diiodide induced Barbier reaction with glycosyl pyridyl sulfones.[10, 11] The key to the success of this reaction lies in the ease of the reduction of the pyridyl sulfone group, which is in part due to the generation of a stabilized anomeric radical.[12] Pertinent to the present work are the successful carbonyl coupling reactions, which proceed even when the monosaccharide possesses an acetamido group at the C2 position,[10c,f,g] implying that the organosamarium intermediate displays a higher reactivity for carbonyl coupling rather than internal or external protonation (Scheme 1). These observations under

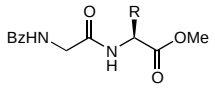
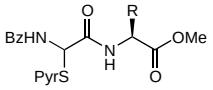
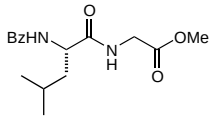
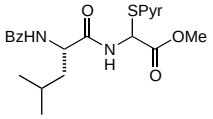
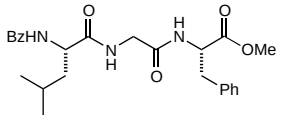
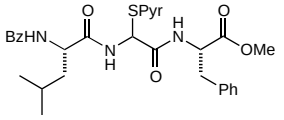


Scheme 1. Previous results [10c,f,g] in the SmI_2-promoted coupling of *N*-acetylgalactosamine pyridyl sulfones with carbonyl compounds. Bn = benzyl, 2-Pyr = 2-pyridyl.

consideration of the fact that α-glycyl radicals display an enhanced stability owing to the captodative effect[7] suggested that similar glycine derivatives could also undergo reductive samariation and concomitant carbonyl coupling reactions as the glycosyl pyridyl sulfones.

The feasibility of this approach was first assessed with the dipeptide derivative **1a** (Table 1, entry 1). The success of this work requires that a reducible group can be selectively introduced at the α-carbon atom of the glycine residue in the presence of other amino acid units. The previous work by Easton and collaborators concerning selective bromination of dipeptides with *N*-bromosuccinimide (NBS) was therefore significant for our studies.[5a,b]

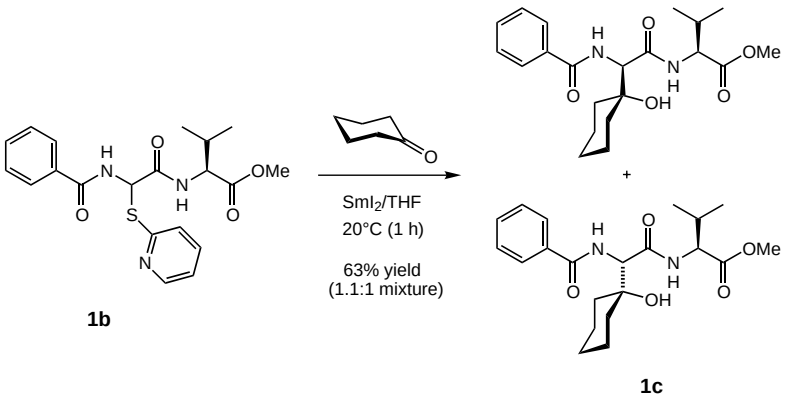
Table 1. Introduction of the pyridyl sulfide group.

Entry	Peptide[a]	Pyridyl sulfide (yield)[b]
		
1	R = *i*Pr **1a**	**1b**, 85 %
2	R = CH_2Ph **2a**	**2b**, 87 %
3	R = CH_2CO_2Me **3a**	**3b**, 74 %
4	R = Me **4a**	**4b**, 42 %
5	 **5a**	 **5b**, 48 %
6	 **6a**	 **6b**, 59 %[c]

[a] For the reaction conditions see the Experimental Section. [b] Yields of isolated product after chromatography on silica gel. [c] Based on recovered starting material (35 %).

