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Cytotoxicity and NMR Studies of Platinum Complexes with Cyclooctadiene Ligands

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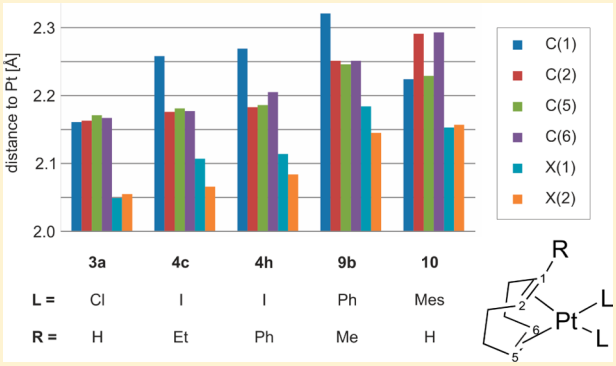
Supporting Information

ABSTRACT: The synthesis of a series of platinum complexes containing cyclooctadiene ligands with the general structure PtMeL(R-cod) (where L = Cl, I, nC_3F_7, iC_3F_7, nC_8F_{17}, Me, aryl, alkynyl and R = H, Me, Et, *i*Pr, *n*Bu, *i*Bu, *n*Hex, Ph) is presented. All complexes are remarkably stable and were obtained in excellent yields. Their structure in both solution and the solid state were explored by crystal structures and multinuclear (^{1}H, ^{13}C, ^{19}F, ^{195}Pt) NMR spectroscopy. Cytotoxicity experiments with selected complexes in HeLa cells revealed higher toxicity in comparison to that of cisplatin for most of the structures.



INTRODUCTION

Platinum(II) complexes containing unsubstituted 1,5-cyclooctadiene (cod) ligands are well-known precursors for the synthesis of other mono- or polynuclear platinum(II) compounds.[1−5] Furthermore, they are widely used in both catalysis[6−8] and material sciences.[9,10] Recently, we presented the syntheses of platinum complexes containing substituted 1,5-cyclooctadiene (cod) ligands or perfluorinated chains and their use as precursors in metal organic vapor deposition (MOCVD)[11,12] and supercritical fluid reactive deposition (SFRD)[13] processes, respectively.

Since the discovery of cisplatin and its antiproliferative effects,[14] numerous other metal complexes have been tested and proven to be highly cytotoxic[15−20] against different cancer cell lines.[21−25] Deacon et al.[26] found evidence that organometallic platinum complexes generally perform better than their nonorganometallic derivatives. They also showed the preparation of some cod platinum complexes with perfluorinated ligands and their cytotoxic activity against L1210 leukemia cells and the resistant cell line L1210/DDP.[26] In line with these findings, Klein et al. presented various studies on complexes containing the [Pt(cod)] fragment and different ligands,[27−31] such as alkyls, alkynyls, and nucleosides. Especially, the alkynyl complexes showed high cytotoxic activity against HT-29 colon carcinoma and MCF-7 breast adenocarcinoma cell lines.[29,31] Deacon et al. also demonstrated the influence of differrent diene ligands, identifying cod complexes as promising anticancer drugs.[26] However, to the best of our knowledge, there have not been any comprehensive studies using monofunctionalized cod ligands so far.[26,27,29,31−35]

During the preparation of the complexes, we came across an obstacle. Until now, there is no reliable, precise, and at the same time fast method to prove the purity of a prepared complex if the resonances of the different species are spread over a wide range of frequencies. Conventional NMR experiments typically cannot acquire more than 50 kHz homogeneously excited bandwidth in a single experiment, and platinum has a chemical shift range of nearly 2 MHz at 14.1 T field strength. Therefore, we developed a reliable NMR method in order to detect impurities of our platinum complex samples covering a bandwidth of 500 kHz. Since there has been no structural study using monofunctionalized cod ligands to distinguish diastereomers, we also wanted to address this issue by NMR spectroscopy.

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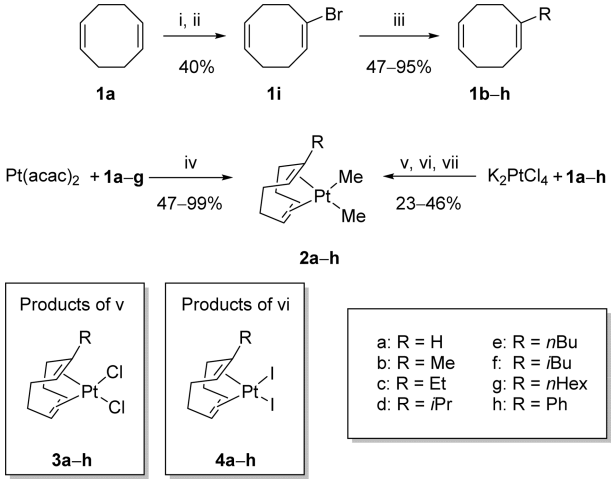
In this paper we describe the syntheses, NMR characterizations, and X-ray and toxicological studies of new platinum complexes having monosubstituted 1,5-cyclooctadiene platinum ligands, $[PtL_2(R\text{-cod})]$[36−46] (for platinum complexes with 1,5-disubstituted cyclooctadiene ligands, see refs 47−53).

