Synthesis, characterization, and biological relevance of hydroxypyrone and hydroxypyridinone complexes of molybdenum

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Abstract: We have prepared a number of complexes of the type *cis*-MoO_2L_2 where L represents a hydroxypyronato or hydroxypyridinonato ligand. Both the maltol (3-hydroxy-2-methyl-4-pyrone, Hma) and kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone, Hka) complexes, *cis*-$MoO_2(ma)_2$ (**1**) and *cis*-$MoO_2(ka)_2$ (**2**), have been characterized by X-ray diffraction studies. The pyrone ligands are bound to molybdenum in a *cis* bidentate fashion via the deprotonated hydroxyl groups and the ketone moieties. Crystals of **1** are orthorhombic, a = 12.107 (1), b = 8.6169 (8), c = 16.472 (1) Å, Z = 4, space group $Pca2_1$, and those of **2** are monoclinic, a = 8.4591 (5), b = 16.3453 (10), c = 10.2954 (7) Å, β = 103.0320 (10)°, Z = 4, space group $P2_1/c$. Hydroxypyridinone molybdenum complexes have been prepared for both maltol and kojic acid derivatives with the substituents Me, *n*-Pr, CH_2Ph, Ph at the ring nitrogen. Crystals of the 3-hydroxy-2-methyl-1-phenyl-4-pyridinone (Hppp) derivative, $MoO_2(ppp)_2$ (**9**), are monoclinic, a = 10.9476 (6), b = 13.5353 (9), c = 17.4877 (10) Å, β = 93.465 (4)°, Z = 4, space group $P2_1/n$. Initial investigations into the effects molybdenum compounds have on diabetic hearts are presented. Both Na_2MoO_4 (used as a control) and **1** were effective in lowering blood glucose and free fatty acid levels. Diabetic rats treated with molybdate showed significant improvements in postischemic cardiac function.

Key words: molybdenum, hydroxypyrones, hydroxypyridinones, heart function.

Résumé : On a préparé un certain nombre de complexes du type *cis*-MoO_2L_2 dans lesquels L est un ligand hydroxypyronato ou hydroxypyridinonato. On a caractérisé ces complexes avec le maltol (3-hydroxy-2-méthyl-4-pyrone, Hma) et l'acide kojique (5-hydroxy-2-hydroxyméthyl-4-pyrone, Hka), *cis*-$Mo(ma)_2L_2$ (**1**) et *cis*-$MoO_2(ka)_2$ (**2**) par diffraction des rayons X. Les ligands pyrone sont liés au molybdène d'une façon bidentate *cis* par le biais des groupes hydroxyméthyles déprotonés et des portions cétoniques. Les cristaux de **1** sont orthorhombiques, groupe d'espace $Pca2_1$, avec a = 12,107 (1), b = 8,6159 (8) et c = 16,472 (1) Å et Z = 4 alors que ceux de **2** sont monocliniques, groupe d'espace $P2_1/c$, avec a = 8,4591 (5), b = 16,3453 (10) et c = 10,2954 (7) Å, β = 103,0320 (10)° et Z = 4. Les complexes du molybdène et de l'hydroxypyrone ont été préparés avec des dérivés du maltol et de l'acide kojique portant des substituants Me, Pr, CH_2Ph et Ph sur l'azote du cycle. Les cristaux du dérivé 3-hydroxy-2-méthyl-1-phényl-4-pyridone (Hppp), $MoO_2(ppp)_2$ (**9**), sont monocliniques, groupe d'espace $P2_1/n$, avec a = 10,9476 (6), b = 13,5353 (9) et c = 17,4877 (10) Å, β = 93,465 (4)° et Z = 4. On présente les résultats d'études préliminaires relatives à l'effet des composés du molybdène sur des coeurs diabétiques. Le Na_2MoO_4 (utilisé comme contrôle) ainsi que le composé **1** sont tous les deux efficaces pour diminuer les niveaux de glucose et des acides gras libres dans le sang. Des rats diabétiques traités au molybdate ont montré des améliorations significatives dans la fonction cardiaque postischémique.

Mots clés : molybdène, hydroxypyrones, hydroxypyridinones, fonction cardiaque.

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Introduction

Maltol (3-hydroxy-2-methyl-4-pyrone, Hma) and kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone, Hka) are naturally occurring nontoxic compounds that have found recent applications in bioinorganic chemistry (1). Interest in maltol and kojic acid arises from their ability to deprotonate readily (pK_a for Hma = 8.38, pK_a for Hka = 7.72) and act as anionic chelating, bidentate O,O′ ligands towards a number of biologically active metals. For instance, iron–maltol complexes have found some potential in the treatment of iron-deficiency anaemia (2) and maltol has been examined as a possible chelating agent for lowering aluminum levels in the body (3).

Although metal complexes containing maltol (4) and kojic acid (5) groups are well known, the most significant and well-studied example is the vanadium complex, $VO(ma)_2$ (BMOV) (4*h*). This remarkable compound displays potent insulinomimetic properties and has been the subject of numerous chemical and physiological studies (6). Indeed, Orvig, McNeill and co-workers have shown that BMOV is effective in lowering blood glucose levels in diabetic rats and is relatively nontoxic over a six month administration period (6*b*). BMOV also facilitates the prevention of long-term diabetes-induced pathology and attenuation of hyperinsulinemia and hypertension in genetically hypertensive rats (6*a*). Prevention of cardiac dysfunction in diabetic rats treated with BMOV is of singular importance as Type I (Insulin-Dependent Diabetes Mellitus – IDDM) diabetics are particularly susceptible to heart failure (7). With the advent of insulin therapy, deaths arising from cardiovascular complications associated with diabetes mellitus have risen from 20% to 80% (7). Attempts to develop new compounds for the oral treatment of diabetes should, therefore, have potent insulinomimetic properties as well as show improvement in cardiac pump function over conventional insulin therapy.

Much effort has focused on generating new vanadium compounds to meet these requirements (8). Vanadium complexes containing 3-hydroxy-2-methyl-pyridinone ligands, derived from the addition of primary amines to maltol, have been reported (8*c*, 8*d*). Variation of the amine substituent allows for fine tuning of the hydrophilic/lipophilic balance of the ligands and, therefore, of the corresponding metal complexes (2*b*). The ability to tailor the physical properties of pyridinone ligands has also been utilized to transport metal ions across biological membranes (9).

Recent studies have shown that other transition metals also display certain insulinomimetic properties (10). For example, insulin-like effects on blood lipids have been reported recently in diabetic rats treated with sodium molybdate, Na_2MoO_4 (10*b*). With this in mind, we postulated that oxomolybdenum complexes containing organic ligands may also prove effective for the oral treatment of diabetes. As part of our initial investigation, we have prepared a number of hydroxypyrone and hydroxypyridinone molybdenum complexes and report herein on the amelioration of heart function defects in diabetic rats treated with Na_2MoO_4 and the molybdenum analogue of BMOV, *cis*-bis(maltolato)dioxomolybdenum(VI) (**1**).

Experimental

Materials and methods

Chemicals used were of reagent grade. Maltol, kojic acid, amines, and 3-hydroxy-1,2-dimethyl-4-pyridinone were obtained from Aldrich Chemicals and molybdic acid was purchased from Strem. NMR spectra were recorded on a JEOL JNM-GSX270 FT-NMR spectrometer. ^1H NMR chemical shifts are reported in ppm and referenced to residual protons in $CDCl_3$, D_2O, and DMSO-d_6 at 270.05 MHz. $^{13}C\{^1H\}$ NMR chemical shifts are referenced to internal solvent peaks at 67.80 MHz. Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad, and (ov) overlapping. Infrared spectra were obtained with Nujol on KBr/NaCl plates using a Perkin–Elmer 710B and a Mattson Polaris spectrometer and are reported in cm^{-1}. Melting points were measured uncorrected with a Mel-Temp apparatus. Microanalyses for C, N, and H were carried out at Desert Analytics (Tucson, Ariz.).

Complex **1** (4*a*) and complex **3** (11*g*) were prepared by established methods using molybdic acid. Compounds Hhmp (5*d*), Hhnp (5*d*), Hbpp (5*d*), Hnpp (9*a*), and Hppp (12*b*) were all prepared by previously reported methods with slight modifications. Selected spectroscopic data for these ligands are reported as follows.