Hence, bromination of **1a** was achieved by photolysis of the dipeptide with one equivalent of NBS in refluxing dichloromethane for 3 h. The bromide proved to be quite unstable and thus the reaction mixture was immediately treated with 2-sulfanylpyridine (2.0 equiv) and diisopropylethylamine (Hünig's base). In this way, the stable pyridyl sulfide **1b**, as an approximately 1.6:1 diastereomeric mixture, could be isolated in 85 % yield after chromatographic separation (Table 1, entry 1). Attempts to oxidize the sulfide to the sulfone were unsuccessful, possibly owing to the sensitivity of the sulfone towards hydrolysis, but this obstacle was of no importance as the glycyl pyridyl sulfide displayed a high reactivity with SmI_2.

Treatment of a mixture of dipeptide **1b** and cyclohexanone with a solution of blue SmI_2 in THF led to the consumption of two equivalents of the one-electron reducing agent over a period of 1 h. After chromatographic purification, an approximately 1:1 diastereomeric mixture of the dipeptide derivatives **1c** was obtained in an encouraging 63 % yield (Scheme 2). This implied that carbonyl coupling is indeed a

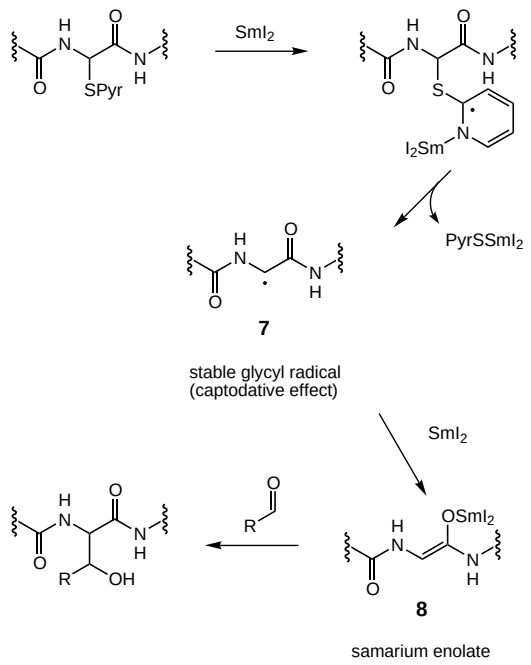


Scheme 2. SmI_2-induced coupling of dipeptide **1b** with cyclohexanone.

fast event in comparison to either intramolecular or intermolecular protonation involving the two amide groups.

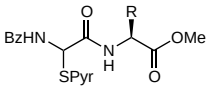
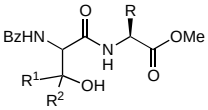
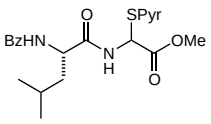
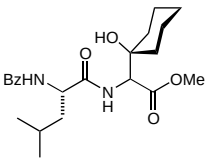
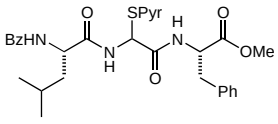
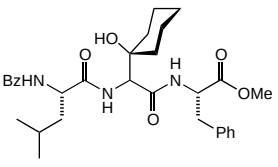
A series of other dipeptides and one tripeptide were then tested in which the glycine residue is located either as a C- or N-terminal residue in the dipeptides **2a**–**5a** (Table 1, entries 2–5) or as the middle unit of tripeptide **6a** (entry 6), in order to assess the effect of the glycine position on both yields and diastereoselectivities. The pyridyl sulfides **2b**–**6b** were obtained in good to acceptable yields (42–87%) using the Easton protocol for bromination. It was pleasing to see that reductive samariation and coupling also proceeded in good yields (43–65%) to afford the modified dipeptides **2c**–**5c** as approximately 1:1 diastereomers (Table 2, entries 1, 4–6). The use of *n*-octanal or cyclohexanecarbaldehyde with **2b** furnished inseparable diastereomeric mixtures of **2d** and **2e** (entries 2 and 3), although only three isomers could be seen in the ^{1}H NMR spectrum. Quite remarkable was the coupling of tripeptide **6b** to cyclohexanone to give the modified peptide **6c** in a good yield of 50% considering the presence of three amide protons in **6b** (entry 7). In this latter case, a small diastereoselectivity (2:1) was noted for this reaction.[13]