RESULTS AND DISCUSSION

Preparation. Selective bromination of one COD double bond,[54] elimination,[55] and Kumada cross-coupling reactions[56] with various Grignard reagents gave the monofunctionalized cod ligands **1b−h** in good to excellent yields, as we have recently reported elsewhere.[12] Complexes with the general structure $[PtMe_2(R\text{-cod})]$ (**2a−h**, where R = H, Me, Et, *i*Pr, *n*Bu, *i*Bu, *n*Hex, Ph) are accessible through either a direct method[57] or a three-step procedure,[58] both starting from cod itself (**1a**) or cod ligands **1b−h** and $Pt(acac)_2$ or K_2PtCl_4, respectively. While the direct method is very fast and gives much better yields, the longer synthetic route gives interesting dichloro and diiodo intermediates **3a−h** and **4a−h** which can be used as precursors for the synthesis of other complexes (see Scheme 1).[12]

Scheme 1. Synthesis of Functionalized cod Complexes 1b−h and Dimethyl Complexes 2a−h[a]



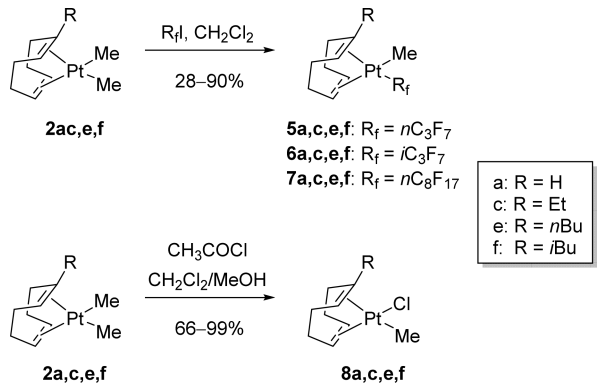
[a]Legend: (i) Br_2, hexane/*t*BuOH, −10 °C, 30 min, 56%;[54] (ii) KO*t*Bu, THF, 0 °C, 2 h, 72%;[55] (iii) RMgX, $NiCl_2$(dppp), THF, 0 °C to reflux, 4 h;[56] (iv) $AlMe_3$, toluene, room temperature, 24 h;[57] (v) $SnCl_2$, H_2O/*n*PrOH, room temperature, 2−6 days; (vi) NaI, acetone, room temperature, 3 h; (vii) MeLi, Et_2O, 0 °C, 2 h.[58]

Dimethyl complexes **2a,c,e,f** were further functionalized by exchanging one methyl group. Insertion of perfluorinated alkyl chains using an excess of perfluorinated alkyl iodides R_fI gave the complexes $[PtMeR_f(R\text{-cod})]$ (**5a,c,e,f−7a,c,e,f**, with R_f = nC_3F_7, iC_3F_7, nC_8F_{17}) in good to excellent yields (see Scheme 2).[13] All products were purified by column chromatography and are remarkably stable against water and oxygen. Following the procedure of Clark et al., we obtained the monochlorinated complexes $[PtMeCl(R\text{-cod})]$ (**8a,c,e,f**; see Scheme 2).[58]

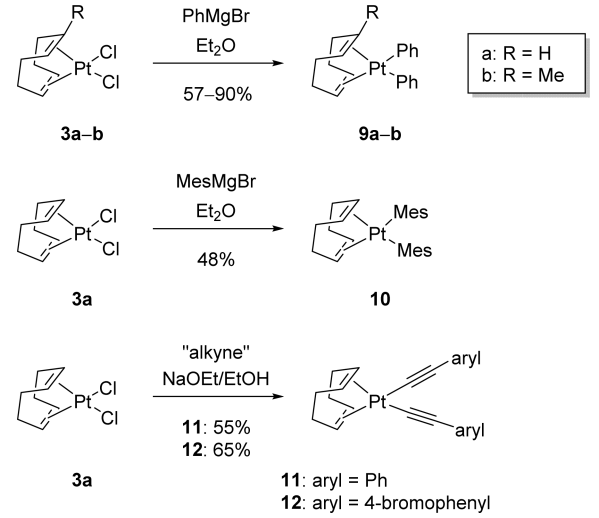
Chloro ligands are easily convertible into other ligands. Therefore, to widen the scope of complexes for our NMR investigations, dichloro complexes **3a−b** were further functionalized, using Grignard reagents[59] or alkynyls (see Scheme 3).[60]

Crystal Structures. Crystal structures of the following complexes were obtained: **3a**, **4c,h**, **9b**, and **10**. Please note that

Scheme 2. Further Modifications of Dimethyl Complexes 2a,c,e,f



Scheme 3. Further Modifications of Dichloro Complexes 3a,b



3a is a redetermination of dichloro(η^4-cycloocta-1,5-diene)-platinum(II) at 123 K. Selected molecular structures are presented in Figure 1.[61−63]

Due to the residue R at the cod ligand, the geometry of the complex is shifted. Distances from platinum to the carbon atoms of the double bond are given in Table 1. In the case of unsubstituted cod (**3a**), the bond length is similar for all carbon atoms and the two centroids. The centroids X(1) and X(2) represent the olefinic bond. In complex **10** with two space-consuming mesityl groups, the cod ligand is distorted and the bond length to two opposite carbon atoms (C(2) and C(6)) is longer while the distance to the others (C(1) and C(5)) is shorter. Therefore, the binding position X′ of the platinum atom at the olefinic bond, which is defined by the square-planar geometry, is not identical with the centroids X and thus does not lie exactly in the center between the two carbon atoms. Still, the distances to the centroids are nearly equal. For the complexes with substituted cod ligands (**4c,h** and **9b**), the distance from platinum to C(1) and therefore to X(1) is always longer in comparison to the distances from platinum to C(2), C(5), C(6), and X(2), as shown in Table 1. Accordingly, the two binding moieties of the cod ligand are not identical and exhibit different distances to the platinum atom.

