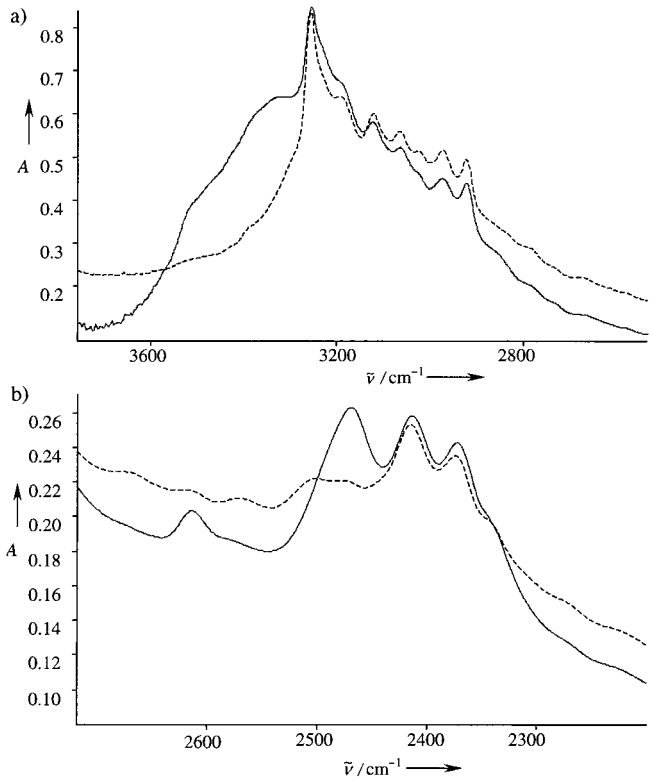

Figure 5. a) FT-IR spectra of the initial $\mathbf{1}\cdot 2.5\,H_2O$ (solid line) and after evacuation of water from the channels (dotted line); b) analogous spectra of $\mathbf{1}(ND_2)\cdot 2.5\,D_2O$. A = absorbance.

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The First Solid-Phase Synthesis of a Peptide-Tethered Platinum(II) Complex**

Marc S. Robillard, A. Rob P. M. Valentijn, Nico J. Meeuwenoord, Gijs A. van der Marel, Jacques H. van Boom,* and Jan Reedijk*

It is well established that removal of cisplatin- and carboplatin-induced DNA adducts contributes to tumor resistance to these drugs.[1] To overcome this problem, a plethora of platinum(II) complexes which interact with DNA in a manner distinct from that of the parent drugs have been designed and evaluated with respect to the distortion of DNA, as well as the interaction with proteins and antitumor activity.[2] In addition, amino acid residues, peptides, and polyamides have been successfully employed as site-specific DNA-interacting elements conjugated to metal complexes.[3a–h] For example, Kelland et al.[4] reported minor-groove-directed platinum complexes derived from the polyamides netropsin and distamycin. Despite these efforts, only a few

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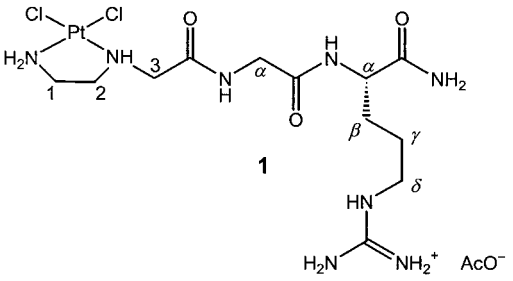
successful antitumor candidates have emerged.[1, 5] The latter observations, together with the fact that efficient screening protocols are now available,[6] strongly underline the need to develop a methodology which allows a rapid synthesis (e.g. solid-phase) of a wide variety of platinum(II) complexes.

Thus far, only a few metal–peptide conjugates (rhodium, ruthenium, and rhenium) have been prepared by solid-phase peptide synthesis.[3b,d,g] However, the general usefulness of this approach has remained largely unexplored. It has also been shown that constructs containing guanidinium functions exhibit an interaction with the phosphate backbone and guanine bases in DNA.[3e, 7]

