Microwave-Assisted and Pd^{II}-Mediated Nitrile–Oxime Coupling

Dmitrii A. Garnovskii,[a] Nadezhda A. Bokach,[b] Armando J. L. Pombeiro,*[a]
Matti Haukka,[c] João J. R. Fraústo da Silva,[a] and Vadim Yu. Kukushkin*[b]

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Refluxing $PdCl_2$ with the ketoximes $R^1R^2C{=}NOH$ (R^1R^2 = MeMe, MeEt, C_5H_{10}) in RCN (R = Me, Et, *n*Pr, Ph) for 2–3 h results in precipitation of the oxime complexes $[PdCl_2(R^1R^2C{=}NOH)_2]$, whereas further reflux of the reaction mixture for an additional 6–12 h leads to formation of the chelated species $[PdCl_2\{NH{=}C(R)ON{=}CR^1R^2\text{-}\kappa^2N\}]$ (R/R^1R^2 = Me/MeMe **1**; Et/MeMe **2**; *n*Pr/MeMe **3**; Me/MeEt **4**; Me/C_5H_{10} **5**; Ph/MeMe **6**) by a Pd^{II}-mediated coupling between the oximes and the nitriles; complexes **1**–**6** were isolated in the solid state in 60–75 % yields. The reaction time could be drastically reduced, to 15–30 min, when the system was additionally irradiated with microwaves (100 W, about 60 °C). Compounds **1**–**6** can also be obtained without isolation of the intermediate oxime complexes either by refluxing for 8–15 h or by microwave irradiation (100 W, about 60 °C) for 15–30 min. The formulation of **1**–**6** is based upon satisfactory C, H, and N elemental analyses, FAB mass spectrometry, and IR, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, while the structures of $\mathbf{1}\cdot(Me_2CO)$, $\mathbf{1}\cdot(CHCl_3)$, $\mathbf{2}\cdot(H_2O)$, and $\mathbf{6}\cdot\frac{1}{2}(H_2O)$ were determined by X-ray single-crystal diffraction.

Introduction

In the past five years, microwave irradiation (MWI) has become an increasingly useful tool in synthetic chemistry.[1–12] The major advantages of microwave-assisted syntheses are associated with a substantial decrease of reaction times, an increase of the selectivities of the processes, and, consequently, better purity of the products formed.[2,4,6–8,10–12] In the overwhelming majority of cases, MWI has been applied in organic synthesis. However, some reports on the application of MWI in the synthesis of coordination compounds are also present in the literature.[13–25] In particular, microwave syntheses have been used for the preparation of nanophases and nanocrystalline materials starting from metal complexes,[16,19,20] for preparations by substitution,[17,18,21] and for phthalocyanine syntheses.[13–15,22,23] Recently, some of us have demonstrated that MWI also efficiently promotes reactions of coordinated ligands, such as in the [2+3]-cycloaddition[24] and the addition of hydroxamic acids to metal-bound nitriles.[25]

In the current work, we have extended our previous results on microwave-assisted reactions of ligated nitriles to another system by applying MWI for the nitrile–oxime coupling to form the imino species $HN{=}C(R)ON{=}CR'R''$. In a series of previous papers,[26] we have found that these processes are especially efficient when metal centers are in high oxidation states, for example Pt^{IV},[27] Re^{IV},[28] or Rh^{III},[29] whereas low-oxidation-state metal centers, such as Pt^{II},[30] are insufficiently strong activators to provide the coupling under conventional conditions. Hence, we believed that MWI could provide an additional activation for the addition of oximes to nitriles complexed by low-oxidation-state metal centers and to expand, in this way, the number of this type of compounds with their potential application in organic[31] and phthalocyanine syntheses.[32]

Results and Discussion

In organic chemistry, oximes are known as ambidentate nucleophiles and their reactions with electrophilic reagents, such as acylation, have been extensively studied and reviewed.[33] Metal-mediated oxime–nitrile coupling (or, in other words, iminoacylation by complexed nitriles), is a little-explored area and only recently have publications on this subject started to appear in the literature. The largest fraction of these reports is devoted to the coupling induced by high-oxidation-state metal centers, while reactions at low-oxidation-state metal centers, such as Pd^{II}, are scarce. It is important to note that the first data on metal-mediated iminoacylation, reported at a conference,[34] deal with the reaction between 3,3-dimethyl-2-butanone oxime and $[PdCl_2(PhCN)_2]$ to yield, among other products, the imino

