Inorganica Chimica Acta, 131 (1987) 105–112

On the Rate Laws for Proton Exchange in Aminecobalt(III) Complexes, and the Question of Intramolecular Proton Transfer in the Conjugate Base

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(Received July 18, 1986; revised January 22, 1987)

Abstract

It is well known that aminemetal complexes such as $(NH_3)_5CoCl^{2+}$ undergo base catalyzed proton exchange and ligand substitution, and that both reactions go via the conjugate base $(NH_2)(NH_3)_4$-$CoCl^+$. The timescale of intramolecular scrambling of an aminate (NH_2–) centre amongst inequivalent sites is an important question which hitherto has not been satisfactorily answered. Herein we show that the rate laws for proton exchange can comment on this problem, provided due account is taken of the number of equivalent protons in each site, and, where appropriate, of the relative site reactivity. In general, specific exchange rates for individual sites are levelled when conjugate base equilibration is more rapid than reprotonation, contrary to a recent report. It is shown that, under particular circumstances, individual exchange rates are nonetheless distinguished for some complexes although the values extracted experimentally are unlikely to coincide with the true values. Previous experimental data are reviewed to construct a case for negligible conjugate base scrambling in all aminecobalt(III) systems studied to date, for the solvents water and liquid ammonia.

Introduction

Recently Balt and Gamelkoorn [1] claimed to have demonstrated the absence of intramolecular proton scrambling in the conjugate bases derived from *trans*-$Co(en)_2AX^{n+}$ and NH_2^- or NH_3 in $NH_3(l)$*. They showed that individual rates for proton exchange at inequivalent sites should follow multiple exponential rate laws, when the respective conjugate bases are rapidly equilibrated, and they argued that the opportunity to test this arises if the exchange rates are comparable. The *trans*-$Co(en)_2$ AX^{n+} ions contain two sets of four NH_2 protons, those on the A side of the CoN_4 plane and those adjacent to the X group, and it was shown that these exchange at different (but not greatly different) rates. They demonstrated that the two exchange processes each 'strictly' obeyed a simple one – exponential function**, and it was therefore concluded that the two conjugate bases were not directly interconverted.

While these authors have tackled an important problem which previously had not been properly considered, several aspects of this publication are in need of correction or clarification.

Results and Discussion

We commence by reproducing below the essence of Balt and Gamelkoorn's reaction scheme (Scheme 1), and retain their rate constant nomenclature. The reactant R contains two inequivalent protons, at sites 1 and 2†, which undergo base catalyzed exchange‡ in deuterated solvent. For the point of the exercise, we can ignore both primary and secondary isotope effects, and need consider only the top half of Scheme 1 for which the relevant rate equations are

$$d[R]/dt = -(k_1 + k_2)[R] \qquad (1)$$

$$d[CB1]/dt = k_1([R] + [D1]) + k_{21}[CB2] - (k_{12} + k_{-1})[CB1] \qquad (2)$$

$$d[CB2]/dt = k_2([R] + [D2]) + k_{12}[CB1] - (k_{21} + k_{-2})[CB2] \qquad (3)$$

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*l = liquid.

**That, a first-order rate law. Proton exchange is of course base catalyzed, but since base is not consumed and buffers are employed, pseudo first-order conditions prevail.

†Hereafter, and interchangeably, these are referred to as the α and β sites.

‡The specific rates for each site follow the relation $k = k^0 + k^1[ND_4^+]^{-1}$ in $ND_3(l)$; k^0 refers to deprotonation by ND_3. k^1 deprotonation by ND_2^-. Note that the factors 10^4 and 10^6 in Table I of this ref. 1 appear to have been inadvertently interchanged.