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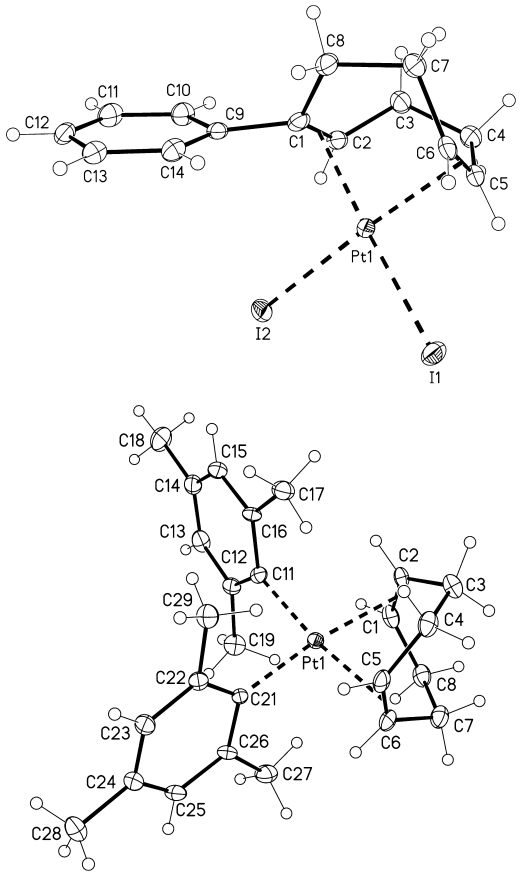

Figure 1. Molecular structures of **4h** (top) and **10** (bottom). Displacement parameters are drawn at the 50% probability level.

NMR Investigations. Structural analysis of the new complexes was performed by multinuclear NMR spectroscopy. The results are summarized in Tables 2 and 3.

Platinum chemical shifts are in the expected range of Pt(II) complexes (−5500 to −1500 ppm)[64] and change slightly by 15−80 ppm (1−10 kHz at 600 MHz) due to the residue R at the cod ligand except for the phenyl group. The phenyl group has a larger influence on the platinum atom, probably due to its ring current, and therefore changes the chemical shift by 140−165 ppm (18−21 kHz at 600 MHz). While most complexes resonate in the range of approximately −3700 to −3000 ppm, it is notable that the diiodo complexes resonate at lower values (between −4300 and −4150 ppm). They are also more sensitive to the substituent at the cod ligand (45−90 ppm), probably due to the high electron density of the iodine atoms.

As shown previously,[27−31] the $^2J_{Pt,H}$(=CH,cod) coupling constant to the olefinic protons of the cod ligand is strongly dependent on the substituent *trans* to the olefinic bond. This so-called *trans* influence[65] can be used to determine which diastereomers of the differently substituted complexes (**5**−**8**) are formed during the reaction. For a strong ligand such as methyl in [$PtMe_2$(cod)] (**2a**), the $^2J_{Pt,H}$(=CH, cod) coupling constant is approximately 38 Hz. This anti correlation of bond strength to $^2J_{Pt,H}$ coupling constants seems to be a general rule that has been reported previously.[31,65] For weaker ligands such as chlorine in [$PtCl_2$(cod)] (**3a**) the value is approximately 67 Hz. In the mixed complex [PtMeCl(cod)] (**5a**) there is a change in the binding situation. As shown in Table 3, the bond from chlorine to platinum is weakened (increased *trans* coupling) while the bond to the methyl group is strengthened (decreased *trans* coupling). For substituted cod ligands (**8c,e,f**), there is always one coupling with a coupling constant around 35 Hz and two between 70 and 77 Hz. This means that the methyl group is *trans* to the substituted side of the cod ligand. The group with the smaller van der Waals radius, in this case chlorine, seems to prefer the position next to the substituent R.

Similar findings are made in the case of the unbranched, perfluorinated ligands (**5c,e,f** and **7c,e,f**). The bond to the methyl group is stronger ($^2J_{Pt,H}$(*trans*) = 33 Hz) than the one to the other ligand ($^2J_{Pt,H}$(*trans*) = 43 Hz). However, this time there are two couplings *trans* to the methyl group and therefore the smaller methyl ligand is in direct proximity to the substituted side of the cod ligand. The perfluorinated isopropyl group appears to require space similar to the methyl group, because both diastereomers can be found. Nevertheless, the diastereomer with the methyl group in proximity to the substituent dominates and the ratios vary with the substituent (Table 4). The findings are confirmed by NOESY spectra of selected complexes.