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[a] Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Av. Rovisco Pais,
1049-001 Lisboa, Portugal
E-mail: pombeiro@ist.utl.pt
[b] Department of Chemistry, St. Petersburg State University,
198904 Stary Petergof, Russian Federation
E-mail: kukushkin@VK2100.spb.edu
[c] Department of Chemistry, University of Joensuu,
P. O. Box 111, 80101 Joensuu, Finland
E-mail: matti.haukka@joensuu.fi

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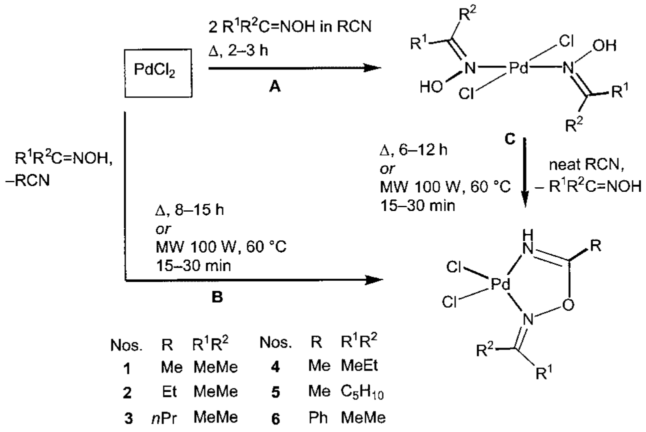
complex $[PdCl_2\{NH{=}C(Ph)ON{=}CMe\textit{t}Bu\}_2]$. The latter observation, which was not developed further, prompted us to investigate the coupling at a Pd^{II} center under both microwave and conventional thermal conditions. For this work we used $PdCl_2$ in neat RCN (R = Me, Et, *n*Pr, Ph) and the ketoximes $R^1R^2C{=}NOH$ (R^1R^2 = MeMe, MeEt, C_5H_{10}).

Refluxing $PdCl_2$ with the ketoximes $R^1R^2C{=}NOH$ in RCN for 2–3 h results in precipitation of the known[35] oxime complexes $[PdCl_2(R^1R^2C{=}NOH)_2]$ (Scheme 1, route **A**). However, further reflux of the reaction mixture for an additional 6–12 h leads to formation of the chelated species $[PdCl_2\{NH{=}C(R)ON{=}CR^1R^2\text{-}\kappa^2N\}]$ (**1**–**6**) (route **C**); these complexes were isolated in the solid state in 60–75% yields.



Scheme 1.

The reaction time could be drastically reduced, to 15–30 min, when the system was additionally irradiated with microwaves (100 W, about 60 °C). The yields of the complexes for both conventional and microwave methods were almost identical. Compounds **1**–**6** can also be obtained by route **B** without isolation of the intermediate oxime complexes.

We believe that a plausible mechanism for the oxime–nitrile coupling at the Pd^{II} center involves the formation of the bis(oxime) complexes $[PdCl_2(R^1R^2C{=}NOH)_2]$, which, in neat RCN, can form an equilibrium concentration of $[PdCl_2(R^1R^2C{=}NOH)(RCN)]$ by displacement of one oxime ligand. In the latter intermediate, the ligated nitrile is subject to intramolecular attack by the adjacent oxime (or oximato ligand formed upon deprotonation). In general, the coupling between electrophilically activated species and nucleophiles is highly probable when the two species are bound to a common metal center,[36] and, moreover, the chelate effect also drives the reaction.

All isolated compounds (**1**–**6**) gave satisfactory C, H, and N elemental analyses and the expected molecular ion and fragmentation patterns in the FAB^+ mass spectra. The IR spectrum of each product displays two strong ν(C=N) bands in the range between 1672 and 1613 cm^{-1} and a strong band in the high frequency region between 3265 and 3217 cm^{-1} that can be attributed to the ν(N–H) stretching vibration. The ^1H NMR spectra of **1**–**6** in [D$_6$]acetone show a broad peak for the =N*H* group at δ = 9.01–9.44 ppm. This range is specific for imino hydrogens involved in hydrogen bonding.[27] The latter was unambiguously determined in the solid state for the solvates **1**·(Me$_2$CO), **2**·(H$_2$O), and **6**·½(H$_2$O) (see below). We anticipate that complexes **1**–**6** should also exhibit a similar type of H-bond with either [D$_6$]acetone or with traces of water in the commercially available solvent. In the ^1H NMR spectrum, complex **4** displays two set of signals for the alkyl groups (two Me's and Et) of the chelated ligand [the latter derived from the coupling with a mixture of *syn*/*anti*-MeC(=NOH)Et] due to *syn*/*anti*-isomers of the ligand.