In all cases, diastereoselectivities at the glycyl α-carbon atom were low. This is somewhat surprising considering the high Lewis acid character of samarium(III) salts and hence their ability to form strong complexes with amides or other carbonyl groups.[14] The mechanism of this reaction (Scheme 3) proceeds via the stable glycyl radical **7** by the initial reduction of the pyridyl sulfide group by the divalent lanthanide reagent. Further reduction of this carbon radical by a second equivalent of SmI_2 would lead to a Sm^{III} enolate intermediate **8**. The presence of other possible coordination sites for the metal ion may therefore give rise to cyclic enolate structures, where attack of the incoming electrophile could be directed by the distal side-chain substituent of the neighboring amino acid unit.[10c,f,g, 11, 15] The low selectivity suggests that this is not the case, but it is nevertheless an important feature in the application of this approach for combinatorial chemistry.



Scheme 3. A mechanistic proposal for the coupling of pyridyl sulfide containing peptides with carbonyl compounds. Pyr = pyridyl.

Table 2. C-Alkylation of peptides **2b**–**6b**.

Entry	Pyridyl sulfide	Carbonyl compound[a]	Alkylated peptide (yield)[b]
			
1	R = CH_2Ph **2b**	cyclohexanone	**2c**, 64% (1:1)
2	R = CH_2Ph **2b**	*n*-octanal	**2d**, 60% (2.2:1.8:1.0)
3	R = CH_2Ph **2b**	cyclohexanecarbaldehyde	**2e**, 57% (2.0:1.1:1.0)
4	R = CH_2CO_2Me **3b**	cyclohexanone	**3c**, 61% (1:1)
5	R = Me **4b**	cyclohexanone	**4c**, 43% (1:1)
6	 **5b**	cyclohexanone	 **5c**, 45% (1.1:1)
7	 **6b**	cyclohexanone	 **6c**, 50% (2:1)

[a] For the reaction conditions see the Experimental Section. [b] Yields of isolated products after chromatography on silica gel. The numbers in parantheses refer to the diastereomeric ratio as determined by ^{1}H NMR spectroscopy.

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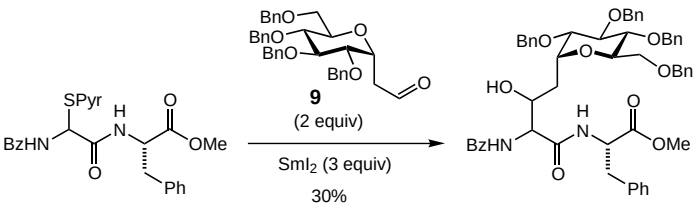
Finally, motivated by the recent interest in the synthesis of C-glycopeptides,[16] a hydrolytically stable analogue of the parent N- or O-glycoside, we have applied the above methodology as an alternative and direct approach to such compounds, as illustrated with the example in Scheme 4. Hence, the dipeptide derivative **2b** was coupled to the easily accessible aldehyde **9**,[17] affording the C-glycopeptide **10** in 30% yield as a mixture of diastereomers.



2b **10**

Scheme 4. Preparation of a C-glycopeptide.

In conclusion, we have presented a novel and mild approach to the alkylation of peptides via reductive samariation. Further work is now in progress to identify other conditions which will increase the diastereoselectivities of these reactions, such as modifying the coordination sphere of the lanthanide ion with chiral ligands or the use of other transition metal reductants.

Experimental Section

Pyridyl sulfide formation: **1b**: A solution of *N*-bromosuccinimide (65 mg, 0.37 mmol) and dipeptide **1a** (99 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) was irradiated with a 150-W lamp for 3 h. The heat from the lamp was sufficient to maintain refluxing. The solution was then cooled to 0 °C, after which 2-sulfanylpyridine (57 mg, 0.51 mmol) and diisopropylethylamine (89 μL, 0.51 mmol) were added. The reaction mixture was stirred for 3 h at 0 °C, then diluted with CH_2Cl_2 and washed with water (2 ×) and brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness, whereafter the residue was purified by flash chromatography (diethyl ether/pentane 7/3) to afford a diastereomeric mixture (1.6:1) of the pyridyl sulfide **1b** (116 mg, 85%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.72$ (d, $J = 4.5$ Hz, 3H), 0.85 (d, $J = 4.5$ Hz, 3H), 0.97 (d, $J = 4.6$ Hz, 3H), 1.00 (d, $J = 4.6$ Hz, 3H), 2.20 (m, 2H), 3.60 (s, 3H), 3.76 (s, 3H), 4.55 (dd, $J = 5.8$, 3.0 Hz, 1H), 4.60 (dd, $J = 5.8$, 3.0 Hz, 1H), 6.47 (d, $J = 5.0$ Hz, 2H), 7.14–7.89 (m, 9H), 8.48 (m, 1H), 8.55 (m, 1H), 9.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.94$, 171.64, 169.36, 165.75, 157.88, 149.34, 149.11, 137.08, 136.96, 133.38, 132.16, 128.69, 127.37, 123.57, 120.78, 58.01, 57.75, 54.36, 54.18, 52.31, 52.06, 31.64, 31.12, 19.26, 19.06, 17.77, 17.40.