Toxicological Investigations. In our studies we also want to apply these newly synthesized platinum(II) complexes in vitro. It is widely known that platinum(II) complexes play a key role in medicinal chemistry. They are applied as chemotherapeutic agents, in particular for cancer of the lung, testes, and ovaries.[66−70] In the class of platinum-based antitumor drugs cisplatin was the first member, discovered by Rosenberg et al. in 1965. It has been used for the treatment of breast, bowel, lung, pancreatic, and prostate gland tumors since 1978.[71] However, there are substantial drawbacks involved in the administration of cisplatin. One is the drug resistance of tumor cells, which is a grave issue in cisplatin treatment. Furthermore, the drug shows severe side effects, especially nephro- and neurotoxicity.[72] Therefore, newly synthesized platinum(II) complexes of the general formula [PtMeL(R-cod)] were tested for in vitro cytotoxicity in HeLa cells. Several studies have shown high cytotoxicity of platinum complexes with organic ligands, such as perfluoro[26] or chloro ligands,[73]

Table 1. Selected Distances (Å) of the Complexes 3a, 4c,h, 9b, and 10[a]

	Pt−C(1)	Pt−C(2)	Pt−C(5)	Pt−C(6)	Pt−X(1)[b]	Pt−X(2)[b]	Pt−L(1)[c]	Pt−L(2)[c]
3a	2.161 (4)	2.163 (5)	2.171 (5)	2.168 (4)	2.049	2.055	2.300 (1)	2.309 (1)
4c	2.258 (4)	2.176 (4)	2.180 (4)	2.177 (5)	2.107	2.066	2.6180 (4)	2.6179 (4)
4h	2.269 (4)	2.184 (4)	2.187 (4)	2.204 (4)	2.114	2.084	2.6080 (3)	2.6168 (3)
9b	2.321 (4)	2.251 (4)	2.246 (4)	2.251 (4)	2.184	2.145	2.029 (4)	2.027 (4)
10	2.224 (4)	2.291 (4)	2.229 (3)	2.293 (4)	2.153	2.157	2.053 (3)	2.045 (4)

[a]Standard deviations are given in parentheses. [b]Centroids X(1) and X(2) are defined as the average olefinic bond between C(1) and C(2) and C(5) and C(6), respectively. [c]Ligands L(1) and L(2) are the ligands next to and opposite of the residue R at the cod ligand, respectively (e.g., L(1) = Me, L(2) = Cl for molecules **8a,c,e,f** in Scheme 2).

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Table 2. Selected Chemical Shifts and Coupling Constants of the Complexes with Substituted cod Ligands and the General Formula [PtL(1)L(2)(R-cod)][a]

	L(1)[b]	L(2)[b]	R	δ^{195}_{Pt}	$\Delta(\delta^{195}_{Pt})$ (to R = H)	δ^{1}_{H}(Me)	$^{2}J_{Pt,H}$(Me)	δ^{1}_{H}(=CH,cod), $^{2}J_{Pt,H}$(=CH,cod)					
								trans L(1)[b]				*trans* L(2)[b]	
2b	Me	Me	Me	−3521	41	0.70 0.71	*81* *82*	*c*	*c*	*c*	*c*	*c*	*c*
2c	Me	Me	Et	−3534	28	0.69	*82*	*c*	*c*	*c*	*c*	*c*	*c*
2d	Me	Me	*i*Pr	−3527	35	0.69 0.69	*81* *82*	*c*	*c*	*c*	*c*	*c*	*c*
2e	Me	Me	*n*Bu	−3537	25	0.69 0.70	*82* *82*	4.70	*c*	4.70	*c*	4.74	*40*
2f	Me	Me	*i*Bu	−3523	39	0.65 0.68	*81* *82*	*c*	*c*	*c*	*c*	*c*	*c*
2g	Me	Me	*n*Hex	−3527	35	0.69	*81*	4.69	*c*	4.69	*c*	4.74	*40*
2h	Me	Me	Ph	−3401	160	0.74	*83*	*c*	*c*	*c*	*c*	*c*	*c*
3b	Cl	Cl	Me	−3298	32			5.56	*c*	5.61	*66*	5.48	*67*
3c	Cl	Cl	Et	−3315	15			*c*	*c*	*c*	*c*	*c*	*c*
3d	Cl	Cl	*i*Pr	−3307	23			5.53	*c*	5.53	*c*	5.35	*c*
3e	Cl	Cl	*n*Bu	−3305	25			5.51[d]	*63*[d]	5.51[d]	*63*[d]	5.57	*38*[d]
3f	Cl	Cl	*i*Bu	−3287	43			5.51[d]	*64*[d]	5.51[d]	*64*[d]	5.60	*70*
3g	Cl	Cl	*n*Hex	−3304	26			*c*	*c*	*c*	*c*	5.58[d]	*26*[d]
3h	Cl	Cl	Ph	−3192	138			5.71	*c*	5.77	*c*	6.15	*67*
4b	I	I	Me	−4240	74			5.72[d]	*66*[d]	5.72[d]	*66*[d]	5.86	*66*
4c	I	I	Et	−4268	46			5.66	*73*[d]	5.78	*57*[d]	5.93	*66*
4d	I	I	*i*Pr	−4239	75			*c*	*c*	*c*	*c*	*c*	*c*
4e	I	I	*n*Bu	−4257	57			5.68	*73*[d]	5.76	*62*[d]	5.92	*66*
4f	I	I	*i*Bu	−4225	89			5.68	*c*	5.77	*c*	5.84	*66*
4g	I	I	*n*Hex	−4248	66			5.65[d]	*c*	*c*	*c*	5.92	*66*
4h	I	I	Ph	−4149	165			*c*	*c*	*c*	*c*	*c*	*c*
5c	Me	nC_3F_7	Et	−3748	42	0.86	*79*	5.29[d]	*<40*[d]	5.32[d]	*<30*[d]	4.95	*43*
5e	Me	nC_3F_7	*n*Bu	−3748	42	0.85	*79*	5.30	*30*	5.30	*30*	4.94	*42*
5f	Me	nC_3F_7	*i*Bu	−3723	67	0.84	*79*	5.22	*c*	5.40	*36*[d]	4.88	*44*
6c	Me	iC_3F_7	Et	−3768	−4	0.82	*76*	5.38	*40*	5.55	*44*[d]	4.80	*49*
	iC_3F_7	Me		−3743	21	0.83	*76*	4.63	*39*	4.94	*58*	5.48	*35*
6e	Me	iC_3F_7	*n*Bu	−3750	14	0.74	*76*	5.39	*40*[d]	5.52	*<30*[d]	4.78	*47*
	iC_3F_7	Me		−3734	30	0.75	*76*	4.61	*38*	4.93	*58*	5.47	*41*[d]
6f	Me	iC_3F_7	*i*Bu	−3729	35	0.72	*76*	5.41	*<35*[d]	5.53	*<35*[d]	4.71	*47*
	iC_3F_7	Me		−3720	44	0.76	*76*	4.57	*38*	4.93	*57*	5.49	*36*[d]
7c	Me	nC_8F_{17}	Et	−3766	24	0.87	*79*	5.07[d]	*<40*[d]	5.13[d]	*<40*[d]	4.95	*43*
7e	Me	nC_8F_{17}	*n*Bu	−3763	27	0.86	*78*	5.31	*<35*[d]	5.31	*<35*[d]	4.94	*39*
7f	Me	nC_8F_{17}	*i*Bu	−3740	50	0.85	*78*	5.24	*<35*[d]	5.41	*<35*[d]	4.88	*39*
8c	Cl	Me	Et	−3471	25	0.87	*71*	4.36	*73*[d]	4.40	*68*[d]	5.36	*36*
8e	Cl	Me	*n*Bu	−3471	25	0.87	*71*	4.38	*72*	4.38	*72*	5.34	*35*
8f	Cl	Me	*i*Bu	−3470	26	0.89	*71*	4.36	*70*	4.41	*77*	5.31	*33*
9b	Ph	Ph	Me	−3564	31			4.99[d]	*c*	5.03[d]	*c*	4.90	*36*[d]