The structures of **1**·(Me$_2$CO), **1**·(CHCl$_3$), **2**·(H$_2$O), and **6**·½(H$_2$O) were determined by single-crystal X-ray diffraction; the molecular structure of **1**·(Me$_2$CO) is depicted in Figure 1. The atoms in the other similar structures are numbered correspondingly and bond lengths and angles are given in Table 1.

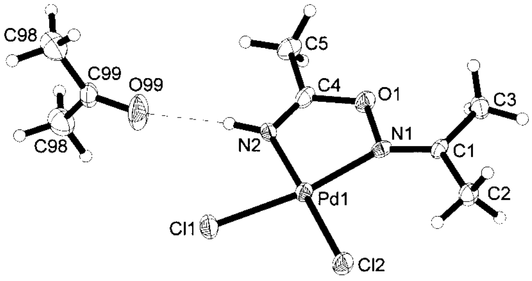


Figure 1. Thermal ellipsoid view of $[PdCl_2\{NH{=}C(Me)\text{-}ON{=}CMe_2\text{-}\kappa^2N\}]\cdot(Me_2CO)$ (**1**·Me$_2$CO) with the atomic numbering scheme. Thermal ellipsoids are drawn with 50% probability. N(2)···O(99) = 2.954(6) Å.

Table 1. Selected bond lengths [Å] and angles [°] **1**·(Me$_2$CO), **1**·(CHCl$_3$), **2**·(H$_2$O), and **6**·½(H$_2$O).

	1·(Me$_2$CO)	**1**·(CHCl$_3$)	**2**·(H$_2$O)	**6**·½(H$_2$O)
Pd(1)–Cl(1)	2.2769(14)	2.2883(4)	2.2846(13)	2.2810(10)
Pd(1)–Cl(2)	2.3058(13)	2.3022(4)	2.3054(14)	2.3119(11)
Pd(1)–N(1)	2.068(4)	2.0622(15)	2.052(4)	2.069(3)
Pd(1)–N(2)	1.968(4)	1.974(2)	1.965(4)	1.980(4)
N(1)–O(1)	1.463(5)	1.4615(19)	1.454(5)	1.454(4)
N(2)–C(4)	1.271(7)	1.267(2)	1.262(6)	1.260(5)
C(4)–O(1)	1.342(6)	1.339(2)	1.333(5)	1.352(5)
Cl(1)–Pd(1)–Cl(2)	88.93(5)	88.87(2)	87.38(5)	88.48(4)
N(1)–Pd(1)–N(2)	79.2(2)	79.20(6)	78.80(15)	79.12(13)
Pd(1)–N(1)–O(1)	110.0(3)	109.66(10)	110.3(2)	109.5(2)
Pd(1)–N(2)–C(4)	117.0(4)	117.05(13)	117.6(3)	117.6(3)
C(4)–O(1)–N(2)	113.0(4)	113.57(13)	113.3(3)	114.4(3)

Inspection of Table 1 shows that the relevant bond lengths and angles of the four complexes agree with each other within 3σ and they are also well-coherent with the normal bond lengths and angles.[37]

In conclusion, one should note that (*i*) the observed oxime coupling is metal-mediated (as we have shown previously,[1] the addition of oximes to nonactivated organonitriles RCN, i.e. those with a donor group R, does not proceed in the absence of any metal complex even under rather harsh reaction conditions) and (*ii*) the reaction is dramatically accelerated by microwave irradiation, thus allowing the formation of (imino)Pd^{II} complexes in a short time.