Herein we report for the first time the construction of a potentially active trimeric arginine-containing peptide–dichloroplatinum(II) complex (**1**) by a solid-phase approach.[8] The target molecule **1** encompasses an arginine–glycine dipeptide tethered to an ethylenediamine moiety, which—in turn—serves as a platinum-chelating ligand. The route to the target compound **1** is presented in Scheme 1 and comprises the assembly of the immobilized and functionalized tripeptide derivative **8a**, platination of the ethylenediamine moiety in **8a**, and subsequent deprotection and release from the solid support. The synthesis of the functionalized tripeptide **8a** could be effected by condensing the immobilized dipeptide **3** with Fmoc-protected *N*-2-aminoethyl-glycine derivative **6**. Thus, stepwise elongation of the Fmoc-protected Rink amide resin (**2**) with the commercially available protected amino acids Fmoc-Arg(Pbf)-OH and Fmoc-Gly-OH following a standard Fmoc protocol[9] gave immobilized dipeptide **3**. Condensation of the latter with the platinum-binding unit **6**, obtained by the reaction of the known[10] partially protected compound **4** with Fmoc-Cl, and subjection of the resulting bis-Fmoc-protected derivative **5** to acidolysis gave immobilized trimer **7a**. Removal of both Fmoc-protecting groups in **7a** led to the isolation of the partially protected tripeptide **8a**.



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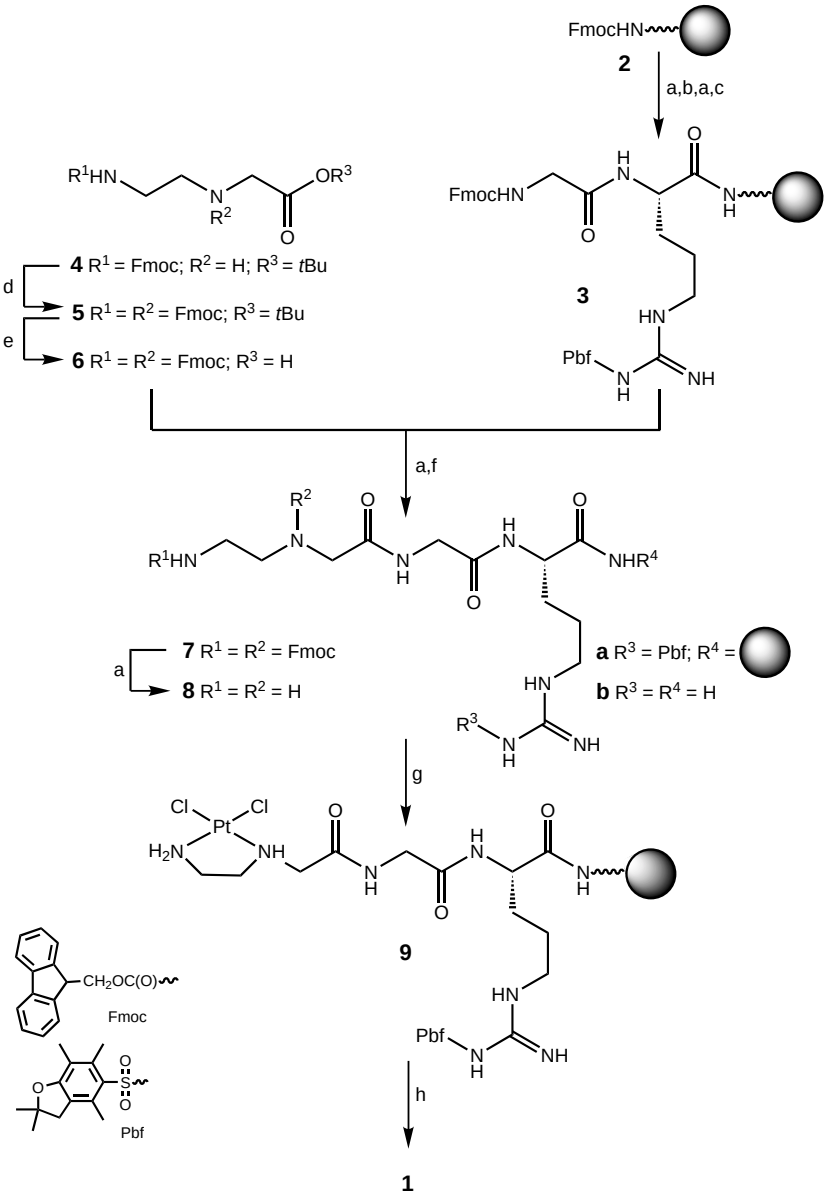

Scheme 1. Solid-phase synthesis of platinum complex **1**. Reagents and conditions: a) piperidine; b) Fmoc-Arg(Pbf)-OH, PyBOP, DiPEA, NMP; c) Fmoc-Gly-OH, PyBOP, DiPEA, NMP; d) DiPEA (2 equiv), Fmoc-Cl (1.15 equiv), CH_2Cl_2, 1 d, 80% of **5;** e) TFA, CH_2Cl_2, 2 h, 100% of **6;** f) PyBOP, DiPEA, NMP; g) K_2PtCl_4 (10 equiv, 0.05 M), DMF/H_2O (9/1, v/v), 24 h in the dark; h) TFA/H_2O (95/5, v/v), 2 h, 56% (based on **8a**). DiPEA = diisopropylethylamine; NMP = *N*-methylpyrrolidone, PyBOP = benzotriazol-1-yl-oxytris(pyrrolidino)-phosphonium hexafluorophosphate.