[a]Samples were measured in $CDCl_3$. Chemical shifts are given in ppm and coupling constants in Hz (in italics). [b]Ligands L(1) and L(2) are the ligands next to and opposite of the residue R at the cod ligand, respectively (e.g., L(1) = Cl, L(2) = Me for molecules **8a,c,e,f** in Scheme 2). [c]Not accessible due to strong overlap and coupling artifacts. [d]Tentative value due to overlap.

against different cell lines. It is known that cod-linked platinum(II) complexes exhibit an unusually high acute toxicity against HT-29 and MCF-7 cells.[74] Despite these findings, there have been, to the best of our knowledge, no further experiments with derivatized cod ligands until now.

To test the toxicity, 5×10^3 HeLa cells were plated on a 96-well ibidi plate and incubated at 37 °C and 5% CO_2 atmosphere for 24 h. Then the cells were treated with various concentrations of different platinum(II) complexes (100, 250, 500, 750 nM and 1, 1.5, 2, 3, 4, 5, and 10 μM) at 37 °C and 5% CO_2 atmosphere. After 3 days of incubation 15 μL of MTT reagent was added. After 3 h of incubation 100 μL solubilization solution/stop mix was added. Finally, the plates were measured by an microplate reader at 595 nm.

To our surprise, all of the tested complexes exhibited higher cytotoxicity in comparison to cisplatin (Table 5). However, IC_{50} values varied strongly. To evaluate the influence of different ligands L and substituents R, one has to differentiate between complexes with perfluorinated ligands L (**5**−**7**) and complexes where L = Me (**2**), Cl (**8**). In general, complexes with perfluorinated ligands L (**5**−**7**) and where R = H were slightly more cytotoxic than other tested complexes. A reason for this behavior might be the lipophilic character of the ligands, which allows the compounds to pass through membranes more easily. In this case, substitution of the cod ligand led to reduced

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Table 3. Selected Chemical Shifts and Coupling Constants of the Complexes with an Unsubstituted cod Ligand and the General Formula [PtL(1)L(2)(cod)][a]

	L(1)	L(2)	δ^{195}_{Pt}	δ^{1}_{H}(Me)	$^{2}J_{Pt,H}$(Me)	δ^{1}_{H}(=CH,cod), $^{2}J_{Pt,H}$(=CH,cod)			
						trans L(1)		*trans* L(2)	
2a	Me	Me	−3562	0.74	*82*	4.81	*38*	4.81	*38*
3a	Cl	Cl	−3330			5.61	*67*	5.61	*67*
4a	I	I	−4314			5.76	*66*	5.76	*66*
5a	Me	nC_3F_7	−3790	0.88	*78*	5.37	*33*	5.14	*43*
6a	Me	iC_3F_7	−3764	0.79	*76*	5.52	*31*	4.97	*49*
7a	Me	nC_8F_{17}	−3790	0.88	*78*	5.39	*34*	5.14	*43*
8a	Cl	Me	−3496	0.90	*71*	4.49	*76*	5.51	*33*
9a	Ph	Ph	−3595			5.12	*38*	5.12	*38*
12[b]	alkynyl	alkynyl	−3935			5.62	*41*	5.62	*41*

[a]Samples were measured in $CDCl_3$ if not noted differently. Chemical shifts are in ppm and coupling constants in Hz (in italics). [b]Sample was measured in CD_2Cl_2.