Experimental Section

Materials and Instrumentation: All reagents and solvents were obtained from commercial sources and used as received. C, H, and N elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. Melting points were determined on a Kofler Table. For TLC, Merck UV 254 SiO_2 plates were used. Positive-ion FAB mass spectra were obtained on a Trio 2000 instrument by bombarding 3-nitrobenzyl alcohol (NBA) matrices of the samples with 8 keV (ca. 1.28×10^{15} J) Xe atoms. Mass calibration for the data system acquisition was achieved with CsI. IR spectra (4000–400 cm^{-1}) were recorded on a JASCO FT/IR-430 instrument in KBr pellets. ^1H NMR spectra were measured on a Varian UNITY 300 spectrometer at ambient temperature. The microwave irradiation experiments were undertaken in a focused microwave CEM Discover®LabMate™ reactor (100 W, 2.45 Hz) fitted with a rotational system and an IR temperature detector; reactions were performed in 10-mL pressure-rated reaction tubes, volumes of reaction mixtures were about 3 mL. Detailed information on the reactor is given at http://www.combichemlab.com/website/files/Combichem/Microwave/cem.htm.

$[PdCl_2\{NH=C(R)ON=CMe_2\text{-}\kappa^2N\}]$ (R = Me 1, Et 2, *n*Pr 3, Ph 6): $PdCl_2$ (20.0 mg, 0.11 mmol) and 2-propanone oxime (17.0 mg, 0.23 mmol) were suspended in the corresponding RCN (1 mL) and the reaction mixture was heated under reflux conditions for 2–3 h until the yellow solid complex $[PdCl_2(HON=CMe_2\text{-}\kappa N)_2]$ had formed. However, if the reaction mixture was refluxed for an additional 6 (**1**), 8 (**2**), or 9 h (**3**), it leads to (*i*) R = Me: the release of orange complex **1**, which was filtered off, washed three times with a small amount of acetonitrile and dried in vacuo. Yield: 25 mg (76%). The latter reaction was also performed under MW irradiation (100 W, about 60 °C) and was complete in 15 min (yield: 24 mg, 73%). (*ii*) R = Et and *n*Pr: formation of an orange solution. The solvent was removed under a gentle stream of nitrogen and the orange solid was washed with diethyl ether and dried in vacuo. Yields: 23 mg (67%; **2**) and 25 mg (69%; **3**). The latter reaction was also performed under MW irradiation (100 W, about 60 °C) and was complete in 30 min. Yields: 22 mg (64%; **2**) and 27 mg (74%; **3**). (*iii*) After refluxing for more than 10 h (R = Ph), the dissolution of the oxime complex was complete and the solution turned orange. The solvent was removed under a gentle stream of nitrogen and the orange crystalline residue was washed three times with diethyl ether and dried in vacuo. Yield: 23.5 mg (59%; **6**). The use of MW irradiation (100 W, about 60 °C) allowed the completion of this reaction in 30 min.

1: $C_5H_{10}Cl_2N_2OPd$ (291.5): calcd. C 20.60, H 3.46, N 9.61; found C 20.80, H 3.42, N 9.31. FAB^+-MS: *m*/*z* = 313 $[M - H + Na]^+$, 289 $[M - 2H]^+$, 255 $[M - HCl]^+$. M.p. 187–188 °C. IR (KBr): $\tilde{\nu}$ = 3239 s cm^{-1} ν(N–H), 1672 s and 1625 s ν(C=N). ^1H NMR ($[D_6]$acetone): δ = 2.36 (s, 3 H, Me), 2.44 (s, 3 H, Me), 2.68 (s, 3 H, Me), 9.01 (br. s, 1 H, NH) ppm.

2: $C_6H_{12}Cl_2N_2OPd$ (305.5): calcd. C 23.60, H 3.93, N 9.18; found C 23.82, H 3.69, N 9.19. FAB^+-MS: *m*/*z* = 306 $[M + H]^+$, 271 $[M + H - Cl]^+$, 235 $[M + H - 2Cl]^+$. M.p. 194–195 °C. IR (KBr): $\tilde{\nu}$ = 3217 s cm^{-1} ν(N–H), 1665 s and 1621 s ν(C=N). ^1H NMR ($[D_6]$acetone): δ = 1.27 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H, Me from Et), 2.38 (s, 3 H, Me), 2.69 (s, 3 H, Me), 2.95 (q, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2 from Et), 9.13 (br. s, 1 H, NH) ppm.