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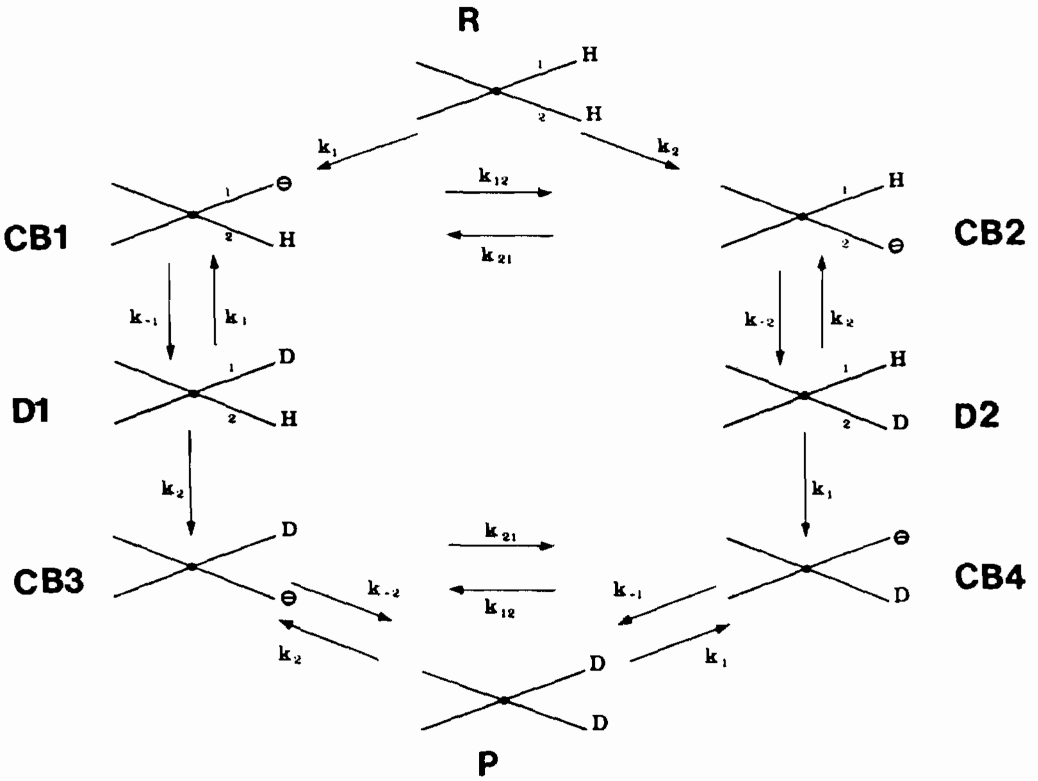

Scheme 1.

$$d[D1]/dt = k_{-1}[CB1] - (k_1 + k_2)[D1] \qquad (4)$$

$$d[D2]/dt = k_{-2}[CB2] - (k_2 + k_1)[D2] \qquad (5)$$

These differ from those given by Balt and Gamelkoorn [1], who approached the problem somewhat differently. However, it is important to develop the problem in the context of the experimental method for the determination of the specific rates of exchange, k_1 and k_2. For the reactions in question, the ^1H NMR spectra of *trans*-$Co(en)_2AX^{n+}$ in $ND_3(l)$ show two well-separated resonances for NH_2 protons above and below the NMR time-scale averaged $Co(en)_2$ plane, and as expected these disappear with time at different rates. At normal resolution, deuteration at one site will not significantly affect the chemical shift of the proton at the other site, and thus the signal intensity at site 1 is a measure of [R] + [D2], and for site 2, [R] + [D1] (Scheme 1). We therefore look for the time dependence of [R] + [D2] and [R] + [D1] in terms of Scheme 1 to ascertain what is being measured, and to scrutinize the effect of direct interconversion (k_{12}, k_{21}) between the conjugate bases CB1 and CB2 on these measurements.

At the outset, it need be noted that the two-site exchange problem for the *trans*-$Co(en)_2AX^{2+}$ complexes ($4H_\alpha$, $4H_\beta$) is not correctly modelled by Scheme 1, where just one proton in each site (H_α, H_β) is indicated. The ramifications of this oversight [1] are the purpose of the second part of this article, but it will be seen to be important to develop first the simplest case of two-site exchange.