Table 4. Ratios (%) of the Two Possible Diastereomers of the Mixed Complexes 5c,e,f−8c,e,f

	5c	5e	5f	6c	6e	6f	7c	7e	7f	8c	8e	8f
L(1) = Me[a]	100	100	100	61	58	54	100	100	100	0	0	0
L(2) = Me[a]	0	0	0	39	42	46	0	0	0	100	100	100

[a]Ligands L(1) and L(2) are the ligands next to and opposite of the residue R at the cod, respectively (e.g., L(1) = Cl, L(2) = Me for molecules **8a,c,e,f** in Scheme 2).

Table 5. IC_{50} Values of Selected Platinum(II) Complexes with the General Formula [PtMeL(R-cod)]

compd	R	L	IC_{50} (μM)
2a	H	Me	2.47 ± 0.28
2c	Et	Me	0.52 ± 1.62
2e	*n*Bu	Me	2.66 ± 0.13
2f	*i*Bu	Me	2.64 ± 0.30
5a	H	nC_3F_7	1.60 ± 0.35
5c	Et	nC_3F_7	1.96 ± 0.25
5e	*n*Bu	nC_3F_7	3.21 ± 0.54
5f	*i*Bu	nC_3F_7	1.98 ± 0.24
6a	H	iC_3F_7	1.22 ± 0.09
6c	Et	iC_3F_7	2.24 ± 0.75
6e	*n*Bu	iC_3F_7	2.74 ± 0.40
6f	*i*Bu	iC_3F_7	2.95 ± 0.72
7a	H	nC_8F_{17}	1.44 ± 0.08
7c	Et	nC_8F_{17}	2.56 ± 0.68
7e	*n*Bu	nC_8F_{17}	3.67 ± 0.06
7f	*i*Bu	nC_8F_{17}	2.40 ± 0.51
8a	H	Cl	2.64 ± 0.21
8c	Et	Cl	1.79 ± 0.36
8e	*n*Bu	Cl	3.14 ± 0.16
8f	*i*Bu	Cl	2.88 ± 0.05
cisplatin			3.82 ± 0.52

biological activity, perhaps due to the increased bulkiness of the compounds.

A different behavior was observed for complexes **2** and **8**, both having smaller, less lipohilic ligands L. Compounds **2c** and **8c** with an ethyl-substituted cod ligand were the most cytotoxic complexes of these two classes. Longer alkyl chains again led to reduced activity. A reasonable explanation for this might be that the ethyl substituent is a perfect compromise between increased lipophilicity and bulkiness of the complex.

CONCLUSIONS

In this work, we have described the syntheses of new organometallic complexes [PtMeL(R-cod)] (where L = Cl, I, iC_3F_7, nC_3F_7, nC_8F_{17}, Me, aryl, alkynyl and R = H, Me, Et, *i*Pr, *n*Bu, *i*Bu, *n*Hex, Ph) in excellent yields. All complexes were characterized in solution by multinuclear (^{1}H, ^{13}C, ^{19}F, ^{195}Pt) NMR spectroscopy and some of them also in the solid state by crystal structures. In addition to standard measurements, we also used a new NMR method that was specifically developed to measure complexes whose resonances are spread over a wide range of frequencies. Using this method, we were able to distinguish diastereomers derived from the monofunctionalized cod ligands. Selected complexes were tested in cytotoxicity experiments with HeLa cells and revealed highly promising activities for most of the structures in comparison to cisplatin. Taking all these results into account, we can attribute the difference in biological activity mainly to differences in solubility and lipophilicity depending on ligands L and substituents R. If L is a perfluorinated ligand, substitution of cod leads to reduced cytotoxicity, while for L = Me, Cl, complexes with an ethyl chain (**2c**, **8c**) are the most cytotoxic. Future studies will focus on the underlying mechanism in vivo.

EXPERIMENTAL SECTION

General Procedures. The starting materials, solvents, and reagents were purchased from Acros, ABCR, Alfa Aesar, or Sigma-Aldrich and used without further purification. All reactions involving moisture-sensitive reactants were executed under an argon atmosphere using oven-dried or flame-dried glassware. Dry tetrahydrofuran and dry diethyl ether were distilled from sodium under argon using benzophenone as indicator prior to use. Dry toluene was distilled from sodium under argon prior to use. Dry dichloromethane was distilled from calcium chloride under argon prior to use. TLC: ready-to-use plates with silica gel 60 (F254). Column chromatography: silica gel 60 (0.04−0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a 300 MHz (300 MHz (^{1}H) and 75 MHz (^{13}C)) and a 400 MHz (400 MHz (^{1}H), 100 MHz (^{13}C)) spectrometer. All spectra are referenced to tetramethylsilane as the internal standard (δ = 0 ppm) by using the signals of the residual protons of $CHCl_3$ (7.26 ppm (^{1}H)