3: $C_7H_{14}Cl_2N_2OPd$ (319.5): calcd. C 26.33, H 4.38, N 8.77; found C 25.98, H 4.06, N 8.81. FAB^+-MS: *m*/*z* = 320 $[M + H]^+$, 285 $[M + H - Cl]^+$. M.p. 174–175 °C. IR (KBr): $\tilde{\nu}$ = 3222 s cm^{-1} ν(N–H), 1667 s and 1620 s ν(C=N). ^1H NMR ($[D_6]$acetone): δ = 0.98 (t, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 1.76 (q, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 2.37 (s, 3 H, Me), 2.69 (s, 3 H, Me), 2.77 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 9.11 (br. s, 1 H, NH) ppm.

6: $C_{10}H_{12}Cl_2N_2OPd$ (353.5): calcd. C 34.09, H 3.44, N 7.96; found C 34.17, H 3.23, N 8.25. FAB^+-MS: *m*/*z* = 319 $[M - Cl + 3H]^+$, 317 $[M - Cl + H]^+$, 316 $[M - Cl]^+$. M.p. 169–170 °C. IR (KBr): $\tilde{\nu}$ = 3218 s cm^{-1} ν(N–H), 1649 s and 1617 s ν(C=N), 1579 s ν(C=C). ^1H NMR ($[D_6]$acetone): δ = 2.55 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3), 7.61–8.13 (m, 5 H, Ph), 9.44 (br. s, 1 H, NH) ppm.

$[PdCl_2\{NH=C(Me)ON=CMeEt\text{-}\kappa^2N\}]$ (4): $PdCl_2$ (20.0 mg, 0.11 mmol) and 2-butanone oxime (20.0 mg, 0.23 mmol; a mixture of *syn* and *anti* isomers) were suspended in acetonitrile (1 mL). The reaction mixture was refluxed for 9 h until the complete dissolution of $PdCl_2$ to give an orange solution, whereupon acetonitrile was evaporated with a flow of nitrogen and the yellow oily residue was crystallized under a layer of diethyl ether to give an orange yellow solid that was filtered off and dried in air at room temperature. Yield: 23 mg (67%). The latter reaction was also performed under MW irradiation (100 W, about 60 °C) and was complete in 15 min. Yield: 22 mg (63%). $C_6H_{12}Cl_2N_2OPd$ (305.5): calcd. C 23.60, H 3.93, N 9.18; found C 22.97, H 3.91, N 9.13. FAB^+-MS: *m*/*z* = 305 $[M]^+$, 269 $[M - HCl]^+$. IR (KBr): $\tilde{\nu}$ = 3237 s cm^{-1} ν(N–H), 1670 s and 1617 s ν(C=N). ^1H NMR ($[D_6]$acetone): two *syn-anti* isomers in ca. 3:2 ratio. Major isomer: δ = 1.16 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H) and 3.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H) (C_2H_5), 2.37 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3 from oxime), 9.05 (br. s, 1 H, NH); minor isomer: δ = 1.22 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H) and 2.75 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H) (C_2H_5), 2.68 (s, 3 H, CH_3 from oxime), 2.45 (s, 3 H, CH_3), 9.05 (br. s, 1 H, NH) ppm.

$[PdCl_2\{NH=C(Me)ON=C(C_5H_{10})\text{-}\kappa^2N\}]$ (5): $PdCl_2$ (20.0 mg, 0.11 mmol) and cyclohexanone oxime (26.0 mg, 0.23 mmol) were suspended in acetonitrile (1 mL) and refluxed for 4 h, whereupon a yellow, crystalline precipitate of $[Pd\{HON=C(C_5H_{10})\}_2]$ formed. If this suspension was refluxed for an additional 11 h, the oxime complex gradually dissolved to give an orange solution. The solvent was removed under a stream of nitrogen and the orange solid was washed with diethyl ether and dried in vacuo. Yield: 26 mg (69%). The latter reaction was also performed under MW irradiation (100 W, 60 °C) for 30 min. Yield: 25 mg (68%). $C_8H_{14}Cl_2N_2OPd$ (331.5): calcd. C 29.00, H 4.22, N 8.45; found C 28.72, H 3.71, N 8.69. FAB^+-MS: *m*/*z* = 331 $[M]^+$, 330 $[M - H]^+$, 260 $[M - 2Cl]^+$. M.p. 191–193 °C. IR (KBr): $\tilde{\nu}$ = 3265 s cm^{-1} ν(N–H), 1658 s and 1613 s ν(C=N). ^1H NMR ($[D_6]$acetone): δ = 1.65 (m, 2 H, C_5H_{10}), 1.85 (m, 4 H, C_5H_{10}), 2.46 (s, 3 H, CH_3), 2.50 (m, 2 H, C_5H_{10}), 2.60 (m, 2 H, C_5H_{10}), 9.20 (br. s, 1 H, NH) ppm.