3-Hydroxy-6-hydroxymethyl-1-methyl-4-pyridinone, (Hhmp): mp 204°C (dec.); IR (Nujol): 870 (m), 1079 (w), 1129 (m), 1225 (w), 1268 (w), 1310 (m), 1454 (s), 1480 (m), 1552 (s), 1627 (m), 2964 (s), 3310 (br); $^{13}C\{^1H\}$ (in D_2O), δ: 43.2, 62.1, 116.5, 131.3, 148.4, 150.6, 173.3.

3-Hydroxy-6-hydroxymethyl-1-propyl-4-pyridinone, (Hhnp): mp 186°C (dec.); IR (Nujol): 722 (m), 859 (s), 972 (s), 1083 (s), 1131 (s), 1217 (s), 1270 (m), 1454 (s), 1463 (m), 1564 (m), 1643 (m), 2722 (m), 3178 (br); $^{13}C\{^1H\}$ (in D_2O), δ: 12.5, 26.3, 57.3, 62.0, 116.9, 130.1, 148.5, 150.1, 173.3.

Benzyl-3-hydroxy-2-methyl-4-pyridinone, (Hbpp): mp 204°C (dec.); IR (KBr): 855 (m), 1455 (m), 1500 (m), 1570 (s), 1620 (s), 3152 (m); $^{13}C\{^1H\}$ (in $CDCl_3$), δ: 12.2, 57.4, 111.3, 126.0, 128.5, 128.6, 129.5, 135.4, 137.8, 146.6, 170.0; ^1H δ: 2.27 (s, 3H), 4.72 (br s, 1H), 5.09 (s, 2H), 6.45 (d, J = 7 Hz, 1H), 7.01 (br d, J = 7 Hz, 2H), 7.31 (m, 4H).

3-Hydroxy-2-methyl-1-propyl-4-pyridinone, (Hnpp): mp 161°C (dec.); IR (Nujol): 844 (s), 1033 (m), 1223 (s), 1349 (m), 1462 (s), 1504 (m), 1571 (s), 1625 (s), 2971 (s), 3145 (br); $^{13}C\{^1H\}$ (in D_2O), δ: 12.5, 14.0, 25.9, 58.6, 114.8, 137.1, 141.0, 147.3, 171.1.

3-Hydroxy-2-methyl-1-phenyl-4-pyridinone, (Hppp): $^{13}C\{^1H\}$ (in $CDCl_3$), δ: 13.8, 111.2, 126.9, 128.9, 129.7, 130.1, 137.5, 141.9, 145.9, 170.4.

Preparation of *cis*-bis(5-hydroxy-2-hydroxymethyl-4-pyronato)dioxomolybdenum(VI), $MoO_2(ka)_2$, 2

To a stirred suspension of molybdic acid (0.25 g, 0.74 mmol) in 10 mL of water, a 10 mL aqueous solution of kojic acid (0.42 g, 2.96 mmol) was added dropwise. The addition of isopropanol to the solution resulted in the crystallization of white starting material. The yellow product was crystallized following further addition of isopropanol and was collected by suction filtration. The product was washed with ether (2 × 50 mL) and dried under vacuum. Yield: 0.22 g (36%) of a light yellow powder; mp 170°C (dec.). IR

(Nujol): 701 (s), 876 (m), 919 (m), 1154 (m), 1405 (s), 1520 (s), 1574 (m), 1647 (s), 3112 (m). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 4.56 (s, 4H), 5.98 (s, 2H), 6.93 (s, 2H), 8.67 (s, 2H); ^{13}C{^{1}H} δ: 59.8, 106.9, 142.4, 154.1, 173.8, 179.3.

Preparation of *cis*-bis(3-hydroxy-6-hydroxymethyl-1-methyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(hmp)_2$, 4

3-Hydroxy-6-hydroxymethyl-1-methyl-4-pyridinone (0.38 g, 2.45 mmol) was added as a solid to a 35 mL aqueous solution of molybdic acid (0.20 g, 0.59 mmol). After 24 h, the resulting yellow precipitate was collected by suction filtration and washed with water (3 × 10 mL) and methanol (2 × 10 mL). Yield 0.34 g (66%) of a yellow solid; mp 295°C (dec.). IR (KBr): 900 (s), 935 (s), 1100 (m), 1135 (m), 1255 (m), 1305 (s), 1380 (m), 1470 (s), 1515 (s), 1560 (s), 1620 (m), 3070 (w), 3390 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 3.77 (s, 6H), 4.48 (s, 4H), 5.82 (s, 2H), 6.53 (s, 2H), 7.67 (s, 2H); ^{13}C{^{1}H} δ: 41.2, 59.4, 108.9, 126.7, 149.4, 155.7, 172.0. Anal. calcd. for $MoO_8C_{14}H_{16}N_2$: C 38.55, H 3.70, N 6.42; found: C 38.42, H 3.90, N 6.29.

Preparation of *cis*-bis(3-hydroxy-2-methyl-1-propyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(npp)_2$, 5

A 10 mL water solution of molybdic acid (0.16 g, 0.47 mmol) was cooled to 0°C in an ice–water bath. To this chilled solution, Hnpp (0.35 g, 2.10 mmol) was added in small portions as a solid. After 18 h of stirring, the solution was allowed to return to room temperature and the yellow precipitate collected by vacuum filtration. Complex **5** was recrystallized from a methylene chloride – hexane solution and collected by suction filtration. Yield: 0.33 g (76%) of a yellow solid; mp 283°C (dec.). IR (Nujol): 721 (w), 818 (w), 890 (w), 1268 (m), 1377 (m), 1462 (s), 1496 (m), 1551 (m), 1612 (w), 2940 (s). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 0.89 (t, $J_{H–H}$ = 5 Hz, 6H), 1.73 (m, $J_{H–H}$ = 5 Hz, 4H), 2.50 (s, 6H), 4.08 (t, $J_{H–H}$ = 5 Hz, 4H), 6.47 (d, $J_{H–H}$ = 5 Hz, 2H), 7.87 (d, $J_{H–H}$ = 5 Hz, 2H); ^{13}C{^{1}H} δ: 10.4, 11.6, 23.3, 54.8, 108.3, 133.0, 137.7, 154.4, 169.6. Anal. calcd. for $MoO_6C_{18}H_{24}N_2$: C 46.95, H 5.25, N 6.09; found: C 46.60, H 5.35, N 5.95.

Preparation of *cis*-bis(3-hydroxy-6-hydroxymethyl-1-propyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(hnp)_2$, 6

Solid Hhnp (0.12 g, 0.65 mmol) was added in small portions to a stirred 15 mL aqueous solution of molybdic acid (0.05 g, 0.15 mmol). After 18 h, a yellow precipitate was collected by vacuum filtration and washed with water (3 × 10 mL) and diethyl ether (3 × 10 mL). Yield: 0.07 g (47%) of a yellow solid; mp 238°C (dec.). IR (Nujol): 722 (s), 863 (m), 927 (m), 1106 (s), 1244 (s), 1290 (m), 1454 (s), 1537 (m), 1620 (m), 2883 (s). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 0.92 (t, $J_{H–H}$ = 8 Hz, 6H), 1.77 (d, $J_{H–H}$ = 5 Hz, 4H), 4.02 (s, 4H), 4.50 (s, 4H), 5.76 (br s, 2H), 6.54 (s, 2H), 7.75 (s, 2H); ^{13}C{^{1}H} δ: 10.7, 23.9, 54.4, 59.2, 109.3, 125.3, 148.5, 155.8, 171.9. Anal. calcd. for $MoO_8C_{18}H_{24}N_2 \cdot 3H_2O$: C 39.56, H 5.53, N 5.13; found: C 40.04, H 5.63, N 5.19.