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or 77.0 ppm (^{13}C)) in $CDCl_3$ and of CH_2Cl_2 (5.32 ppm (^1H) or 54.0 ppm (^{13}C)) in CD_2Cl_2. Multiplicities of signals are described using standard abbreviations or as follows: s d, singlet + doublet (of singlets) due to coupling with ^{195}Pt; dd, doublet of doublets; d d, doublet + doublet (of doublets) due to coupling with ^{195}Pt; dd d, doublet of doublets + doublet (of doublet of doublets) due to coupling with ^{195}Pt; t d, triplet + doublet (of triplets) due to coupling with ^{195}Pt; quin d, quintet + doublet (of quintets) due to coupling with ^{195}Pt; m d, multiplet + doublet (of multiplets) due to coupling with ^{195}Pt. Coupling constants (J) are given in Hz. The assignments of the signal structure in ^1H NMR were made by the multiplicity and for ^{13}C NMR by DEPT 90 and DEPT 135 spectra (DEPT = distortionless enhancement by polarization transfer) and are described as follows: +, primary or tertiary C atom (positive DEPT signal); −, secondary C atom (negative DEPT signal); C_{quart}, quaternary C atom (no DEPT signal). ^{195}Pt NMR spectra were recorded at 300 K on a 600 MHz spectrometer using either an inversely detected double-resonance ^1H-BB probe head or an inversely detected triple-resonance $^1H-^{13}C$,BB probe head. Platinum frequencies were determined by 1D ^{195}Pt spectra or an ultra-broad-band version of a gradient-selected ^1H,^{195}Pt-HMBC. Due to the very large chemical shift range of platinum complexes (15000 ppm, 1.94 MHz @ 14.1 T), it is not possible to cover this range in one conventional experiment. Conventional experiments are acquired with hard pulses that can excite a bandwidth of about 50 kHz. Therefore, to cover the complete chemical shift range, nearly 40 experiments would be needed. With new ultra-broad-band versions of conventional experiments that can acquire a bandwidth of 500 kHz, the number of needed spectra is decreased by a factor of 10. Although Pt(II) complexes only have a chemical shift range of 4000 ppm, three experiments would still be needed to determine the chemical shift of a complex reliably. With the new experiments, only one broad-band spectrum is needed. Broad-band spectra are achieved via application of broad-band saturation pulses on platinum,[83] which have been designed by optimal control derived optimizations.[75−81] IR (infrared spectroscopy) spectra were recorded on a FT-IR Bruker IFS 88 or a Bruker Alpha T spectrometer. IR spectra were recorded using the DRIFT technique (diffused reflectance infrared Fourier transform spectroscopy) or ATR Diamond (attenuated total reflection) for solids. IR spectra of oils were determined as KBr plates, prepared under an argon atmosphere. The absorption bands are given in wavenumbers $\tilde{\nu}$ in cm^{-1}.

General Method for the Preparation of Functionalized cod Ligands 1b−h.[12,82] For the R-cod ligands **1b−h**, 1-bromo-1,5-cyclooctadiene (**1i**; 1.00 equiv) and $NiCl_2$(dppp) (2.00 mol %) were dissolved in dry tetrahydrofuran. At 0 °C, the corresponding Grignard solution (2.00 equiv) in diethyl ether or tetrahydrofuran was added to the reaction mixture, which was then stirred for 30 min at this temperature. The mixture was warmed to room temperature and was stirred for another 1 h, at that temperature and was finally stirred for a further 2 h under reflux. After it was cooled to room temperature, the mixture was quenched with saturated NH_4Cl. The aqueous layer was extracted three times with diethyl ether, and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (pentane) to give a colorless oil.

General Method for the Preparation of Dichloro Complexes 3a−h.[12,82] For the [$PtCl_2$(R-cod)] complexes **3a−h**, K_2PtCl_4 (1.00 equiv) was dissolved in water and *n*-propanol and the R-cod ligands **1a−h** (6.90 equiv) and $SnCl_2$ (3.00 mol %) were added sequentially. The mixture was stirred for 2−5 days at room temperature until complete decoloration of the solution was achieved. The resulting solid was filtered off, washed twice with water and once with ethanol, and dried in vacuo.

General Method for the Preparation of Diiodo Complexes 4a−h.[12,82] For the [PtI_2(R-cod)] complexes **4a−h**, NaI (2.15 equiv) was added to a suspension of [$PtCl_2$(R-cod)] (**3a−h**; 1.00 equiv) in acetone. The mixture turned yellow immediately and was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and [PtI_2(R-cod)] complexes **4a−h** were obtained as a solid or wax without further purification.

General Method for the Preparation of Dimethyl Complexes 2a−h (Method A).[12,82] For the [$PtMe_2$(R-cod)] complexes **2a−h**, to a suspension of [PtI_2(R−cod)] (**4a−h**; 1.00 equiv) in dry diethyl ether was added a solution of MeLi in pentane (1.6 M, 3.00 equiv) at 0 °C. The mixture was stirred for 2 h at this temperature and was finally quenched with ice-cold saturated aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether three times, and the combined organic layers were washed with brine and dried over Na_2SO_4. After addition of a small amount of charcoal, the solution was filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (cyclohexane, 2% NEt_3).