X-ray Structure Determinations. Crystals were immersed in cryo-oil, mounted in a Nylon loop, and measured at a temperature of 100 K or 110 K. The X-ray diffraction data were collected with a Nonius KappaCCD diffractometer using Mo-K_α radiation (λ = 0.71073 Å). The Denzo-Scalepack[38] or EvalCCD[39] program packages were used for cell refinements and data reduction. The structures were solved by direct methods using SIR2000[40] or by the Patterson method with DIRDIF-99.[41] A multiscan absorption correction based on equivalent reflections (XPREP in SHELXTL v. 6.14)[42] was applied to all of the data (the T_{min}/T_{max} values were 0.7411/0.8986, 0.5614/0.8510, 0.5097/0.8461, and 0.4884/0.8636 for **1**·(Me_2CO), **1**·$(CHCl_3)$, **2**·(H_2O), and **6**·½(H_2O), respectively). Structural refinements were carried out with SHELXL-97 with the WinGX graphical user interface.[43,44] NH and H_2O were located from the difference Fourier map but not refined in **6**·½(H_2O) [N(2)

Table 2. Crystallographic data for **1**·(Me_2CO), **1**·($CHCl_3$), **2**·(H_2O), and **6**·½(H_2O).

	1·(Me_2CO)	**1**·($CHCl_3$)	**2**·(H_2O)	**6**·½(H_2O)
Empirical formula	$C_8H_{16}Cl_2N_2O_2Pd$	$C_6H_{11}Cl_5N_2OPd$	$C_6H_{14}Cl_2N_2O_2Pd$	$C_{10}H_{13}Cl_2N_2O_{1.5}Pd$
Formula mass	349.53	410.82	323.49	362.52
Temperature [K]	100(2)	100(2)	110(2)	100(2)
λ [Å]	0.71073	0.71073	0.71073	0.71073
Crystal system	monoclinic	triclinic	monoclinic	triclinic
Space group	$C2/m$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$
a [Å]	20.8502(12)	7.7792(2)	7.112(2)	7.1582(6)
b [Å]	6.8143(3)	8.9921(3)	11.014(3)	8.1661(7)
c [Å]	9.2995(5)	10.4116(3)	14.391(3)	11.5194(11)
α [°]	90	105.127(2)	90	110.343(5)
β [°]	100.117(3)	96.913(2)	101.245(17)	90.897(5)
γ [°]	90	105.504(2)	90	95.358(6)
V [Å^3]	1300.72(12)	663.19(3)	1105.6(5)	627.77(10)
Z	4	2	4	2
$\rho_{\mathrm{calcd.}}$ [Mg m^{-3}]	1.785	2.057	1.944	1.918
μ(Mo-K_α) [mm^{-1}]	1.821	2.382	2.134	1.888
R_1[a] [$I \geq 2\sigma(I)$]	0.0277	0.0181	0.0375	0.0388
wR_2[b] [$I \geq 2\sigma(I)$]	0.0705	0.0425	0.0666	0.0993

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma\{w(F_o{}^2 - F_c{}^2)^2\}/\Sigma\{w(F_o{}^2)^2\}]^{1/2}$.

and O(99)] but refined as riding atoms with a fixed distance of 0.85 Å. Other hydrogens were placed in idealized position and constrained to ride on their parent atom. The crystal water in **6**·½(H_2O) is disordered over two sites with equal occupancy of 0.5. The crystallographic data are summarized in Table 2, with selected bond lengths and angles given in Table 1. CCDC-267621 to -267624 [for **1**·(Me_2CO), **1**·($CHCl_3$), **2**·(H_2O), and **6**·½(H_2O), respectively] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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