Preparation of *cis*-bis(1-benzyl-3-hydroxy-2-methyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(bpp)_2$, 7

To a 25 mL aqueous solution of molybdic acid (0.14 g, 0.41 mmol), 1-benzyl-3-hydroxy-2-methyl-4-pyridinone (0.39 g, 1.81 mmol) was added as a solid in small portions. After 24 h, a yellow precipitate was collected by vacuum filtration and washed with water (2 × 10 mL) and methanol (3 × 10 mL). Yield: 0.38 g (83%) of a yellow solid; mp 295°C (dec.). IR (KBr): 830 (w), 895 (s), 930 (m), 1270 (s), 1360 (m), 1490 (s), 1550 (s), 1615 (m), 3170 (w). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 2.27 (s, 6H), 5.46 (s, 4H), 6.58 (d, $J_{H–H}$ = 8 Hz, 2H), 7.12–7.44 (ov m, 10H), 8.06 (d, $J_{H–H}$ = 8 Hz, 2H). ^{13}C{^{1}H} δ: 12.2, 57.4, 108.9, 126.6, 128.2, 129.2, 133.6, 135.9, 139.0, 154.9, 170.3. Anal. calcd. for $MoO_6C_{26}H_{24}N_2$: C 56.12, H 4.35, N 5.03; found: C 56.06, H 4.40, N 5.00.

Synthesis of 1-benzyl-3-hydroxy-6-hydroxymethyl- 4-pyridinone, (Hhbp)

1-Benzyl-3-hydroxy-6-hydroxymethyl-4-pyridinone was prepared by modification of a known procedure (5*d*). Kojic acid (1.40 g, 9.85 mmol) was dissolved in a 3:1 mixture of water:ethanol (40 mL) whereupon benzylamine (1.50 g, 14.00 mmol) was added dropwise. The reaction mixture was heated to reflux under an atmosphere of dinitrogen for 12 h and then cooled to 5°C. After 3 h, a dark brown precipitate was collected by vacuum filtration and washed with water (2 × 10 mL) and methanol (3 × 10 mL). Yield: 0.24 g (11%) of light brown crystals; mp 258°C. IR (Nujol): 879 (m), 1124 (m), 1245 (m), 1377 (m), 1462 (s), 1518 (w), 1563 (m), 1643 (m), 2930 (s), 3196 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 4.28 (s, 2H), 5.19 (s, 2H), 6.29 (s, 1H), 7.13 (d, $J_{H–H}$ = 5 Hz, 2H), 7.35 (m, 3H), 7.48 (s, 1H); ^{13}C{^{1}H} δ: 54.2, 59.2, 112.2, 123.9, 126.3, 127.6, 128.8, 136.9, 146.8, 147.6, 170.8.

Preparation of *cis*-bis(1-benzyl-3-hydroxy-6-hydroxymethyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(hbp)_2$, 8

1-Benzyl-3-hydroxy-6-hydroxymethyl-4-pyridinone (0.40 g, 1.73 mmol) was added in small portions to a stirred 15 mL aqueous solution of molybdic acid (0.13 g, 0.38 mmol). After 24 h, complex **8** had precipitated from solution and was collected by filtration and washed with water (3 × 10 mL) and methanol (2 × 15 mL). Yield: 0.40 g (89%) of a yellow solid; mp 240°C (dec.). IR (KBr): 895 (m), 924 (m), 1172 (m), 1248 (s), 1313 (m), 1468 (s), 1522 (s), 1563 (s), 1614 (s), 1642 (m), 3219 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 4.44 (t, $J_{H–H}$ = 16 Hz, 4H), 5.41 (s, 4H), 5.84 (br s, 2H), 6.66 (s, 2H), 7.18–7.42 (m, 10H), 7.85 (s, 2H); ^{13}C{^{1}H} δ: 55.7, 58.9, 109.9, 125.9, 126.6, 128.0, 128.7, 135.6, 149.2, 155.6, 172.2. Anal. calcd. for $MoO_8C_{26}H_{24}N_2 \cdot H_2O$: C 51.49, H 4.32, N 4.62; found: C 51.73, H 4.26, N 4.67.

Preparation of *cis*-bis(3-hydroxy-2-methyl-1-phenyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(ppp)_2$, 9

To a stirred 30 mL aqueous solution of molybdic acid (0.20 g, 0.59 mmol), 3-hydroxy-2-methyl-1-phenyl-4-pyridinone (0.59 g, 2.93 mmol) was added in small portions as a solid. After 18 h, **9** precipitated from solution and was

collected by vacuum filtration. The resulting solid was washed with water (5 × 25 mL) and methanol (3 × 5 mL). Yield: 0.51 g (82%) of a yellow powder; mp 272°C. IR (Nujol): 895 (s), 1298 (s), 1365 (s), 1480 (s), 1515 (w), 1543 (s), 1610 (m), 2925 (s), 3058 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 2.09 (s, 6H), 6.64 (s, 2H), 7.61 (m, 10H), 7.90 (s, 2H); ^{13}C{^{1}H} δ: 13.8, 108.6, 126.7, 129.9, 133.3, 138.6, 141.2, 154.1, 170.9. Anal. calcd. for $MoO_6C_{24}H_{20}N_2$: C 54.55, H 3.82, N 5.30; found: C 54.11, H 4.02, N 5.21.

Synthesis of 3-hydroxy-6-hydroxymethyl-1-phenyl-4-pyridinone, (Hhpp)

Aniline was added dropwise (1.38 g, 14.82 mmol) to a 25 mL aqueous solution of kojic acid (1.00 g, 7.04 mmol). The reaction was heated to reflux for 96 h and was filtered hot to remove a black oil. After the mixture was allowed to stand for 18 h at 0°C a dark precipitate was collected and dissolved in 5 mL of methanol. Following the addition of 25 mL of water, a brown solid precipitated and was discarded. The filtrate was collected and solvent removed under vacuum to afford a red oil and dark solid. This mixture was dissolved in a minimum of hot methanol and cooled to 2°C. Within 18 h, Hhpp precipitated and was collected by suction filtration. Yield: 0.11 g (7%) of a light brown solid; mp 224°C. IR (Nujol): 703 (m), 854(m), 1152 (m), 1314 (m), 1488 (m), 1515 (m), 1573 (s), 1644 (s), 3057 (br), 3219 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 4.02 (s, 2H), 5.91 (br s, 1H), 6.47 (s, 1H), 7.32 (s, 1H), 7.48 (s, 2H), 7.53 (s, 3H); ^{13}C{^{1}H} δ: 59.2, 111.1, 123.6, 126.9, 129.3, 129.7, 140.7, 146.3, 148.2, 171.4. Isolation of Hhpp was problematic. This is presumably due to a significant amount of hydrogen bonding between aniline and the resulting pyridinone compound. Indeed, a pyridinone–aniline adduct (Hhpp·H_2NPh) could be isolated in certain instances from solutions of hot methanol. IR (Nujol): 700 (m), 745 (m), 863 (m), 1210 (m), 1307 (m), 1487 (m), 1515 (m), 1573 (s), 1640 (m), 3068 (br). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 3.87 (d, J_{H-H} = 5 Hz, 2H), 6.25 (s, 1H), 6.34 (s, 1H), 6.52 (d, J_{H-H} = 8 Hz, 2H), 6.62 (t, J_{H-H} = 8 Hz, 1H), 7.12 (t, J_{H-H} = 8 Hz, 2H), 7.41 (s, 1H), 7.65 (s, 5H); ^{13}C{^{1}H} δ: 43.7, 111.0, 112.1, 116.5, 123.7, 127.0, 129.0, 129.4, 130.0, 140.8, 146.0, 146.3, 147.5, 171.0.

Preparation of *cis*-bis(3-hydroxy-6-hydroxymethyl-1-phenyl-4-pyridinonato)dioxomolybdenum(VI), $MoO_2(hpp)_2$, 10

To a stirred 10 mL aqueous solution of molybdic acid (0.02 g, 0.06 mmol), 3-hydroxy-6-hydroxymethyl-1-phenyl-4-pyridinone (0.06 g, 0.28 mmol) was added in small portions as a solid. After 18 h, **10** precipitated from solution and was collected by vacuum filtration. The solid was washed with water (5 × 25 mL) and methanol (3 × 5 mL). Yield: 0.03 g (45%) of a yellow solid; mp 261°C. IR (Nujol): 771 (m), 853 (m), 902 (m), 935 (m), 1163 (m), 1305 (s), 1523 (s), 1552 (s), 1590 (m), 1611 (m), 3205 (w). NMR spectroscopic data (in DMSO-d_6): ^{1}H δ: 4.09 (s, 4H), 5.68 (s, 2H), 6.73 (s, 2H), 7.60 (s, 8H), 7.72 (s, 2H); ^{13}C{^{1}H} δ: 59.2, 108.0, 125.7, 126.6, 129.8, 130.0, 140.2, 150.0, 155.1, 173.1. Anal. calcd. for $MoO_8C_{24}H_{20}N_2$: C 51.44, H 3.60, N 5.00; found: C 51.24, H 3.51, N 4.80.

