Supporting Information for:

Kinetics and mechanism for oxidation of the anti-tubercular prodrug isoniazid and its analog by iridium(IV) as models for biological redox systems

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Three supporting tables (**Tables S1–S3**) and six supporting figures (**Figures S1-S6**) are included in the Supporting Information.

[Nicotinic hydrazide] _{tot}	$k_{\rm obsd}~({ m s}^{-1})^{ m a}$	$k_{ m obsd}~(m s^{-1})^{ m b}$
0.50	0.466 ± 0.008	0.467 ± 0.009
1.00	0.97 ± 0.03	0.97 ± 0.03
2.00	1.93 ± 0.05	1.94 ± 0.04
3.00	2.90 ± 0.06	2.94 ± 0.06
4.00	3.91 ± 0.08	3.97 ± 0.07
5.00	4.92 ± 0.09	5.01 ± 0.08

Table S1. Oxidation of nicotinic hydrazide (NH) by $[IrCl_6]^{2-}$ from two different sources in a buffer of pH 4.46 at 25.0 °C and $\mu = 1.0$ M. No difference between the two samples is observed.

^a [IrCl₆]²⁻ was from Sigma-Aldrich Na₂IrCl₆•6H₂O.

^b $[IrCl_6]^{2-}$ was from a sample of Ir(IV) complex treated with chlorine in the following way: 1g Na₂IrCl₆•6H₂O from Sigma-Aldrich was dissolved in 15 mL water in a glass vial, and chlorine gas (generated from KMnO₄ and concentrated HCl) slowly bubbled the solution for 15 min. The solution was aged for 15 min and then bubbled with nitrogen for 15 min. After being frozen at - 80 °C, the sample was lyophilized for 48 h. Finally, the sample was preserved in a desiccator.

t∕°C	[Isoniazid] _{tot} /mM	$k_{ m obsd}/ m s^{-1}$	
10.0	0.50	0.81	
	1.00	1.81	
	2.00	3.68	
	3.00	5.60	
	4.00	7.48	
	5.00	9.09	
15.0	0.50	1.14	
	1.00	2.20	
	2.00	4.96	
	3.00	6.98	
	4.00	9.34	
	5.00	11.6	
20.0	0.50	1.51	
	1.00	2.95	
	2.00	6.01	
	3.00	8.99	
	4.00	12.1	
	5.00	15.0	
25.0	0.50	1.94	
	1.00	3.87	
	2.00	7.51	
	3.00	11.6	
	4.00	15.2	
	5.00	19.6	
30.0	0.50	2.39	
	1.00	5.04	
	2.00	9.65	
	3.00	14.4	
	4.00	18.8	
	5.00	23.4	

Table S2. Observed first-order rate constants as a function of temperature for the oxidation of isoniazid (INH) by $[IrCl_6]^{2-}$ in a buffer with pH 4.48 and $\mu = 1.0$ M, where species III is predominant.

t∕°C	[Nicotinic hydrazide] _{tot} /mM	$k_{ m obsd}/ m s^{-1}$	
15.0	0.50	0.316	
	1.00	0.600	
	2.00	1.16	
	3.00	1.76	
	4.00	2.34	
	5.00	2.89	
20.0	0.50	0.357	
	1.00	0.719	
	2.00	1.47	
	3.00	2.24	
	4.00	3.01	
	5.00	3.82	
25.0	0.50	0.466	
	1.00	0.97	
	2.00	1.93	
	3.00	2.90	
	4.00	3.91	
	5.00	4.92	
30.0	0.50	0.577	
	1.00	1.20	
	2.00	2.46	
	3.00	3.79	
	4.00	4.98	
	5.00	6.45	
35.0	0.50	0.75	
	1.00	1.57	
	2.00	3.29	
	3.00	5.05	
	4.00	6.68	

Table S3. Observed first-order rate constants as a function of temperature for the oxidation of nicotinic hydrazide (INH) by $[IrCl_6]^{2-}$ in a buffer with pH 4.33 and $\mu = 1.0$ M, where species III is predominant.



Figure S1. Spectrophotometric titrations in acidic media. Absorbances at 488 nm for a series of reaction mixtures in which $[IrCl_6^{2-}] = 0.40$ mM was kept constant and $[Hydrazide]_{tot}$ was varied from 0 to 0.40 mM. Reaction medium: 0.010 - 0.020 M HClO₄ with $\mu = 1.0$ M; reaction time 2 h; room temperature. **Top**: INH. **Bottom**: NH. *Cf.* corresponding plots for neutral media in Fig 4.



Figure S2. Reaction mechanism proposed for the oxidation of NH by $[IrCl_6]^{2-}$.



Figure S3. (**Top**): Species of NH versus pH distribution diagram for at 25.0 °C and $\mu = 1.0$ M. (**Bottom**): The reactivity of the NH species versus pH diagram calculated by use of the p K_a values from Ref. 52 (p $K_{a1} = 2.12$, p $K_{a2} = 3.49$ and p $K_{a3} = 11.35$) and the rate constants in Table 2.



Figure S4. Plots of k_{obsd} versus [Isoniazid]_{tot} at 5 different temperatures for the oxidation of INH in an acetic acid/acetate buffer of pH 4.48 and $\mu = 1.0$ M.



Figure S5. Plots of k_{obsd} versus [Nicotinic Hydrazide]_{tot} at 5 different temperatures for the oxidation of NH in an acetic acid/acetate buffer of pH 4.46 and $\mu = 1.0$ M.



Figure S6. Eyring plots for the temperature dependence of the rate constants k_3 for INH and NH, respectively, *cf*. Scheme 1 and Figure S2, derived from data in Tables S2 and S3.