Peptide alkylation: **1c**: A 0.1M solution of SmI_2 in THF (5.5 mL, 0.55 mmol) was added to a stirred solution of pyridyl sulfide **1b** (82 mg, 0.20 mmol) and cyclohexanone (62 μL, 0.60 mmol) in THF (0.5 mL) at 20 °C. After stirring for 1 h, saturated aq. NH_4Cl was added to the reaction mixture, which was then extracted twice with CH_2Cl_2. The combined organic phases were washed twice with water, dried with $MgSO_4$, and evaporated to dryness. Flash chromatography (pentane/EtOAc 3/1) gave dipeptides **1c** (49 mg, 63%) as a colorless solid in a 1:1 diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta =$ ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.90$ (d, $J = 4.4$ Hz, 3H), 0.91 (d, $J = 4.4$ Hz, 3H), 0.94 (d, $J = 4.9$ Hz, 3H), 0.97 (d, $J = 4.9$ Hz, 3H), 1.19–1.86 (m, 20H), 2.21 (m, 2H), 3.64 (s, 3H), 3.76 (s, 3H), 4.46 (dd, $J = 5.8$, 3.2 Hz, 1H), 4.50 (dd, $J = 5.9$, 3.3 Hz, 1H), 4.56 (d, $J = 5.4$ Hz, 1H), 4.59 (d, $J = 5.6$ Hz, 1H), 6.85 (d, $J = 5.8$ Hz, 1H), 7.13 (m, 3H), 7.40–7.56 (m, 6H), 7.77–7.84 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.94$, 172.00, 171.54, 168.13, 168.00, 133.75, 132.10, 128.81, 127.28, 73.03, 72.76, 58.31, 57.84, 57.56, 57.41, 52.45, 52.35, 35.67, 35.40, 33.86, 33.59, 30.92, 25.70, 21.89, 21.78, 21.61, 19.23, 19.14, 18.02, 17.70; HR-MS (ES) calcd for $C_{21}H_{30}N_2O_5Na$ ($M + Na$): 413.2052, found: 413.2043.

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Antiferromagnetic Coupling in a Gadolinium(III) Semiquinonato Complex**

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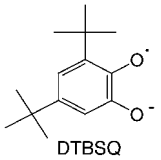
Rare earth ions have long been exploited to influence the properties of magnets by introducing anisotropic contributions and by changing the compensation temperature.[1] In general little is known about the nature of the exchange interactions of rare earth ions among themselves and with other magnetic groups, because until recently few simple compounds containing magnetically coupled f-block ions were available. Recently, complexes of lanthanide ions with various paramagnetic ligands, ranging from metal complexes to organic radicals, were reported.[2–6] In particular gadolinium(III) complexes exhibited ferromagnetic couplings ranging from 0.5 to 10 cm^{-1}. The rather unexpected sign of the coupling was explained by a mechanism in which the magnetic orbitals of the paramagnetic ligands have negligible overlap with the 4f orbitals, but overlap with the empty d and s orbitals of gadolinium polarizes the f electrons with their spins parallel to that of the paramagnetic ligand.[7, 8]

Some exceptions to ferromagnetic coupling were recently reported for copper(II) complexes and nitronyl nitroxide radicals.[9, 10] An antiferromagnetic coupling of 6 cm^{-1} was observed in a chelating nitronyl nitroxide triazole derivative. This suggests that the observed coupling is actually the sum of two contributions, one from the direct overlap of the magnetic orbitals of the ligands with the f orbitals, which presumably results in antiferromagnetism, and the other from the overlap with the s and d orbitals, which leads to ferromagnetism. The former may become dominant when the radical ligands are stronger donors. Therefore we investigated the coupling of gadolinium(III) with semiquinonates, which are much better ligands than nitroxide-type radicals.