At this stage, the crucial platination step of the immobilized peptide trimer **8a** was explored. Preliminary experiments indicated that platination of **8a** with excess K_2PtCl_4 (i.e. 20 equiv, 0.1 M) in DMF/water (4/1) for 24 h was promising, gauged on the results of atomic absorption spectroscopy. Unfortunately, cleavage of the resin and removal of the protecting group Pbf with trifluoroacetic acid (TFA)/water/triisopropylsilane (TIS) (95/2.5/2.5) led to metallic platinum, as well as free ligand **8b**.[11] The latter is probably formed by reduction of the coordinated $PtCl_2$ moiety by the scavenger TIS. Indeed, executing the cleavage step in the absence of TIS in TFA/water (95/5) afforded the crude peptide–platinum complex **1**, as evidenced by ^1H and ^{195}Pt NMR spectroscopy and electrospray-ionization mass spectrometry (ESI-MS), in an encouraging 87% conversion. However, quantitative

transformation of the immobilized ligand **8a** into the platinum complex **9** is a prerequisite for a rapid purification of an array of closely related platinum complexes. To achieve this goal, additional platination experiments in DMF/water and THF/water mixtures were performed. The results of this study are summarized in Table 1. Perusal of the data in Table 1 clearly

Table 1. Results of platination experiments on the solid support in various media.[a]

Entry	K_2PtCl_4 [equiv, M][b]	Solvent	Conversion [%][c]
1	10, 0.05	DMF/water (1/1)	0
2	20, 0.10	DMF/water (1/1)	0
3	10, 0.05	THF/water (1/1)	63
4	20, 0.10	THF/water (1/1)	64
5	10, 0.05	DMF/water (9/1)	96

[a] Experiments were performed for 24 h at room temperature in the dark. [b] Amount of equivalents with respect to the loading of the immobilized trimer **8a**, and molar concentration. [c] Conversion of unplatinated **8a** to platinated trimer **9** as calculated from ^{1}H NMR spectra of crude products deprotected and cleaved from the resin (characterized by ^{1}H and ^{195}Pt NMR spectroscopy).

indicates that the amount and concentration of platinum does not significantly influence the effectivity of the complexation. It is also evident (entries 1–4) that poor or virtually no complexation occurs by executing the platination of the immobilized peptide in 50% aqueous solutions; this may be due to insufficient swelling of the resin. In these cases, reduction to metallic platinum was observed. However, nearly quantitative conversion of **8a** was observed in DMF/water (9/1) (entry 5). Thus, treatment of **8a** with excess K_2PtCl_4 (10 equiv, 0.05 M) in DMF/water (9/1) for 24 h, followed by concomitant cleavage of the rather acid-stable Pbf group and release of **9** from the solid support with TFA/water (95/5) for 2 h, yielded crude **1**. Analysis of the reaction mixture showed nearly quantitative conversion of **8a** into **1** (Figure 1). Purification of the product by gel permeation chromatography (HW-40, 1% acetic acid) gave homogeneous **1** (in 56% yield), as evidenced by capillary electrophoresis (CE). The identity of **1** was fully confirmed by NMR spectroscopy (^{1}H, ^{13}C, ^{195}Pt) and ESI-MS.