X-ray crystallography

Crystal data for complexes **1**, **2**, and **9** are provided in Table 1. Data for **1** and **9** were collected on a Nicolet LT2 equipped Siemens P4 diffractometer using the ω method ($4° \leq 2\theta \leq 60°$). Data for **2** were collected on a Siemens SMART/CCD diffractometer equipped with an LT-II low-temperature device. The data were corrected for absorption by a faced-indexed analytical method. Three standard reflections every 100 showed no significant decay. The structures were solved by Patterson and Fourier methods, and refined by full-matrix least squares (SHELXTL IRIS). For complex **1**, the alternate polarity cell gave R and wR values of 0.0221 and 0.0251. A weighting scheme of $w^{-1} = \sigma^2(F)$ was used in the last cycles of refinement. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located and refined using a riding model. Atomic coordinates, thermal parameters, bond lengths and angles, and alternate views of the complexes have been deposited as supplementary material.[4]

Animal model and induction of diabetes

Male Sprague–Dawley rats with an initial body weight of 200 g were used in this study. Diabetes was induced in ether-anesthetized rats by an intravenous injection of 60 mg/kg of streptozotocin freshly dissolved in 50 mM sodium citrate buffer, pH 4.5. Control animals received citrate buffer only. After 48 h, the induction of diabetes was confirmed by glucose testing in the urine using Keto-diastix (Ames). Animals were caged in groups of two and provided with food and water ad libitum until the time of experimentation. Animals used in this study were cared for according to the recommendations in the Canadian Council on Animal Care's Guide to the Care and Use of Experimental Animals.

Treatment protocol

After confirmation of diabetes, treatment was initiated by adding $MoO_2(ma)_2$ and sodium molybdate to the drinking water. Intake of compounds was determined on a molar basis adjusted for body weight over a 24 h period. During the 6 week treatment period, the average daily intake of $MoO_2(ma)_2$ by diabetic animals was 0.15 mmol/kg per 24 h and that of molybdate-treated diabetic animals was 0.13 mmol/kg per 24 h. Analytically pure $MoO_2(ma)_2$ was used in this study (Anal. calcd. for $MoO_8C_{12}H_{10}$: C 38.12, H 2.67; found: C 38.08, H 2.66). The pH of the drinking water was adjusted to 7.4 with sodium hydroxide. Under these conditions complex **1** formed a salt that could be recovered by titration with HCl (as ascertained by ^{1}H NMR spectroscopy). Treatment was initiated immediately following the

[4] A complete set of data may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council of Canada, Ottawa, ON K1A 0S2, Canada. Tables of atomic coordinates, bond distances and angles, and alternative views of the complexes have also been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Table 1. Crystallographic data for **1, 2,** and **9**.

Complex	**1**	**2**	**9**
Formula	$C_{12}H_{10}MoO_8 \cdot CH_2Cl_2$	$C_{12}H_{10}MoO_{10}$	$C_{24}H_{20}MoN_2O_6 \cdot (CH_3)_2CO$
Crystal system	Orthorhombic	Monoclinic	Monoclinic
fw	463.1	410.14	586.4
Space group	$Pca2_1$	$P2_1/c$	$P2_1/n$
a, Å	12.107(1)	8.4591(5)	10.9476(6)
b, Å	8.6169(8)	16.3453(10)	13.5353(9)
c, Å	16.472(1)	10.2954(7)	17.4877(10)
β		103.0320(10)	93.465(4)
V, Å^3	1718.4(3)	1386.8(2)	2586.6(3)
Z	4	4	4
D_{calcd} g cm^{-3}	1.790	1.964	1.506
Size, mm	0.58{100} × 0.60{010} × 0.42{001}	0.04 × 0.4 × 0.4	0.21(1$\bar{1}$0)($\bar{1}$10) × .36{101} × 0.38{10$\bar{1}$} × 0.40{001}
Temperature, K	160	293	180
μ, cm^{-1}	11.11	10.01	5.56
Max 2θ, deg	60	27.90	56.0
Reflections:			
Measured	2580	8458	6540
Observed[a]	2466	3214	4747
Parameters	229	216	390
Data collection method	ω	ω	ω
Max. res. density/hole, e Å^{-3}	0.45/–0.41	0.555/–0.762	0.35/–0.36
R[b]	0.0210	0.0288	0.0255
R_w	0.0237	0.0862	0.0290
GoF	2.69	0.713	1.93

[a] $F_o > 6\sigma(F_o)$.

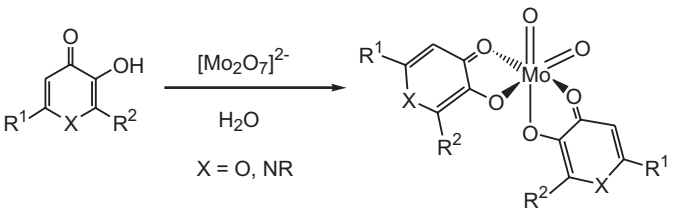
[b] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $Rw = [\Sigma(w(|F_o| - |F_c|)^2/\Sigma(w|F_o|)^2]^{1/2}$.

confirmation of diabetes for a 6 week period. Control animals received water only.

Heart perfusions

Following treatment, hearts from sodium pentobarbital-anesthetized rats were quickly excised, placed in ice-cold buffer and immediately perfused retrogradely via the aorta with Krebs–Henseleit buffer containing 11 mM glucose and 1.75 mM Ca^{2+} (pH 7.4, gassed with 95% O_2 – 5% CO_2). During this perfusion, the hearts were trimmed of excess tissue, the pulmonary arteries were cut, and the openings of the left atria were cannulated. Hearts were then switched to the working mode and perfused at a 15 cm H_2O left atrial filling pressure and 100 cm H_2O hydrostatic aortic afterload in a recirculating buffer system containing 11 mM glucose and 1.2 mM palmitate prebound to 3% bovine serum albumin. Hearts were initially perfused under aerobic conditions for a 15 min period. Global ischemia was induced by clamping off both aortic and preload lines for a period of 25 min. Following ischemia, flow was restored and hearts were allowed to recover for a further 30 min period. Throughout the perfusion, heart rate and aortic pressure development were recorded using a Biotronix pressure recorder (model BL630) interfaced with a Biotronix chart recording system (model BL882). Aortic flow was measured by timed collections. At the end of the reperfusion period, hearts were rapidly frozen with clamps cooled to the temperature of liquid nitrogen, and stored at –80°C.

Fig. 1. Synthesis of molybdenum hydroxypyrone and hydroxypyridinone complexes.



Statistical analysis

A one-way analysis of variance, followed by the Newman–Keuls test, was used to determine statistical significance for comparisons between group means. A value of $p < 0.05$ was considered significant. All data are reported as mean ± S.E.M.