General Method for the Preparation of Dimethyl Complexes 2a−g (Method B).[12,82] For the [$PtMe_2$(R-cod)] complexes **2a−g**, R-cod ligands **1a−g** (1.10 equiv) and $Pt(acac)_2$ (1.00 equiv) were dissolved in dry toluene. Then, $AlMe_3$ (2 M in toluene, 3.00 equiv) was slowly added and the mixture was stirred for 24 h at room temperature. The solution was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with diethyl ether four times. The combined organic layers were washed three times with 1 M HCl and once with brine and were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (cyclohexane, 2% NEt_3).

General Method for the Preparation of Complexes with *n*C_3F_7 Ligand 5a,c,e,f.[13] For the [$PtMenC_3F_7$(R-cod)] complexes **5a,c,e,f**, dimethyl complexes **2a,c,e,f** (1.00 equiv) were dissolved in dry dichloromethane and treated with heptafluoro-1-iodopropane (10.0 equiv) at room temperature. The mixture was stirred for 5 days at 35 °C with exclusion of light. The volatiles were removed in vacuo, and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 30/1).

General Method for the Preparation of Complexes with *i*C_3F_7 Ligand 6a,c,e,f.[13] For the [$PtMeiC_3F_7$(R-cod)] complexes **6a,c,e,f**, dimethyl complexes **2a,c,e,f** (1.00 equiv) were dissolved in dry dichloromethane and treated with heptafluoro-2-iodopropane (15.0 equiv) at room temperature. The mixture was stirred for 5 days at 35 °C with exclusion of light. The volatiles were removed in vacuo, and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 30/1).

General Method for the Preparation of Complexes with *n*C_8F_{17} Ligand 7a−d.[13] For the [$PtMenC_8F_{17}$(R-cod)] complexes **7a,c,e,f**, dimethyl complexes **2a,c,e,f** (1.00 equiv) were dissolved in dry dichloromethane and treated with heptadecafluoro-1-iodooctane (5.00 equiv) at room temperature. The mixture was stirred for 5 days at 35 °C with exclusion of light. The volatiles were removed in vacuo, and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 30/1).

General Method for the Preparation of Monochloro Complexes 8a,c,e,f. For the [PtMeCl(R-cod)] complexes **8a,c,e,f**, dimethyl complexes **2a,c,e,f** (1.00 equiv) were dissolved in dichloromethane/methanol 3/2 and treated with acetyl chloride (1.00 equiv) at room temperature. The mixture was stirred for a further 10 min and then concentrated in vacuo. Solids were stored overnight at −20 °C and then filtered, washed twice with small portions of pentane, and finally dried in vacuo. Oils were further dried in vacuo.

General Method for the Preparation of Diphenyl Complexes 9a,b.[82] For the [$PtPh_2$(R-cod)] complexes **9a,b**, dichloro complexes **3a,b** (1.00 equiv) were dissolved in dry diethyl ether and treated with phenylmagnesium bromide (2 M in tetrahydrofuran, 2.20 equiv) at room temperature. The mixture was stirred for 12 h at room temperature and finally treated with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the colorless residue was purified by recrystallization from dichloromethane and pentane.

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Further Functionalized Molecules 10−12. *[PtMes$_2$(cod)] (**10**).* Dichloro complex **3a** (1.00 equiv) was dissolved in dry diethyl ether and treated with mesitylmagnesium bromide (1 M in tetrahydrofuran, 2.02 equiv) at room temperature. The mixture was stirred for 12 h at room temperature and finally treated with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the colorless residue was purified by recrystallization from dichloromethane and pentane to give a colorless solid. Yield: 141 mg (0.256 mmol, 48%).

*[Pt(CCPh)$_2$(cod)] (**11**).* NaOEt (2.00 equiv., 21 wt % in ethanol) was diluted with dry ethanol, and phenylacetylene (2.00 equiv) was added. After it was stirred for 25 min, the mixture was cooled to 0 °C and a suspension of dichloro complex **3a** (1.00 equiv) in dry ethanol was added. The mixture was warmed to room temperature within 1 h. The solvent was removed under reduced pressure, and the pale yellow residue was extracted with dichloromethane several times. The combined organic layers were concentrated and treated with *n*-hexane. The obtained precipitate was filtered off and washed twice with *n*-hexane to give a colorless solid. Yield: 72.0 mg (0.147 mmol, 55%).

*[Pt(CCArBr)$_2$(cod)] (**12**).* Sodium (2.00 equiv) was dissolved in dry ethanol and stirred for 20 min, and then 4-bromophenylactylene (2.00 equiv) was added. After another 20 min, the solution was cooled to 0 °C and a suspension of dichloro complex **3a** (1.00 equiv) in dry ethanol was added. The mixture was warmed to room temperature within 1 h and was stirred for another 1 h at room temperature. The solvent was removed under reduced pressure, and the pale brown residue was extracted with dichloromethane several times. The combined organic layers were concentrated and treated with *n*-hexane. The obtained precipitate was filtered off and washed twice with *n*-hexane to give a colorless solid. Yield: 288 mg (0.434 mmol, 65%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, figures, and CIF files giving characterization data for all new compounds, toxicological measurements, and crystallographic data for **3a**, **4c**,**h**, **9b** and **10** (CCDC 993788-993792). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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