It is undisputed that these complexes are weak acids and that, under the conditions [1], $k_{-2}, k_{-1} \gg k_2, k_1$. A steady-state treatment for [CB1] and [CB2] is therefore appropriate, irrespective of slow or fast equilibration (k_{12}, k_{21}) between CB1 and CB2. Setting d[CB1]/dt and d[CB2]/dt (eqns. (2) and (3)) to zero gives

$$k_1([R] + [D1]) + k_{21}[CB2] - (k_{12} + k_{-1})[CB1] = 0 \qquad (6)$$

$$k_2([R] + [D2]) + k_{12}[CB1] - (k_{21} + k_{-2})[CB2] = 0 \qquad (7)$$

With the inclusion of the restriction imposed by the principle of detailed balance [1, 2]

$$k_1 k_{12} k_{-2} = k_2 k_{21} k_{-1} \qquad (8)$$

k_{12} or k_{21} (but not both) can be eliminated. Equations (6) and (7) when solved for [CB1] and [CB2] yield

$$[\mathrm{CB1}] = \frac{k_1}{k_{-1}} \times \left\{ [\mathrm{R}] + \frac{k_2 k_{12}[\mathrm{D2}] + (k_1 k_{12} + k_2 k_{-1})[\mathrm{D1}]}{k_2 k_{12} + k_1 k_{12} + k_2 k_{-1}} \right\} \tag{9}$$

$$[\mathrm{CB2}] = \frac{k_2}{k_{-2}} \times \left\{ [\mathrm{R}] + \frac{k_1 k_{12}[\mathrm{D1}] + k_2(k_{12} + k_{-1})[\mathrm{D2}]}{k_1 k_{12} + k_2 k_{12} + k_2 k_{-1}} \right\} \tag{10}$$

The expressions for d([R] + [D2])/dt and d([R] + [D1])/dt, which relate directly to the experiment can now be written. From eqns. (1)–(5), (9) and (10)

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D2}])/\mathrm{d}t = a([\mathrm{R}] + [\mathrm{D2}]) + b([\mathrm{R}] + [\mathrm{D1}]) \tag{11}$$

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D1}])/\mathrm{d}t = c([\mathrm{R}] + [\mathrm{D2}]) + d([\mathrm{R}] + [\mathrm{D1}]) \tag{12}$$

where

$$a = -k_1(k_1 k_{12} + k_2 k_{-1} + 2k_2 k_{12})/d$$

$$b = k_1 k_2 k_{12}/d$$

$$c = -k_2(k_2 k_{12} + k_2 k_{-1} + 2k_1 k_{12})/d$$

$$d = k_1 k_{12} + k_2 k_{-1} + k_2 k_{12}$$

Equations (11) and (12) are readily solved to give explicit expressions for [R] + [D2] and [R] + [D1] as a function of time; these are complicated expressions but each is essentially the sum of two exponentials with common exponents but different pre-exponential factors. We need to consider these expressions only under limiting conditions.

(i) If reprotonation is much faster than intramolecular proton transfer in the conjugate base ($k_{-1}, k_{-2} \gg k_{12}, k_{21}$), eqns. (28) and (12) reduce to

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D2}])/\mathrm{d}t = -k_1([\mathrm{R}] + [\mathrm{D2}]) \tag{13}$$

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D1}])/\mathrm{d}t = -k_2([\mathrm{R}] + [\mathrm{D1}]) \tag{14}$$

Denoting $[\mathrm{A_1}]$ and $[\mathrm{A_2}]$ as the ^{1}H NMR signal intensities for the two sites*, it follows that

$$[\mathrm{A_1}]/[\mathrm{A_1}]_0 = \alpha = \exp(-k_1 t) \tag{15}$$

$$[\mathrm{A_2}]/[\mathrm{A_2}]_0 = \beta = \exp(-k_2 t) \tag{16}$$

Thus each site will obey first order kinetics and yield the specific rate of deprotonation appropriate to each. This result can be generalized to exchange at any number of inequivalent centres, for which simple first order rate laws will apply.