Results and discussion

Hydroxypyrone complexes

$MoO_2(ma)_2$ (**1**, ma = maltolato) is readily prepared in high yield (87%) from addition of maltol to molybdic acid, $(NH_4)_2Mo_2O_7$, in aqueous solutions at neutral pH (Fig. 1, ref. 4*a*). IR and NMR spectroscopic data are consistent with a *cis*-dioxo complex containing two chelating maltolato ligands. Analogous reactions with kojic acid afford the corresponding complex, $MoO_2(ka)_2$ (**2**), in much lower yields (36%). Both **1** and **2** are yellow crystalline complexes, stable indefinitely in the solid state and relatively soluble in water.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **1** and **2**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	*y*	*z*	*U*(eq)
Compound 1				
Mo(1)	3148.9(2)	2171.0(2)	2500	181.2(5)
O(1)	1935(1)	1167(2)	2499(2)	251(5)
O(2)	3812(2)	1581 (3)	1646(1)	259(6)
O(3)	4370(2)	4037(2)	2690(1)	248(6)
O(4)	2382(2)	4096(2)	2130(1)	230(5)
O(5)	2744(2)	3009(2)	3754(1)	249(6)
O(6)	4128(2)	948(2)	3225(1)	225(5)
O(7)	3218(2)	8048(3)	1788(2)	419(9)
O(8)	4391(2)	401(4)	5374(2)	435(9)
C(1)	4054(2)	5345(3)	2419(2)	234(7)
C(2)	2963(2)	5420(3)	2094(2)	236(8)
C(3)	2562(3)	6761(4)	1786(2)	342(9)
C(4)	4235(3)	8004(4)	2088(3)	438(12)
C(5)	4690(2)	6720(3)	2401(3)	329(10)
C(6)	1465(3)	7015(5)	1416(3)	547(15)
C(7)	3241(2)	2238(3)	4295(2)	220(8)
C(8)	4007(2)	1085(3)	4029(2)	201(7)
C(9)	4570(3)	198(4)	4566(2)	289(8)
C(10)	3676(3)	1452(6)	5635(2)	480(13)
C(11)	3098(3)	2410(5)	5143(2)	362(10)
C(12)	5377(3)	–1044(5)	4380(2)	405(12)
C(13)	1430(3)	6237(4)	3993(2)	405(11)
Cl(1)	902(1)	5817(2)	4961(1)	666(4)
Cl(2)	2352(1)	7804(2)	4016(1)	773(5)
Compound 2				
Mo(1)	3747(1)	1260(1)	7138(1)	36(1)
O(1)	3327(3)	398(1)	8388(2)	41(1)
O(2)	2139(2)	1870(1)	8370(2)	35(1)
O(3)	1692(3)	325(1)	11315(2)	45(1)
O(4)	–440(3)	1964(1)	12480(2)	47(1)
O(5)	4266(2)	2405(1)	6757(2)	38(1)
O(6)	5504(2)	1668(1)	8986(2)	38(1)
O(7)	6711(3)	4018(1)	8548(2)	44(1)
O(8)	8818(4)	3891(2)	11944(3)	71(1)
O(9)	5217(3)	701(1)	6675(3)	57(1)
O(10)	2140(3)	1216(2)	5817(2)	58(1)
C(1)	2584(3)	598(2)	9360(3)	35(1)
C(2)	2440(4)	89(2)	10340(3)	43(1)
C(3)	1055(3)	1080(2)	11302(3)	36(1)
C(4)	1122(3)	1629(2)	10333(3)	34(1)
C(5)	1917(3)	1412(2)	9312(3)	32(1)
C(6)	327(4)	1211(2)	12489(3)	47(1)
C(7)	5270(3)	2833(2)	7700(3)	33(1)
C(8)	5709(4)	3618(2)	7547(3)	43(1)
C(9)	7314(3)	3646(2)	9716(3)	36(1)
C(10)	6965(3)	2856(2)	9942(3)	35(1)
C(11)	5925(3)	2416(2)	8928(3)	31(1)
C(12)	8359(4)	4218(2)	10682(3)	50(1)

Increased solubility observed for **2** in aqueous solutions presumably arises due to the pendant CH_2OH group on the pyrone ring. Unlike the maltol derivative, however, **2** decomposes in water at elevated temperatures to give a mixture of molybdates.

As with **1** (4*a*), the IR spectrum for **2** shows that the strong band at 1660 cm^{-1}, assigned as mainly ν(C=O) in kojic acid, decreases in intensity and shifts to a lower wavenumber (1647 cm^{-1}) upon coordination to the d^0 metal centre. Likewise, the bands at 1611 cm^{-1} (strong) and 1578 cm^{-1} (medium), belonging to the strongly mixed ν(C=C) and ν(C=O) modes in pyrones (3*a*, 4*a*), also shift to lower energies upon complexation and are observed at 1574 cm^{-1} and 1520 cm^{-1}, respectively. The band at

Table 3. Selected bond lengths (Å) and angles (°) for **1**.

Bond lengths			
Mo(1)—O(1)	1.705(2)	Mo(1)—O(2)	1.697(2)
Mo(1)—O(3)	2.207(2)	Mo(1)—O(4)	1.997(2)
Mo(1)—O(5)	2.242(2)	Mo(1)—O6)	1.986(2)
O(3)—C(1)	1.207(3)	O(4)—C(2)	1.341(3)
O(5)—C(7)	1.265(4)	O(6)—C(8)	1.336(4)
O(7)—C(3)	1.364(4)	O(7)—C(4)	1.327(5)
O(8)—C(9)	1.360(4)	O(8)—C(10)	1.325(5)
C(1)—C(2)	1.427(4)	C(1)—C(5)	1.413(4)
C(2)—C(3)	1.353(4)	C(3)—C(6)	1.477(6)
C(4)—C(5)	1.339(5)	C(7)—C(8)	1.428(4)
C(7)—C(11)	1.414(5)	C(8)—C(9)	1.353(4)
C(9)—C(12)	1.481(5)	C(10)—C(11)	1.353(6)
Bond angles			
O(1)-Mo(1)-O(2)	104.8(1)	O(1)-Mo(1)-O(3)	161.3(1)
O(2)-Mo(1)-O(3)	91.1(1)	O(1)-Mo(1)-O(4)	91.2(1)
O(2)-Mo(1)-O(4)	102.5(1)	O(3)-Mo(1)-O(4)	75.5(1)
O(1)-Mo(1)-O(5)	88.6(1)	O(2)-Mo(1)-O(5)	164.4(1)
O(3)-Mo(1)-O(5)	77.4(1)	O(4)-Mo(1)-O(5)	85.0(1)
O(1)-Mo(1)-O(6)	104.2(1)	O(2)-Mo(1)-O(6)	93.3(1)
O(3)-Mo(1)-O(6)	84.3(1)	O(4)-Mo(1)-O(6)	154.5(1)
O(5)-Mo(1)-O(6)	75.4(1)	Mo(1)-O(3)-C(1)	113.3(2)
Mo(1)-O(4)-C(2)	118.4(2)	Mo(1)–O(5)-C(7)	112.1(2)
Mo(1)-O(6)-C(8)	118.9(2)		

Fig. 2. The molecular structure of $MoO_2(ma)_2$, **1**.

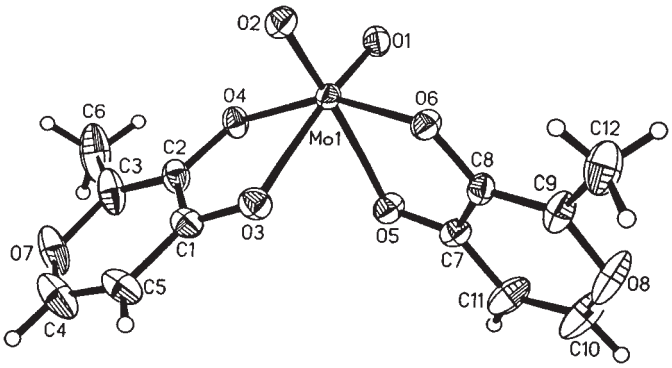
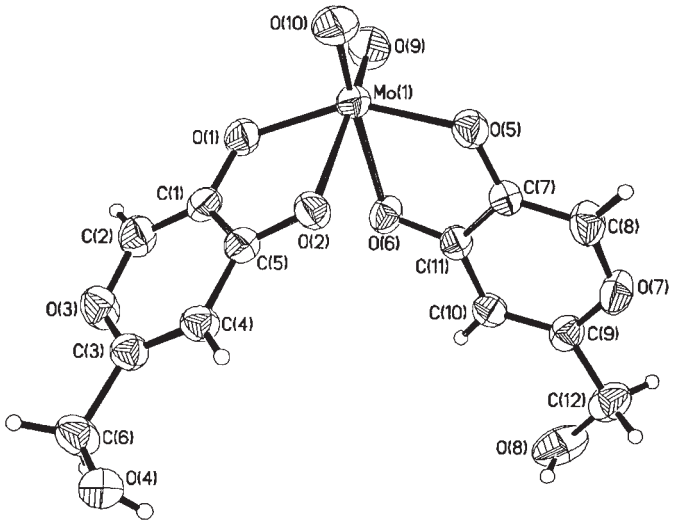


Fig. 3. The molecular structure of $MoO_2(ka)_2$, **2**.