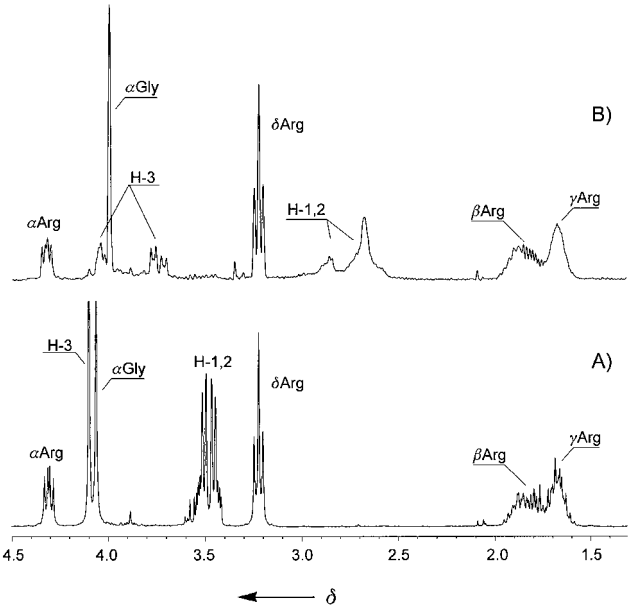

Figure 1. ^{1}H NMR spectrum (300 MHz, D_2O) of the crude TFA salts of ligand **8b** (A) and platinum complex **1** (B) obtained after deprotection and cleavage from the resin.

The results presented herein clearly show that platinum complexes of high quality are readily accessible using standard solid-phase peptide synthesis, thus circumventing laborious liquid-phase synthesis. In addition, it was firmly established that the reactive coordinated dichloroplatinum moiety is compatible with the deprotection and cleavage conditions. The latter is imperative for the facile synthesis and purification of a plethora of peptide–platinum complexes. We therefore believe that this new methodology can be adopted for the preparation of a library of platinum antitumor compounds by a combinatorial synthesis approach. This aspect is currently under investigation and will be published in due course.

Experimental Section

6: To a solution of **4** (10 mmol) in CH_2Cl_2 (50 mL) was added DiPEA (20 mmol) and the reaction mixture was cooled to 0 °C. Fmoc-Cl (11.5 mmol) was then added, and the reaction mixture was stirred overnight. After the mixture was concentrated in vacuo, purification by silica gel column chromatography (diethyl ether/petroleum ether 40–60 (1/1, v/v)) gave **5** in 80% yield. To a solution of **5** (8 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TFA (30 mL), and the reaction mixture was stirred for 2 h at room temperature. The solution was concentrated in vacuo and coevaporated with toluene (3 × 100 mL). Recrystallization from diethyl ether/petroleum ether 40–60 (1/1, v/v) afforded pure **6** in 100% yield, based on **5**.

Solid-phase synthesis of **1**: Peptide **8** was assembled on an ABI 433A (Applied Biosystems, division of Perkin-Elmer) peptide synthesizer employing a Fastmoc peptide synthesis protocol, treated with K_2PtCl_4 (10 equiv, 0.05 M) in DMF/H_2O (9/1, v/v) in the dark for 24 h, washed with H_2O, DMF, and CH_2Cl_2, and dried in a vacuum oven (12 h, 37 °C). Cleavage of the Pbf group and the solid support was effected by treatment of **9** with TFA/H_2O (95/5, v/v) for 2 h, after which the reaction mixture was precipitated with diethyl ether. The resulting solid was washed with diethyl ether, water was added, the mixture was filtered, and the resin was washed with water. Subsequently, the combined water fractions were lyophilized, yielding crude **1** as a yellow powder. Purification by gel permeation chromatography (HW-40, 1% acetic acid) afforded **1** in 56%, based on **8a**. The complete assignment of the nonexchangeable protons was confirmed by a ^{1}H, ^{1}H COSY, and NOESY experiment. ESI-MS: m/z: 597 $[M+H]^+$, 619 $[M+Na]^+$; ^{195}Pt NMR (D_2O): $\delta = -2382$.

Free-zone high-performance capillary electrophoresis (CE) analysis was performed on an Applied Biosystems 270A instrument (Applied Biosystems Inc., Foster City, CA) at 20 kV with 50 μm ID capillaries (effective length 72 cm). Sodium citrate (20 mM, pH 2.5, Applied Biosystems) was employed as a running buffer. Gel permeation chromatography was executed on a HW-40 column (26 mm × 600 mm) at 1.5 mL min^{-1}. NMR spectra were recorded by using a Bruker DPX 300 and DMX 600 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined with respect to external TMS. ^{195}Pt spectra were calibrated by using K_2PtCl_4 as an external reference at $\delta = -1614$. Electrospray mass spectra were recorded on a Finnegan MAT TSQ-70 instrument with a custom-made electrospray interface (ESI).

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[11] To corroborate the identity of trimer **8b**, a small sample of **7a** was withdrawn and subjected to the following conditions. Treatment of **7a** with piperidine, followed by acidic treatment afforded crude trimer **8b**, which was purified by gel permeation chromatography (HW-40, 1% acetic acid). Trimer **8b** was characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI mass spectrometry, and capillary electrophoresis.