(ii) The problem is more complex when conjugate base equilibration is especially rapid, *i.e.* faster than reprotonation of either conjugate base ($k_{12} \gg k_{-1}$, $k_{21} \gg k_{-2}$**). Equations (11) and (12) reduce to

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D2}])/\mathrm{d}t = \mathrm{d}\alpha/\mathrm{d}t = -\left(\frac{k_1^2 + 2k_1 k_2}{k_1 + k_2}\right)\alpha + \left(\frac{k_1 k_2}{k_1 + k_2}\right)\beta \tag{17}$$

$$\mathrm{d}([\mathrm{R}] + [\mathrm{D1}])/\mathrm{d}t = \mathrm{d}\beta/\mathrm{d}t = \left(\frac{k_1 k_2}{k_1 + k_2}\right)\alpha - \left(\frac{k_2^2 + 2k_1 k_2}{k_1 + k_2}\right)\beta \tag{18}$$

These are the conditions considered by Balt and Gamelkoorn [1], and the integrated rate equations are

$$\alpha = p \exp\{-(k_1 + k_2)t\} + (1 - p)\exp\{-2k_1 k_2 t/(k_1 + k_2)\} \tag{19}$$

$$\beta = q \exp\{-(k_1 + k_2)t\} + (1 - q)\exp\{-2k_1 k_2 t/(k_1 + k_2)\} \tag{20}$$

where

$$p = (k_1^2 - k_1 k_2)/(k_1^2 + k_2^2)$$

$$q = (k_2^2 - k_1 k_2)/(k_1^2 + k_2^2)$$

Now if the two sites exchange at vastly different rates these expressions simplify further to single exponential functions

$$k_1 \gg k_2$$

$$\alpha = \exp(-k_1 t) \tag{21}$$

$$\beta = \exp(-2k_2 t) \tag{22}$$

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*α and β as defined in ref. 1 are proportional to our [R] + [D2] and [R] + [D1], respectively; their definition is also clear from eqns. (15) and (16).

**Equations (12) and (13) can be expressed in a similar form but containing k_{21} rather than k_{12} (using eqn. (8)). From these it can be seen that eqns. (17) and (18) arise if $k_{21} \gg k_{-2}$.

$k_2 \gg k_1$

$$\alpha = \exp(-2k_1 t) \tag{23}$$

$$\beta = \exp(-k_2 t) \tag{24}$$

For these conditions, it is clear that two separate exchange rates are measured; they are not levelled out as was apparently [1] suggested earlier [3,4]. Moreover, the measured specific rate for the slower exchanging proton is twice its actual value. This curious result, a direct consequence of rapid conjugate base scrambling, presents an obvious difficulty when the exchange rates are very different; an experimental distinction between the applicability of eqns. (13) and (14) or eqns. (19) and (20) is impossible where strict first-order kinetics apply for the decay of each site.

The work of Balt and Gamelkoorn [1] suggested that 'comparable' exchange rates are required if departures from strict first-order kinetics arising from rapid conjugate base equilibration are to be detected experimentally. When $k_1 = k_2$, each site will be found to exchange at the same rate and follow strict first-order kinetics, irrespective of the rates of conjugate base equilibration (as the substitution $k_1 = k_2$ in eqns. (13) and (14) and eqns. (19) and (20) will quickly verify). Since equal or very different exchange rates both lead to simple first-order kinetics, it is reasonable to enquire as to the optimum k_1/k_2 ratio for the experimental detection of the biphasic kinetics for each site, predicted by eqns. (19) and (20). Such behaviour is, of course, detected as curvature in the conventional rate plots, ln α and ln β *versus* time. However, we have emphasized previously [5,6] that this curvature is not experimentally detectable when the two rate parameters differ by a factor of *ca.* two or less*. Unfortunately, for the four *trans*-$\mathrm{Co(en)_2AX^{n+}}$ systems used by Balt and Gamelkoorn [1] to examine this problem**, k_1/k_2† is less than two under most conditions, except for H-exchange in *trans*-$\mathrm{Co(en)_2(N_3)NCS^+}$ at high $[\mathrm{NH_4^+}]$(k_α(obs.)/k_β(obs.) = 3.6). The point becomes clearer by examining the hypothetical case $k_1 = 2k_2$. Setting $k_2 (= k) = 1$ for convenience, eqns. (19) and (20) become