3168 cm^{-1} for the OH stretches of kojic acid is observed at 3122 cm^{-1} for **2**. The two strong IR bands present at 919 and 890 cm^{-1} assigned to ν_s (Mo=O) and ν_{as}(Mo=O) are similar to those reported previously for **1** and for the tropolone complex, *cis*-$MoO_2(trop)_2$ (12). The wavenumbers observed in kojic acid and its metal derivatives are lower than those for the maltol derivatives, presumably because of the electron-withdrawing nature of the hydroxymethyl group as opposed to the electron-donating ability of the methyl group in maltol (5*b*).

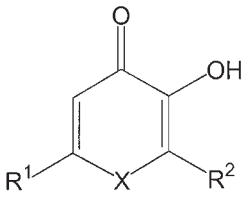
The proton NMR spectra of **2** in D_2O indicates a pair of broad singlets at δ 6.67 and 7.87 due to the ring CH protons. The singlet at 6.67 ppm is shifted downfield by 0.23 ppm in comparison with kojic acid while the other ring proton is shifted upfield by 0.06 ppm. The exocyclic methylene protons of the hydroxymethyl group appear as a singlet at δ 4.42 in **2** while the chemical shift of the analogous protons in starting pyrone appear at δ 4.73.

Single crystals of **1** were grown from a wet methylene chloride solution cooled to 5°C and those for **2** grown from a H_2O–i-PrOH mixture. An X-ray diffraction study of **1** was carried out to determine unequivocally the nature of the compound about to undergo biological testing. The molecular structures of $MoO_2(ma)_2$ and $MoO_2(ka)_2$ are depicted in Figs. 2 and 3, respectively, and crystallographic data for both compounds are given in Table 1. Atomic coordinates and displacement parameters for **1** and **2** are given in Table 2. Selected bond distances and angles for **1** and **2** are provided in Tables 3 and 4, respectively. The coordination sphere about the molybdenum atoms in both cases consists of six oxygen atoms arranged in a distorted octahedral geometry. The molecular structures confirm a *cis* arrangement of dioxo

Table 4. Selected bond lengths (Å) and angles (°) for **2**.

Bond lengths			
Mo(1)—O(10)	1.694(2)	Mo(1)—O(9)	1.695(2)
Mo(1)—O(5)	1.981(2)	Mo(1)—O(1)	1.994(2)
Mo(1)—O(6)	2.236(2)	Mo(1)—O(2)	2.286(2)
O(1)—C(1)	1.337(3)	O(2)—C(5)	1.272(3)
O(3)—C(3)	1.346(3)	O(3)—C(2)	1.357(4)
O(4)—C(6)	1.390(4)	O(5)—C(7)	1.335(3)
O(6)—C(11)	1.278(3)	O(7)—C(9)	1.342(3)
O(7)—C(8)	1.346(4)	O(8)—C(12)	1.378(5)
C(1)—C(2)	1.334(4)	C(1)—C(5)	1.442(3)
C(3)—C(4)	1.352(4)	C(3)—C(6)	1.503(4)
C(4)—C(5)	1.416(4)	C(7)—C(8)	1.355(4)
C(7)—C(11)	1.433(4)	C(9)—C(10)	1.355(4)
C(9)—C(12)	1.499(4)	C(10)—C(11)	1.403(4)
Bond angles			
O(10)-Mo(1)-O(9)	104.95(13)	O(10)-Mo(1)-O(5)	93.15(10)
O(9)-Mo(1)-O(5)	104.13(10)	O(10)-Mo(1)-O(1)	105.10(10)
O(9)-Mo(1)-O(1)	92.82(10)	O(5)-Mo(1)-O(1)	151.05(8)
O(10)-Mo(1)-O(6)	162.77(10)	O(9)-Mo(1)-O(6)	90.64(10)
O(5)-Mo(1)-O(6)	75.65(7)	O(1)-Mo(1)-O(6)	80.94(8)
O(10)-Mo(1)-O(2)	89.64(10)	O(9)-Mo(1)-O(2)	162.99(10)
O(5)-Mo(1)-O(2)	83.36(7)	O(1)-Mo(1)-O(2)	74.64(7)
O(6)-Mo(1-O(2)	76.26(7)	C(1)–O(1)-Mo(1)	119.5(2)
C(5)-O(2)-Mo(1)	112.0(2)	C(3)–O(3)-C(2)	120.3(2)
C(7)-O(5)-Mo(1)	119.0(2)	C(11)–O(6)-Mo(1)	112.6(2)
C(9)-O(7)-C(8)	120.8(2)	C(2)-C(1)-O(1)	123.6(2)
C(2)-C(1)-C(5)	119.9(3)	O(1)-C(1)-C(5)	116.5(2)
C(1)-C(2)–O(3)	121.4(3)	O(3)-C(3)-C(4)	122.2(2)
O(3)-C(3)-C(6)	111.0(2)	C(4)-C(3)-C(6)	126.8(3)

Fig. 4. Hydroxypyrone and hydroxypyridinone ligands and metal complexes.



				Molybdenum Complex	
Pyrones					
R^1 = H	R^2 = CH_3	X = O	(Hma)	$MoO_2(ma)_2$	(**1**)
R^1 = CH_2OH	R^2 = H	X = O	(Hka)	$MoO_2(ka)_2$	(**2**)
Pyridinones					
R^1 = H	R^2 = CH_3	X = NMe	(Hdpp)	$MoO_2(dpp)_2$	(**3**)
R^1 = CH_2OH	R^2 = H	X = NMe	(Hhmp)	$MoO_2(hmp)_2$	(**4**)
R^1 = H	R^2 = CH_3	X = N-*n*-C_3H_7	(Hnpp)	$MoO_2(npp)_2$	(**5**)
R^1 = CH_2OH	R^2 = H	X = N-*n*-C_3H_7	(Hhnp)	$MoO_2(hnp)_2$	(**6**)
R^1 = H	R^2 = CH_3	X = NCH_2Ph	(Hbpp)	$MoO_2(bpp)_2$	(**7**)
R^1 = CH_2OH	R^2 = H	X = NCH_2Ph	(Hhbp)	$MoO_2(hbp)_2$	(**8**)
R^1 = H	R^2 = CH_3	X = NPh	(Hppp)	$MoO_2(ppp)_2$	(**9**)
R^1 = CH_2OH	R^2 = H	X = NPh	(Hhpp)	$MoO_2(hpp)_2$	(**10**)

ligands as predicted by extended spectroscopic data and Hückel calculations (13). The Mo=O bond lengths (avg. = 1.701 (2) Å, **1**; avg. = 1.695 (2) Å, **2**) are comparable to those found in other oxomolybdenum(VI) complexes (14). The two ketonic oxygen atoms of the pyrone moieties are *trans* to the oxo ligands and the stronger field hydroxyl oxygens are *trans* to one another. Similar coordination environments have been observed previously in analogous vanadium–maltol (15) and iron – kojic acid complexes (5*d*).

As expected, a slight lengthening of the ketone C=O bond is observed upon complexation, with a mean distance of 1.268 (4) Å in **1** and 1.275 (3) Å in **2** compared with 1.244 Å found in free kojic acid (16). The molybdenum–oxygen (ketone) bond in this case is somewhat longer (avg. = 2.225 (2) Å, **1**; avg. = 2.261 (2) Å, **2**) than the Mo – deprotonated oxygen distance, the average being only 1.992 (2) Å in **1** and 1.989 (2) Å in **2**. This observation provides a distinction between Lewis acid–base versus covalent bonding for these two types of oxygen atoms. It is interesting to note that the ketone oxygen–molybdenum bond length is slightly longer in **2** than in **1**, indicating weaker bonding interaction for this hydroxypyrone. Low metal-binding constants have been reported previously for kojic acid derivatives (5*c*). Interestingly, average C(6)—O(4) bond lengths of 1.384 (5) Å observed for the hydroxymethyl groups in **2** are somewhat shorter than those seen in kojic acid (1.406 Å), presumably due to a slight reduction in the degree of intermolecular hydrogen bonding for the molybdenum complex. Indeed, O–H···O interactions in **2** occur at 2.887 and 3.069 Å, while distances of 1.87 and 2.08 Å are reported for kojic acid.