The complex $[Gd(Hbpz_3)_2(dtbsq)]\cdot 2CHCl_3$ (**1**; $Hbpz_3$ = hydrotris(pyrazolyl)borate; dtbsq = 3,5-di-*tert*-butylsemiquinonato) was obtained by metathetical reaction between the parent metal benzoato derivative[11] and 3,5-di-*tert*-butylcatechol in alkaline methanol. Recrystallization from chloroform/hexane yielded blue crystals of **1**.



Cyclic voltammetry experiments in acetonitrile showed that **1** undergoes a reversible one-electron redox process at -0.65 V and an irreversible process at $+0.02$ V versus ferrocene/ferrocenyl cation (Fc/Fc^+). Both processes involve the coordinated dioxolene ligand, and the reversible one is assigned to the semiquinonato/catecholato couple, and the irreversible one to the quinone/semiquinonato couple. Given the electrochemical properties of other metal *o*-dioxolene complexes,[12, 13] this behavior is as expected when the different charge density of the metal acceptor is taken into account. The electronic spectrum shows a band at 12600 cm^{-1} and a pattern of bands in the region 26400–28400 cm^{-1}, which were suggested[12] to be internal transitions of the semiquinonato ligand.

Figure 1 shows the X-ray crystal structure of **1**.[14] The coordination sphere around gadolinium comprises six nitro-

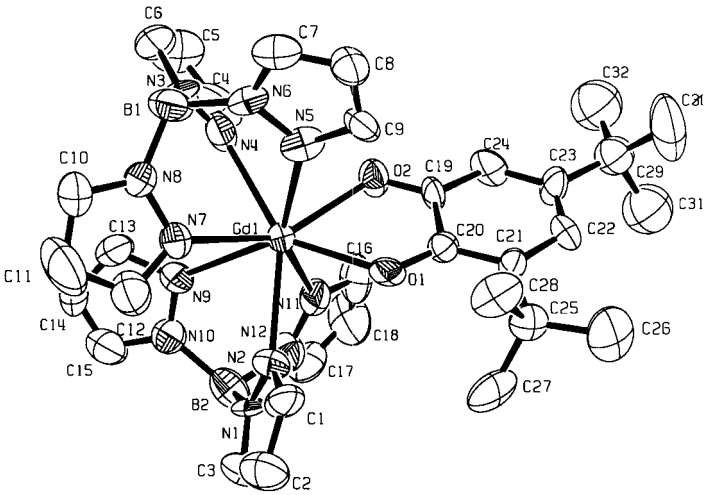


Figure 1. ORTEP view of complex **1** (50% probability thermal ellipsoids); hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Gd1-O1 2.343(9), Gd1-O2 2.354(12), Gd1-N4 2.48(2), Gd1-N2 2.503(14), Gd1-N11 2.53(2), Gd1-N7 2.53(2), Gd1-N5 2.571(11), Gd1-N9 2.585(14), C19-C20 1.49(2), O1-C20 1.27(2), O2-C19 1.25(2); O1-Gd1-O2 67.7(6), O2-Gd1-N4 81.5(5), O1-Gd1-N2 73.1(5), O1-Gd1-N11 88.8(5), O2-Gd1-N11 73.8(5), N2-Gd1-N11 72.9(6), N4-Gd1-N7 79.5(6), N2-Gd1-N7 78.5(5), O1-Gd1-N5 75.6(4), O2-Gd1-N5 78.7(6), N4-Gd1-N5 72.3(5), N7-Gd1-N5 71.3(6), N4-Gd1-N9 75.4(5), N2-Gd1-N9 74.4(5), N11-Gd1-N9 69.3(5), N7-Gd1-N9 72.1(5).

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