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Electronic Supplementary Information

Design of a Magnesium-Pridinolum Complex for Polylactide-Drug Conjugates Formation

Tomasz Han, Józef Utko, Lucjan B. Jerzykiewicz, Piotr Sobota
Faculty of Chemistry, University of Wrocław, 14, F. Joliot-Curie 14, 50-383 Wrocław, (Poland)

General procedures

All reactions were conducted under dinitrogen using standard Schlenk techniques. Solvents were prepared as follows: toluene - distilled from Na/benzophenone; hexane - was heated with metallic sodium under reflux for 24 hours: methanol - was heated with metallic magnesium under reflux for 24 hours; solution of di-n-butylmagnesium (1.0 M in heptane) were obtained from Aldrich; solution of 1,1-diphenyl-3-(piperidin-1-yl) propane-1-ol = PriOH were obtained from Cardinal Pharma Trade.

Synthesis of $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$

To a mixture of 1,1-diphenyl-3-(piperidin-1-yl) propane-1-ol = PriOH (3.574 g; 19.09 mmol) in 80 mL of toluene, $MgBu_2$ (4.8 mL) was slowly and carefully added. The solution under reflux became light gray and evolution of gaseous butane started. At room temperature the solvent were removed under vacuum. The residue of the reaction was filtered off and washed with cold mixture of n-hexane and toluene (3 x 15 ml). The filtrate was left to crystallize at 268 K. White air-sensitive crystals of $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$ were grown after few days. The molecular structure of $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$ was determined by X-ray diffraction study. Yield: 55,5 %.

Anal. calcd for $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$ (MW, 1226.28): C, 80.04; H, 8.00; N, 3.97. Found: C, 79.54; H, 7.87; N, 4.02 ^{1}H NMR (C_6D_6, 298 K): δ = 7.58 (d, 2H); 7.46 (d, 2H); 7.37 (d, 8H); 7.33 (d, 2H); 7.24 (t, 2H); 7.19 (t, 8H); 7.15-7.05 (m, 8H); 7.00-6.92 (m, 5H); 6.88-6.81 (m, 3H); 2.67-2.59 (m, 1H); 2.47-2.36 (m, 3H); 2.33-2,27 (m, 11H); 2.26-2.18 (m, 5H); 2.14-2.06 (m, 2H); 2.01-1.94 (m, 1H); 1.92-1.82 (m, 2H); 1.76-1.57 (m, 5H); 1.53-1.47 (m, 9H); 1.40-1.28 (m, 5H); 1.25-1.18 (m, 4H); 1.17-1.04 (m, 5H); 1.00-0.91 (m, 2H); 0.82-0.72 (m, 1H)

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Pridinolum-Polylactide-Drug Conjugates preparation.

Reactions were performed under an inert atmosphere of N_2 using standard Schlenk techniques. To $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$ (0.26 g; 0.42 mmol) in 40 ml of dichloromethane, L-lactide (1.23 g; 8.54 mmol) was slowly added. Reaction was carried out at room temperature for 24 hours. After reaction was completed it was quenched with methanol, the solution was concentrated in vacuum and the polymer was precipitated with hexane. The obtained polymer was filtrated off and washed with 15 ml of hexane.

X-Ray Structure Determinations. Crystal data and refinement details for $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$ **(1)** are given in Table **S1**. The crystal was mounted on glass fibers and then flash-frozen to 100(2) K (Oxford Cryosystem-Cryostream Cooler). Preliminary examination and intensities data collections were carried out on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoK_α radiation. Data reduction and analysis were carried out with the Oxford Diffraction programs. The structure was solved by direct methods and refined by the full-matrix least-squares method on all F^2 data using the SHELXTL software. Carbon bonded hydrogen atoms were included in calculated positions and refined in the riding mode using SHELXTL default parameters. During the structure refinement of $[Mg(\mu,\eta^2\text{-OPri})(\eta\text{-OPri})]_2$, a region of electron density was identified as a highly disordered molecule of toluene. Attempts to model this electron density as the toluene molecule were not successful due to the extent of the disorder. In the final structure model, the contribution of the electron density from the toluene molecule has been removed from the intensity data using the program SQUEEZE in PLATON. This greatly improved the precision of the refinement but did not affect the geometric parameters of the rest of the structure.

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Table S1. Experimental details for **1.**

Chemical formula	$C_{80}H_{96}Mg_2N_4O_4 \cdot 2(C_7H_8)$
M_r	1410.50
Crystal system, space group	Orthorhombic, *Pbcn*
Temperature(K)	100
a, *b*, *c*(Å)	13.790(4), 18.241(3), 33.719(7)
α, β, γ(°)	90, 90, 90
V(Å^3)	8482(3)
Z	4
Radiation type	Mo *K*a
m(mm^{-1})	0.08
Crystal size(mm)	0.18 × 0.12 × 0.05
Diffractometer	Kuma KM-4 CCD kappa-axis diffractometer
Absorption correction	Analytical *CrysAlis CCD*. Version 1.171.33(Oxford Diffraction Ltd., 2009) Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Comput. Phys. Commun.(1998). 111, 243.
T_{min}, T_{max}	0.921, 0.933
No. of measured, independent and observed [$I > 2s(I)$] reflections	114025, 10216, 5556
R_{int}	0.144
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.057, 0.144, 0.93
No. of reflections	10216
No. of parameters	470
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$(e Å^{-3})	0.28, -0.24