$$\alpha = 0.4 \exp(-3t) + 0.6 \exp(-4t/3) \tag{25}$$

$$\beta = 0.2 \exp(-3t) + 1.2 \exp(-4t/3) \tag{26}$$

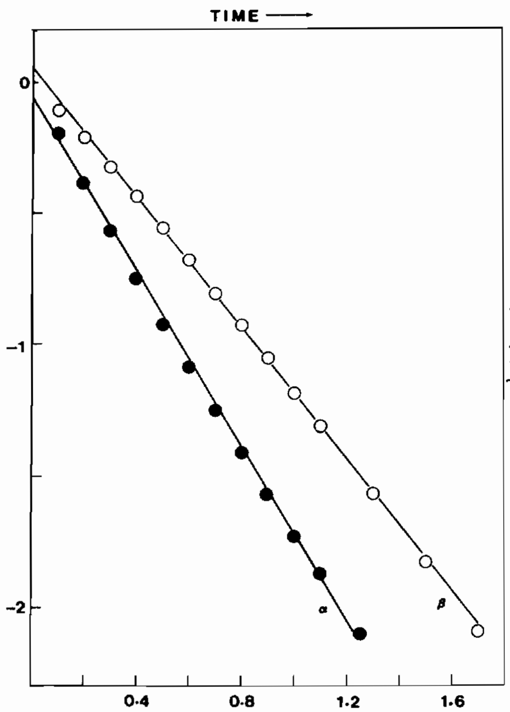

Fig. 1. Rate plots for two-site proton exchange where $k_1 = 2k_2$. The graphs are constructed assuming rapid conjugate base equilibration, whence $\alpha = 0.4 \exp(-3kt) + 0.6 \exp(-4kt/3)$ and $\beta = -0.2 \exp(-3kt) + 1.2 \exp(-4kt/3)$. The linear plots demonstrate that two-exponential functions cannot be split under the conditions (see text).

Plots of ln α and ln β *versus* time are shown in Fig. 1 for synthetically generated data covering three half-lives of H-exchange at each site, and it is clear that these are indistinguishable from linear. Indeed, nonlinear least-squares analysis of each data set, according to a simple first-order function α or $\beta = a \exp(-k(\text{obs.})t)$ yields

$$k_\alpha(\text{obs.}) = 1.77 \pm 0.06(3\%)\ (a = 0.982 \pm 0.020)$$

$$k_\beta(\text{obs.}) = 1.23 \pm 0.02(2\%)\ (a = 1.046 \pm 0.014) \tag{27}$$

Note that each of the values k_α(obs.) and k_β(obs.) lies in between the true values 2 and 1, and the different values arise essentially because of the different pre-exponential factors. More significantly, the precision of the derived rate parameters (better than ±3%) demonstrates that a two-exponential fit is not warranted. It must be concluded that, when $0.2 \leqslant k_1/k_2 \leqslant 2.0$, the observation of linear exchange rate plots cannot exclude the possibility of rapid conjugate base equilibration in the H_α, H_β exchange system.

Returning to the question of the optimum k_1/k_2 value for detecting the biphasic kinetics, the case $k_1 = 4k_2$† merits consideration, partly because this approximates the observed exchange kinetics [1] for *trans*-$\mathrm{Co(en)_2(N_3)NCS^+}$ at high $[\mathrm{NH_4^+}]$. Again using

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*For data covering up to *ca.* 90% reaction see refs. 5 and 6.

**It needs to be recalled that Scheme 1 under consideration does not strictly apply to the *trans*-$\mathrm{Co(en)_2AX^{n+}}$ complexes.

†Note that the ratio of exponents is not k_1/k_2, but it is sufficiently close for our purposes [e.g., $k_1/k_2 = 2$; $(k_1 + k_2)/(2k_1k_2)) = 2.25$, from eqns. (19) and (20); only when $k_1/k_2 = 2.414$ are the ratios identical].

synthetically generated data covering three half-lives of exchange and non-linear/least-squares analysis, a single exponential fit for the β proton exchange is excellent, but for the faster α proton, not as good; k_α(obs.)3.26 ± 0.36(11%) (a 0.917 ± 0.073), k_β(obs.)1.51 ± 0.03(2%) (a 1.081 ± 0.017). Nonetheless, it remains very difficult to argue that the $\ln \alpha$ *versus* time plot is genuinely curved (which would provide direct evidence of rapid conjugate base equilibration).