Hydroxypyridinone complexes

A series of *N*-substituted 3-hydroxy-4-pyridinones were readily prepared (Fig. 4) from the addition of primary amine ($MeNH_2$, *n*-$PrNH_2$, $PhCH_2NH_2$, and $PhNH_2$) and either maltol (9) or kojic acid (5*d*). Functionalization of the ring

Table 5. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for **9**. *U*(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	*y*	*z*	*U*(eq)
Mo(1)	5232.4(2)	733.9(1)	2715.4(1)	21.49(5)
O(1)	6479(1)	829(1)	3344.8(9)	30.4(5)
O(2)	4160(2)	150(1)	3224.1(9)	30.6(5)
O(3)	4011(1)	442(1)	1676.1(9)	24.6(5)
O(4)	6079(1)	–326(1)	2153.2(9)	23.0(5)
O(5)	6050(1)	1697(1)	1869.4(9)	24.5(5)
O(6)	4444(1)	2058(1)	2850.2(9)	24.8(5)
C(1)	4415(2)	–238(2)	1243(1)	21.6(6)
C(2)	5560(2)	–672(2)	1491(1)	21.2(6)
C(3)	6093(2)	–1398(2)	1081(1)	23.0(6)
N(4)	5471(2)	–1731(1)	422(1)	24.9(6)
C(5)	4376(2)	–1336(2)	165(1)	28.6(7)
C(6)	3842(2)	–594(2)	557(1)	26.6(7)
C(7)	5954(2)	–2573(2)	17(1)	26.2(7)
C(8)	5827(3)	–3505(2)	323(2)	40.4(9)
C(9)	6335(3)	4303(2)	–28(2)	48(1)
C(10)	6975(2)	4168(2)	–679(1)	38.2(8)
C(11)	7066(2)	–3240(2)	–988(1)	34.8(8)
C(12)	6551(2)	–2428(2)	–641(1)	29.4(8)
C(13)	7323(2)	–1812(2)	1316(1)	33.4(8)
C(14)	5812(2)	2619(2)	1967(1)	20.0(6)
C(15)	6343(2)	3410(2)	1591 (1)	23.0(7)
C(16)	6054(2)	4349(2)	1787(1)	25.0(7)
N(17)	5219(2)	4550(1)	2316(1)	21.5(5)
C(18)	4638(2)	3802(2)	2690(1)	21.3(7)
C(19)	4939(2)	2846(2)	2517(1)	20.4(6)
C(20)	4965(2)	5587(2)	2462(1)	23.3(7)
C(21)	3808(2)	5965(2)	2283(1)	29.8(7)
C(22)	3598(2)	6965(2)	2385(2)	35.2(8)
C(23)	4537(3)	7570(2)	2658(2)	38.0(9)
C(24)	5685(3)	7185(2)	2834(2)	40.7(9)
C(25)	5911(2)	6183(2)	2742(1)	31.1(8)
C(26)	3736(2)	4049(2)	3273(1)	31.8(8)
50:50 disordered acetone of solvation				
O(7A)	3184(8)	2746(7)	5291(5)	87(3)
O(7B)	2927(9)	2101(10)	5049(7)	154(7)
C(27A)	4131 (22)	2515(18)	5189(10)	98(8)
C(27B)	4009(20)	1931(17)	5064(10)	85(7)
C(28A)	4695(22)	1537(15)	5070(10)	148(11)
C(28B)	4394(17)	884(8)	5180(8)	93(5)
C(29A)	5096(10)	3322(11)	5277(6)	112(6)
C(29B)	5017(14)	2573(12)	4912(8)	101(5)

nitrogen in the hydroxypyridinones allows for fine tuning of physical properties such as water solubility, hydrolytic stability, and lipophilicity without compromising thermodynamic binding constants (9*b*). Indeed, the corresponding pyridinone complexes are somewhat less water soluble and slightly more lipophilic than the pyrone complexes **1** and **2**. For instance, although the N–Me complex $MoO_2(dpp)_2$ **3** is only sparingly soluble in dimethyl sulfoxide, the kojic acid – aniline derivative **10** is readily soluble in methylene chloride. While metal complexes containing *N*-substituted 3-hydroxy-4-pyridinones are well known (2*b*, 8*c*–8*d*, 9, 11), the only molybdenum complex reported containing these biologically relevant ligands is the 3-hydroxy-1,2-dimethyl- 4-pyridinone (Hdpp) derivative, $MoO_2(dpp)_2$ **3** (11*g*).

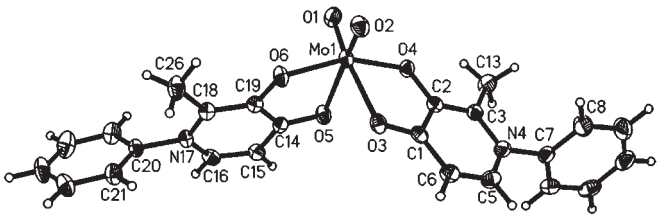
Upon complexation with molybdenum, the four-band infrared spectral pattern between 1400 and 1610 cm^{-1}, characteristic of pyrone and pyridinone ligands (4*a*, 17), is also observed, along with an expected bathochromatic shift. These four bands are assigned collectively as ν(C=C) and ν(C=O). Of the four possible isomers for complexes of the type *cis*-MoO_2L_2 (18), the most likely isomer is the one in which both ketone oxygens of the pyridinone ligands are *trans* to the molybdenum oxo groups (13). A single-crystal X-ray diffraction study was carried out on the 3-hydroxy- 2-methyl-1-phenyl-pyridinone derivative **9** to confirm this assignment.

The molecular structure of **9** is shown in Fig. 5, atomic coordinates and displacement parameters in Table 5, and

Table 6. Selected bond lengths (Å) and angles (°) for **9**.

Bond lengths			
Mo(1)—O(1)	1.705(2)	Mo(1)—O(2)	1.709(2)
Mo(1)—O(3)	2.226(2)	Mo(1)—O(4)	1.999(2)
Mo(1)—O(5)	2.202(2)	Mo(1)—O(6)	2.009(1)
O(3)—C(1)	1.287(3)	O(4)—C(2)	1.343(3)
O(5)—C(14)	1.288(3)	O(6)—C(19)	1.345(3)
C(1)—C(2)	1.427(3)	C(1)—C(6)	1.406(3)
C(2)—C(3)	1.369(3)	C(3)—N(4)	1.379(3)
C(3)—C(13)	1.493(3)	N(4)—C(5)	1.364(3)
N(4)—C(7)	1.458(3)	C(5)—C(6)	1.367(3)
C(7)—C(8)	1.380(3)	C(7)—C(12)	1.372(3)
C(8)—C(9)	1.376(4)	C(9)—C(10)	1.386(4)
C(10)—C(11)	1.373(4)	C(11)—C(12)	1.391(4)
C(14)—C(15)	1.401(3)	C(14)—C(19)	1.430(3)
C(15)—C(16)	1.359(3)	C(16)—N(17)	1.366(3)
N(17)—C(18)	1.380(3)	N(17)—C(20)	1.457(3)
C(18)—C(19)	1.373(3)	C(18)—C(26)	1.500(3)
C(20)—C(21)	1.385(3)	C(20)—C(25)	1.379(3)
C(21)—C(22)	1.386(3)	C(22)—C(23)	1.377(4)
C(23)—C(24)	1.378(4)	C(24)—C(25)	1.390(4)
Bond angles			
O(1)-Mo(1)-O(2)	104.3(1)	O(1)-Mo(1)-O(3)	163.4(1)
O(2)-Mo(1)-O(3)	86.9(1)	O(1)-Mo(1)-O(4)	89.7(1)
O(2)-Mo(1)-O(4)	106.1(1)	O(3)-Mo(1)-O(4)	75.2(1)
O(1)-Mo(1)-O(5)	92.7(1)	O(2)-Mo(1)-O(5)	160.6(1)
O(3)-Mo(1)-O(5)	78.7(1)	O(4)-Mo(1)-O(5)	82.8(1)
O(1)-Mo(1)-O(6)	100.9(1)	O(2)-Mo(1)-O(6)	92.2(1)
O(3)-Mo(1)-O(6)	90.7(1)	O(4)-Mo(1)-O(6)	156.0(1)
O(5)-Mo(1)-O(6)	75.3(1)	Mo(1)-O(3)-C(1)	113.3(1)
Mo(1)-O(4)-C(2)	119.3(1)	Mo(1)-O(5)-C(14)	113.0(1)
Mo(1)-O(6)-C(19)	118.0(1)	O(3)-C(1)-C(2)	116.3(2)
O(3)-C(1)-C(6)	126.6(2)	C(2)-C(1)-C(6)	117.1(2)
O(4)-C(2)-C(1)	115.9(2)	O(4)-C(2)-C(3)	122.0(2)
C(1)-C(2)-C(3)	122.1(2)	C(2)-C(3)-N(4)	117.9(2)
C(2)-C(3)-C(13)	122.1(2)	N(4)-C(3)-C(13)	120.0(2)
C(3)-N(4)-C(5)	121.8(2)	C(3)-N(4)-C(7)	119.1(2)
C(5)-N(4)-C(7)	119.0(2)	N(4)-C(5)-C(6)	121.1(2)
C(1)-C(6)-C(5)	119.9(2)	N(4)-C(7)-C(8)	118.6(2)
N(4)-C(7)-C(12)	120.0(2)	C(8)-C(7)-C(12)	121.4(2)
C(7)-C(8)-C(9)	119.4(3)	C(8)-C(9)-C(10)	120.1(3)

