

Remarkably Favorable Hydration of Carbonyl Substituents in Dicationic Bis(arene) Ruthenium Complexes

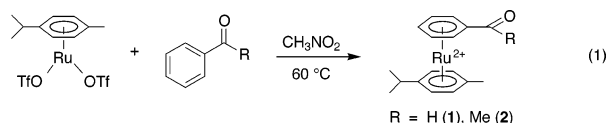
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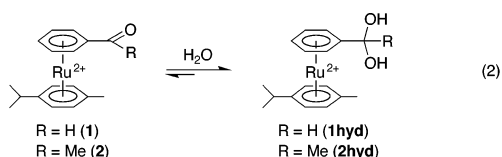
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The aromatic rings in dicationic bis(arene) ruthenium complexes are highly electrophilic, readily participating in aromatic nucleophilic addition and substitution reactions with a variety of nucleophiles.^{1,2} The extreme electrophilic activation of the arenes in these complexes can be attributed to the highly electron-withdrawing nature of and the dicationic charge associated with the ruthenium metal.¹ We report here that this dramatic, metal-induced activation extends to the *substituents* attached to the arene rings, resulting in unprecedented reactivity and selectivity for the addition of weak nucleophiles.

Aromatic carbonyls are notoriously poor substrates for the direct formation of metal arene complexes.^{3,4} We have found, however, that the direct metalation of benzaldehyde and acetophenone with [(*p*-cymene)Ru(OTf)₂]⁵ (OTf = O₃SCF₃) proceeds in excellent yield (>85%) in nitromethane at 60 °C to give the corresponding bis(arene) ruthenium complexes, **1** and **2** (eq 1).^{6,7} The use of CH₃NO₂ as the solvent is absolutely crucial in these reactions—no formation of **1** is observed when other solvents (CH₂Cl₂, CF₃CO₂H) are employed.⁸ Both **1** and **2** have been completely characterized by spectroscopic methods; **1** was also characterized by X-ray crystallography (Figure 1).



Dissolving **1** in wet solvents surprisingly led to its clean conversion into a new bis(arene)ruthenium complex. The absence of an aldehyde resonance and the presence of a new resonance at 6.16 ppm (assignable as $-CH\{OH\}_2$) in the NMR spectrum (CD₃-NO₂) indicated the formation of the corresponding hydrate complex, **1hyd** (eq 2).⁹ As benzaldehyde itself is not extensively hydrated in water,^{10,11} the [(*p*-cymene)Ru]²⁺ moiety must be dramatically promoting the nucleophilic addition of water to the carbonyl group in **1**. Although it was not possible to measure the equilibrium constant (K_{hyd}) for hydration of **1** directly (only **1hyd** is observed in D₂O), the **1/1hyd** ratio could be measured in D₂O/acetone-*d*₆ solutions (at 30 °C). Extrapolating back to pure D₂O yields an approximate value of 1.1×10^4 for K_{hyd} of **1**.^{12,13} Remarkably, **1** is over 1 million times more reactive toward water than benzaldehyde and displays an unprecedented level of reactivity for an aromatic carbonyl (Table 1).¹⁰



A similar level of activation is observed for the acetyl substituent in the acetophenone complex, **2**. The equilibrium constant for the

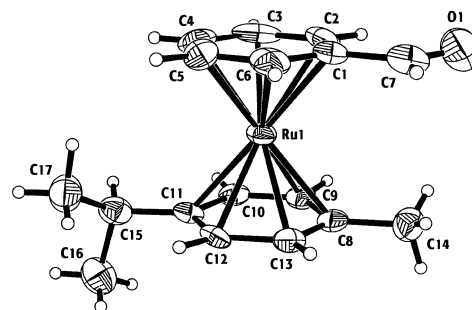


Figure 1. ORTEP diagram of the bis(arene)ruthenium dication in **1**.

Table 1. Equilibrium Constants for Hydration of Aryl Carbonyls

compound	K_{hyd}	compound	K_{hyd}
1	1.1×10^4 ^a	PhCHO	7.9×10^{-3} ^c
2	1.8 ^b	PhC(O)CH ₃	6.6×10^{-6} ^c
3	1.1 ^b	CCl ₃ CHO	2.8×10^4 ^c
4	<0.02 ^b	CH ₂ O	2.3×10^3 ^c
C ₆ F ₅ CHO	1.5 ^b	4-pyCHO	1.5 ^d
4-NO ₂ C ₆ H ₄ CHO	0.17 ^c	[4-pyHCHO] ⁺	52 ^d

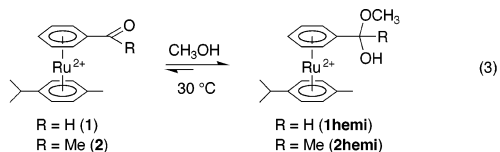
^a Measured in D₂O/acetone-*d*₆ solutions and extrapolated to pure D₂O. ^b Measured by NMR in D₂O at 30 °C. ^c Reference 10. ^d Reference 15.