We conclude that the cited evidence cannot support the case [1] for negligible conjugate base equilibration. An extension of the above analysis to the examples $k_1 \simeq 5k_2 - 6k_2$ (or vice versa) indicates that here lie the optimum prospects for demonstrating (or refuting) the possibility of rapid conjugate base equilibration, and, for simple H_α, H_β two-site exchange, this awaits experimental testing.

In summary, two-site proton exchange for amine-metal complexes should usually follow good first-order kinetics, and specific rates for the different sites will be distinguished, irrespective of conjugate base equilibration. However, the rate for the slower exchanging proton will be overestimated by a factor approaching two if conjugate base equilibration is extremely rapid. Also, for sites exchanging at very similar rates, the measured rate parameters will be inaccurate (although precise). The problem [1, 7] of intramolecular proton scrambling in the conjugate base can be resolved from the exchange kinetics of the faster proton if the relative rates are *ca.* 5 to 6, and especially if accurate exchange data in the critical region 3 to $5t_{1/2}$ [5] are available.

Finally, with respect to an earlier publication [8] where we alluded to the problem, it was claimed [1] that we failed to recognize the consequence of the condition imposed by microscopic reversibility, eqn. (8). This claim is adequately answered here and elsewhere [2]. It should also be noted that 'microscopic reversibility' does not exclude the conditions

$$k_1 \gg k_2 \quad \text{and} \quad k_{-1} = k_{-2} \tag{28}$$

that Balt and Gamelkoorn [1] believe is so. Diffusion controlled limiting rates of conjugate base reprotonation ($k_{-1} = k_{-2}$) and very different rates of proton exchange (e.g. $k_1 \gg k_2$) are not mutually exclusive. All that eqn. (8) requires is that, if this situation obtains, then $k_{21} \gg k_{12}$, *i.e.*, the conjugate base equilibrium favours the more acidic site. It is important to note that this does not imply that CB1 and CB2 are at equilibrium. This will only be true if direct equilibration (k_{12}, k_{21}) is very rapid, as the appropriate substitution into eqns. (9) and (10) will demonstrate. However, it can be readily shown that, whether the direct interconversion path exists or not, microscopic reversibility requires effective equilibration of the deprotonated centre between the two sites. Referring to Scheme 1

$$\frac{[\mathrm{CB2}] + [\mathrm{CB3}]}{[\mathrm{CB1}] + [\mathrm{CB4}]} = \frac{k_2 k_{-1}}{k_1 k_{-2}} \left(= \frac{k_{12}}{k_{12}}, \text{ from eqn. (8)} \right) \tag{29}$$

The Problem of Equivalent Protons

For exchange at a single site containing n equivalent protons, it has been shown that, with the usual experimental probe, the consecutive reaction scheme

$$\mathrm{H}_n \xrightarrow{nk_{\mathrm{ex}}} \mathrm{H}_{n-1}\mathrm{D} \xrightarrow{(n-1)k_{\mathrm{ex}}} \mathrm{H}_{n-2}\mathrm{D}_2 \ldots\ldots \mathrm{HD}_{n-1} \xrightarrow{k_{\mathrm{ex}}} \mathrm{D}_n \tag{30}$$

always leads to simple first-order kinetics because of the statistical relationship between the specific rates of exchange [9, 10]. Moreover, it has been emphasized that the experimentally determined specific rate is always k_{ex} (rather than nk_{ex}*), irrespective of the number (n) of equivalent protons. Balt and Gamelkoorn [1] treated the $4H_\alpha$, $4H_\beta$ exchange problem for the *trans*-$\mathrm{Co(en)_2AX}^{n+}$ complexes in $\mathrm{NH_3}(l)$ as the simpler H_α, H_β system, and in the light of the above, this appears to be reasonable. However, when conjugate base equilibration is rapid, this is not a valid simplification**. The results of detailed analyses† show quite generally that the form of the rate laws for H-exchange at the α and β sites depends critically upon the number of equivalent protons in each site.