Fig. 5. The molecular structure of $MoO_2(ppp)_2$, **9**.



bond distances and angles are provided in Table 6. Similar Mo—O bond distances are observed in **9** and the parent pyrone complex **1**. The bond distances within the pyridinone ring also display trends similar to those described for **1** and other metal–pyridinone complexes (11). A pronounced localization of the formal double bonds in the ring, albeit to a lesser extent than that observed for the pyrone systems, is clearly indicated by the short C(2)—C(3), C(5)—C(6), and ketone C(1)—O(3) bonds. Resonance forms for pyridinone ligands have been described in detail elsewhere (11, 19). A N(4)—C(7) bond distance of 1.458 (3) Å, however, is slightly shorter than that reported for the free ligands 3-hydroxy-1-*p*-methoxyphenyl-2-methyl-4-pyridinone (cf. 1.474 (1) Å) (19) and 3-hydroxy-1,2-dimethyl-4-pyridinone (cf. 1.482 (4) Å) (20). Average C-N-C angles of 120.0° are similar to those reported earlier (11, 19, 20).

Biological relevance

We have begun our investigation into the effect of molybdenum complexes on heart function in diabetic rats and report our findings herein. Initial work was conducted using **1**, the molybdenum analogue of BMOV, because of the efficacy of this latter compound as an insulin mimic, along with the control (10) sodium molybdate, Na_2MoO_4. Confirming the diabetic state, plasma glucose and free fatty acid levels

Table 7. Physical characteristics and blood profile of control and diabetic rats.

Group	Glucose (mM)	Free fatty acids (mM)	Body weight (g)	Fluid intake (mL/kg per 24 h)
Control	6.1 ± 0.1	0.37 ± 0.04	492 ± 8	43 ± 2
Diabetic	23.2 + 1.5[a,c]	0.51 + 0.09[a,c]	291 + 19[a]	163 + 22[a,c]
+ molybdate	13.2 + 1.4[a,b]	0.17 + 0.02[a,b]	286 + 12[a]	90 + 12[a,b]
+ $MoO_2(ma)_2$	16.3 + 1.3[a,b]	0.13 + 0.02[a,b]	328 + 17[a]	115 + 13[a,b]

Values are presented as mean ± S.E.M. for six to eight animals in each group. Average daily intake of $MoO_2(ma)_2$ by diabetic animals was 0.15 mmol/kg per 24 h, whereas that of molybdate was 0.13 mmol/kg per 24 h.

[a]Significant vs. control.

[b]Significant vs. diabetic.

[c]Significant vs. diabetic treated with molybdate.

Table 8. Effects of $MoO_2(ma)_2$ and sodium molybdate treatment on heart function.

Perfusion condition	HR (beats/min)	PSP (mmHg)	RPP (beats mmHg $min^{-1)}$	DP (mmHg)	AF (mL/min)
Aerobic perfusion					
Control	250 ± 8	92 ± 5	23 ± 1	59 ± 2	42 ± 4
Diabetic	200 ± 13[a]	94 ± 4	19 ± 1[a]	63 ± 2	20 ± 3[a]
+ molybdate	243 ± 20	97 ± 3	23 ± 2	62 ± 3	36 ± 4[b]
+$MoO_2(ma)_2$	214 ± 12	87 ± 5	18 ± 1	63 ± 4	17 ± 3[a,c]
Reperfusion following ischemia					
Control	190 ± 21	87 ± 9	16 ± 2	57 ± 5	16 ± 6
Diabetic	164 ± 25	74 ± 11	14 ± 2	61 ± 9	6 ± 2[a]
+ molybdate	235 ± 11	94 ± 3	22 ± 1	64 ± 2	25 ± 3[b]
+ $MoO_2(ma)_2$	114 ± 14[c]	45 ± 16[c]	9 ± 3[c]	35 ± 12	3 ± 2[ac]

Values are presented as mean ± S.E.M. for six to eight animals in each group. HR, heart rate; PSP, peak systolic pressure; RPP, heart rate pressure product; DP, diastolic pressure; AF, aortic flow. Hearts were perfused under aerobic conditions for 15 min, then subjected to 25 min of global ischemia followed by 30 min of aerobic reperfusion. Reperfusion data obtained at the end of the 30 min.

[a]Significant vs. control.

[b]Significant vs. diabetic.

[c]Significant vs. diabetic treated with molybdate.

were markedly elevated in the diabetic rats (Table 7). Body weight, as expected, was lower in diabetic rats than in the controls. Food and fluid intake was maintained during the 6 week period. Treatment of diabetic animals with either sodium molybdate or $MoO_2(ma)_2$ (**1**) significantly reduced levels of plasma glucose but proved to have weaker insulin-like effects when compared to BMOV (4*h*, 5, 6). It is interesting to observe that treatment with $MoO_2(ma)_2$ and sodium molybdate also reduced plasma glucose and free fatty acid levels in diabetic rats. Rats treated with both molybdenum complexes suffered from initial weight loss although those given complex **1** gained weight at the end of the treatment. No animals suffered from diarrhea and all survived treatment with these molybdenum complexes.

The 6 week period of diabetes was selected because alterations in heart function occur within this period (21–23). As shown in Table 8, if hearts from diabetic rats are perfused under aerobic conditions, significant differences in function are noted. Diabetic rat hearts show a significant depression in rate–pressure product as a result of a decrease in heart rate. Aortic flow in these rats is also depressed compared to that in control hearts. Treatment of diabetic rats with sodium molybdate, however, prevented this depression in aortic flow from occurring, an effect not observed in diabetic rats treated with $MoO_2(ma)_2$. During reperfusion of previously ischemic hearts, the benefits of sodium molybdate on mechanical function of diabetic rat hearts are also clearly observed. These are associated with significant and dramatic increases in aortic flow. No benefits of $MoO_2(ma)_2$ treatment on reperfusion recovery of diabetic hearts were seen.

Preventing the diabetes-induced depressions in heart function can be accomplished with agents that decrease circulating levels of lipids and glucose (21–24), which could possibly explain the benefits of molybdate on reperfusion on recovery of diabetic hearts. Diabetic hearts exposed to low levels of fatty acids can oxidize glucose as an additional substrate (24) since the poorly controlled state is characterized by energy requirements met primarily from the oxidation of fatty acids (25). Although conjectural, the possibility exists that molybdate-treated diabetic hearts oxidized more glucose during reperfusion, allowing them to be less sensitive to ischemia (26).

Conclusions

A series of hydroxypyrone and hydroxypyridinone complexes of molybdenum have been prepared and were characterized by a number of physical methods including X-ray diffraction studies. Initial biological data demonstrate that treatment of diabetic animals with sodium molybdate not only reduces plasma levels of glucose and fatty acids, but also prevents the depression in cardiac function from occur-

ring in diabetic hearts. The maltolato complex, $MoO_2(ma)_2$, also showed some improvement in blood glucose and free fatty acid levels but had no effect on heart function. We are currently investigating the physical properties necessary to generate a more active molybdenum complex for the treatment of cardiac dysfunction associated with diabetes.

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