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Table S2. Selected geometric parameters for **[Mg(μ,η^2-OPri)(η-OPri)]$_2$.**

Mg1—O1	1.954(2)	N1—C3	1.497(3)
Mg1—O2	1.852(2)	N1—C4	1.498(3)
Mg1—O1^i	1.983(2)	N1—C8	1.496(3)
Mg1—N1^i	2.183(2)	N2—C23	1.475(3)
O1—C1	1.418(3)	N2—C24	1.462(3)
O2—C21	1.393(3)	N2—C28	1.467(3)
O1—Mg1—O2	119.66(7)	C23—N2—C24	112.07(18)
O1—Mg1—O1^i	82.04(6)	C23—N2—C28	109.53(17)
O1—Mg1—N1^i	116.70(7)	C24—N2—C28	110.14(18)
O1^i—Mg1—O2	120.78(7)	O1—C1—C2	107.63(16)
O2—Mg1—N1^i	116.16(7)	O1—C1—C9	111.16(16)
O1^i—Mg1—N1^i	93.83(7)	O1—C1—C15	109.05(16)
Mg1—O1—C1	139.81(12)	N1—C3—C2	112.76(16)
Mg1—O1—Mg1^i	97.50(7)	N1—C4—C5	115.21(18)
Mg1^i—O1—C1	122.60(12)	N1—C8—C7	114.85(18)
Mg1—O2—C21	158.94(14)	O2—C21—C22	109.56(17)
C3—N1—C4	111.18(17)	O2—C21—C29	111.11(17)
C3—N1—C8	110.73(16)	O2—C21—C35	108.86(17)
Mg1^i—N1—C3	107.47(12)	N2—C23—C22	113.59(18)
C4—N1—C8	108.82(16)	N2—C24—C25	111.4(2)
Mg1^i—N1—C4	108.23(12)	N2—C28—C27	111.49(19)
Mg1^i—N1—C8	110.37(13)		

Symmetry code: (i) -*x*+1, *y*, -*z*+1/2.

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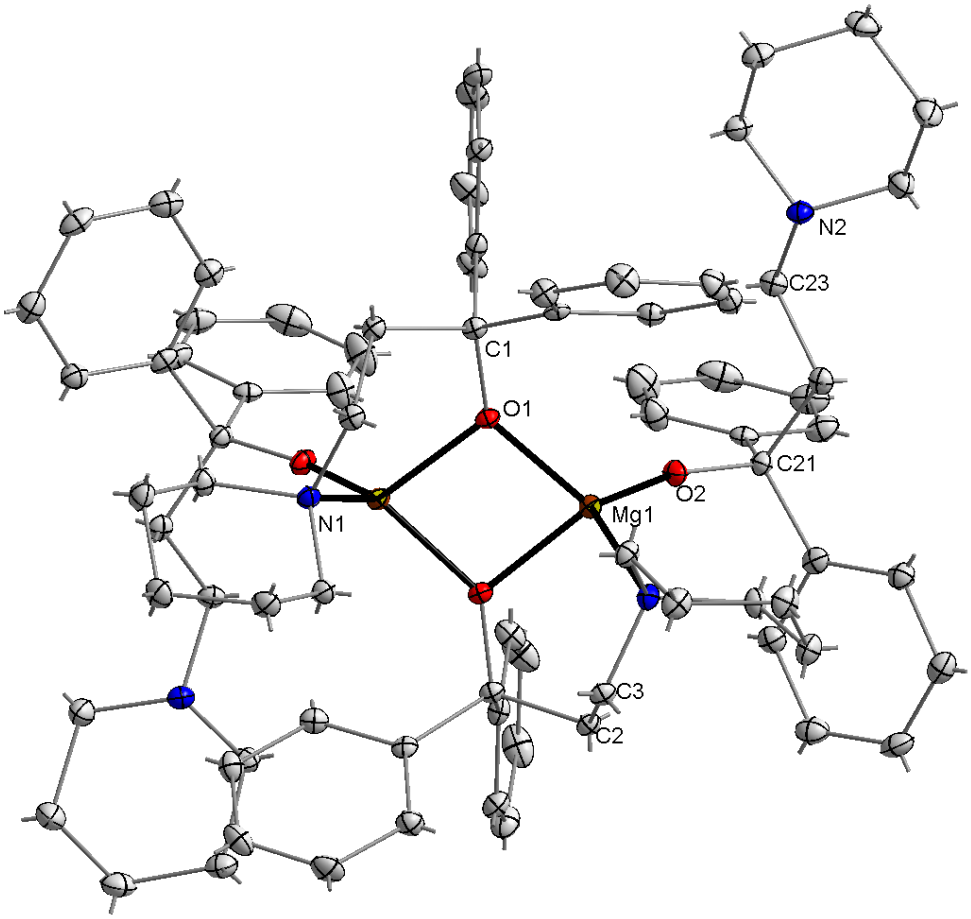

Figure S1. Molecular structure of **[Mg(μ,η^2-OPri)(η-OPri)]$_2$**, as determined by X-ray.