addition of D₂O to **2** to generate the hydrate complex, **2hyd** (eq 2), could be measured directly by NMR in D₂O and was found to be 1.8 at 30 °C, whereas K_{hyd} for free acetophenone is only 6.6×10^{-6} (Table 1).¹⁰ From the temperature dependence of K_{hyd} , it was possible to determine the enthalpy ($\Delta H^\circ = -25 \pm 1$ kJ/mol) and entropy ($\Delta S^\circ = -77 \pm 3$ J/mol K) of hydration for **2**. The thermodynamic parameters for the hydration of **2** are comparable to those found for aldehydes that also have equilibrium constants for hydration near unity at room temperature.¹⁴

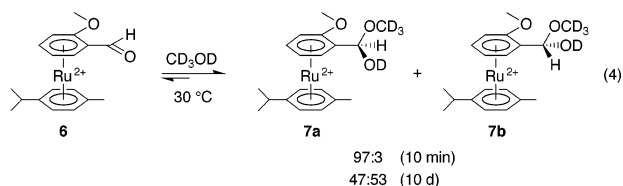
The electron-withdrawing ability of the [(*p*-cymene)Ru]²⁺ group and the close proximity of a dicationic charge to the carbonyl carbon are undoubtedly responsible for the increased Lewis acidity of the carbonyl groups in **1** and **2**. However, the observed 5–6 order-of-magnitude increase for K_{hyd} in **1** and **2** (as compared to the uncomplexed aryl carbonyls) is still surprising, especially when compared to other cationic aldehydes. For example, protonation of 4-pyridine-carboxaldehyde activates the aldehyde group toward hydration by a factor of 35 (Table 1);¹⁵ complexation of 4-pyridine-carboxaldehyde at nitrogen with di- or tricationic metal fragments (e.g., [(NH₃)₅Ru]³⁺) has even less of an effect on K_{hyd} .^{16,17} We have also determined that hydration of **1** is substantially greater than in other less highly charged benzaldehyde complexes. The equilibrium constant for hydration of the cationic complex [Cp*₂Ru(C₆H₅CHO)]⁺ (**3**)⁷ is only 1.1, and resonances corresponding to the hydrate of [(C₆H₅CHO)Cr(CO)₃] (**4**)¹⁸ were not observed by NMR in D₂O, setting an upper limit of 0.02 for K_{hyd} of **4** (Table 1).

The addition of methanol across the carbonyl groups of **1** and **2** also occurs readily to give the corresponding hemiacetal complexes,

1hemi and **2hemi** (eq 3). The equilibrium constants for these additions ($K_{\text{hemi}} \approx 10^5$ for **1**, $K_{\text{hemi}} = 14$ for **2** at 30 °C) are roughly an order of magnitude greater than the corresponding hydration constants.^{19–21} Conversion of **1hemi** and **2hemi** into the corresponding acetal complexes on standing in methanol is not observed. Consistent with these results, the acetal group in the benzaldehyde dimethylacetal complex, [(*p*-cymene)Ru(C₆H₅CH(OMe)₂)][(OTf)₂] (**5**),²² is completely resistant toward acid hydrolysis, *even on long-standing in 1 M HCl solution*. The inability to convert **5** into **1** (and vice versa) indicates that the benzylic cationic intermediate necessary for acid-catalyzed acetal hydrolysis cannot be generated when the arene is bound to [(*p*-cymene)Ru]²⁺, a stark contrast to the effect of a Cr(CO)₃ group, which can significantly stabilize such benzylic cations.²³



Nucleophilic addition reactions at the carbonyl substituents in chiral chromium tricarbonyl arene complexes have been shown to occur with high degrees of stereoselectivity.²⁴ To initially assess the stereoselectivity of carbonyl addition reactions in dicationic bis(arene) ruthenium complexes, we reacted the *o*-anisaldehyde complex, **6**,²² with CD₃OD at 30 °C, which gave within 10 min two diastereomeric hemiacetal complexes, **7a** and **7b**, with a de of 94% (eq 4). On the basis of similar addition reactions for (*o*-anisaldehyde)Cr(CO)₃,^{3,24} it is likely that the major kinetic diastereomer **7a** arises from exo addition of CD₃OD to the anti conformation of **6** (as shown in eq 4), although this has not yet been confirmed. The observed diastereoselectivity for the addition of methanol to **6** is as good as or better than that reported for additions to (*o*-anisaldehyde)Cr(CO)₃,^{3,24} especially given that the reaction was conducted at 30 °C and no Lewis acid coordination of the carbonyl (to favor the anti conformation) is possible. The relative amounts of **7a** and **7b** change on standing in CD₃OD, however, because of the reversible nature of the methanol addition, eventually producing after 10 d at 30 °C an essentially 1:1 thermodynamic mixture of **7a** and **7b**.



The exceptionally favorable addition of water and methanol at the carbonyl groups in **1** and **2** thus demonstrates that coordination

of a dicationic ruthenium metal to an arene substantially activates carbonyl substituents on the arene toward nucleophilic attack. When combined with the well-established ability of metal coordination to effectively control the stereoselectivity of such reactions and the facile synthesis of the air-stable complexes **1** and **2**, this extraordinary activation should prove useful in the development of new synthetic methodologies involving aromatic carbonyls.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, a van't Hoff plot for the hydration equilibrium of **2** (PDF), and crystallographic data for **1** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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