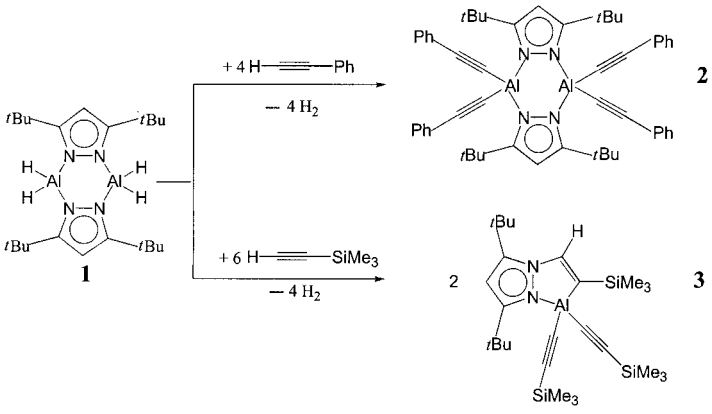
The First Structurally Characterized Aluminum Compounds with Terminal Acetylide Groups**

Wenjun Zheng, Nadia C. Mösch-Zanetti, Herbert W. Roesky,* Manuel Hewitt, Fanica Cimpoesu, Thomas R. Schneider, Andreas Stasch, and Jörg Prust

Aluminum compounds containing acetylide groups have been known since 1960.[1] All the published aluminum acetylides feature a dimeric structure with a bridging acetylide ligand between two aluminum centers[2] or between one aluminum atom and one early transition metal atom.[3] Since the addition of aluminum acetylides to unsaturated hydrocarbons is of interest in organic synthesis,[4] it is surprising that only few structurally characterized aluminum acetylides have been reported.[2, 3] Therefore, we set out to synthesize such complexes starting from an aluminum dihydride precursor with bulky pyrazolato ligands.[5] Herein, we present the preparation and molecular structures of **2** and **3** (see Scheme 1), which to the best of our knowledge, represent the first structurally characterized terminal acetylide complexes of aluminum.

The starting material for **2** and **3**, the aluminum dihydride **1**, is synthesized from H[*t*Bu$_2$pz] (*t*Bu$_2$pz = 3,5-di-*tert*-butylpyrazolate)[6] and $AlH_3 \cdot NMe_3$[7] in high yield.[8]

Compound **2** is prepared from **1** and an excess of HC≡CPh (Scheme 1). The X-ray structure analysis of **2** shows a dimeric species with some interesting features (Figure 1).[9] Most



Scheme 1.

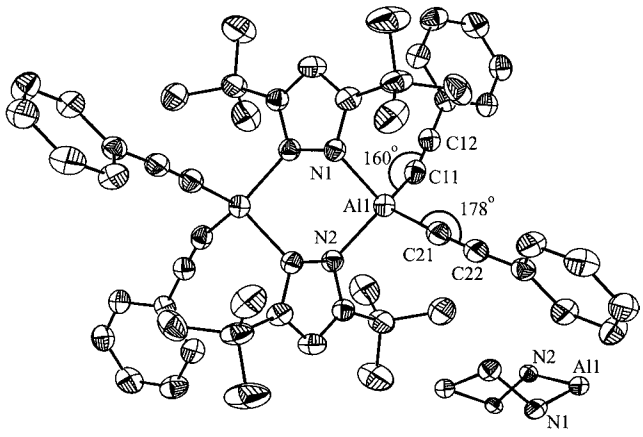


Figure 1. Molecular structure of **2**. Selected bond lengths [Å] and angles [°]: Al1-C11 1.929, Al1-C21 1.913(3), C11-C12 1.211(4), C21-C22 1.218(4); C12-C11-Al1 160.2(3), C22-C21-Al1 178.3(3), C21-Al1-C11 116.99(12), N2-Al1-N1 102.88(10). Bottom right: the twisted core of **2**.

surprisingly, the six-membered Al_2N_4 ring is in a twisted conformation. This is in sharp contrast to other bridged bispyrazolate compounds.[5c] Another interesting finding is the marked deviation of the two Al–C≡C backbones from linearity (Al1-C11-C12 160.2(3)° vs. Al1-C21-C22 178.3(3)°; the C11–C12 and C21–C22 bond lengths are 1.211(4) and 1.218(4) Å, respectively). Whereas some small angles in M–C≡C units in transition metal complexes have been

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