It is appropriate therefore to reconsider Balt and Gamelkoorn's treatment [1] of H-exchange in the *trans*-$\mathrm{Co(en)_2AX}^{n+}$ complexes in $\mathrm{NH_3}(l)$. Under conditions of rapid conjugate base equilibration, the correct rate equations and their integrated forms are found to be

$$\mathrm{d}\alpha/\mathrm{d}t = -\left\{\frac{19k_1^2 + 32k_1k_2 + 12k_2^2}{7(k_1 + k_2)}\right\}\alpha + \left\{\frac{(4k_1 + 3k_2)(4k_2 + 3k_1)}{7(k_1 + k_2)}\right\}\beta \tag{31}$$

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*The exception arises when the usual NMR technique distinguishes individual isotopromers. Such is the case, for example, with H-exchange at each of the two chemically distinct amine sites of $\mathrm{(CH_3NH_2)_5CoCl^{2+}}$ (ref. 11). Proton coupling ($\mathrm{H-CH_3}$) yields distinct $\mathrm{CH_3}$ signal patterns for $\mathrm{-NH_2CH_3}$, $\mathrm{-NHDCH_3}$ and $\mathrm{-ND_2CH_3}$, and thus following the decay of the outer peak of the reactant's $\mathrm{CH_3}$ triplet yields in fact $2k_{\mathrm{ex}}$ (and not k_{ex}). This does not appear to have been recognized [11].

**It is valid only for the case of identical intrinsic specific rates of exchange (*i.e.* $k_1 = k_2$).

†These calculations are trivial but tedious. Sample calculations are available on request from the author.

TABLE I. Predicted Rate Laws for Two-site Proton Exchange in Aminemetal Complexes under Conditions of Rapid Conjugate Base Equilibration $\alpha = p\ \exp(-xt) + (1-p)\exp(-yt)$ [a], $\beta = q\ \exp(-xt) + (1-q)\exp(-yt)$ [a]

mH_α, nH_β [b]		$k_1 = k_2 (= k)$ [c]				$k_1 \gg k_2$ [c]				$k_2 \gg k_1$ [c]			
m	n	p	q	x	y	p	q	x	y	p	q	x	y
1	1	0	0	$2k$	k	1	0	k_1	$2k_2$	0	1	k_2	$2k_1$
2	1	0	0	$3k$	k	$\frac{1}{3}$	$\frac{-1}{3}$	$2k_1$	$\frac{1}{2}k_1$	0	1	k_2	$2k_1$
3	1	0	0	$4k$	k	$\frac{1}{7}$	$\frac{-2}{7}$	$3k_1$	$\frac{2}{3}k_1$	0	1	k_2	$2k_1$
4	1	0	0	$5k$	k	$\frac{1}{13}$	$\frac{-3}{13}$	$4k_1$	$\frac{3}{4}k_1$	0	1	k_2	$2k_1$
1	1	0	0	$2k$	k	1	0	k_1	$2k_2$	0	1	k_2	$2k_1$
2	2	0	0	$4k$	k	$\frac{2}{5}$	$\frac{-1}{5}$	$2k_1$	$\frac{1}{3}k_1$	$\frac{-1}{5}$	$\frac{2}{5}$	$2k_2$	$\frac{1}{3}k_2$
4	4	0	0	$8k$	k	$\frac{4}{25}$	$\frac{-3}{25}$	$4k_1$	$\frac{3}{7}k_1$	$\frac{-3}{25}$	$\frac{4}{25}$	$4k_2$	$\frac{3}{7}k_2$
2	1	0	0	$3k$	k	$\frac{1}{3}$	$\frac{-1}{3}$	$2k_1$	$\frac{1}{2}k_1$	0	1	k_2	$2k_1$
4	2	0	0	$6k$	k	$\frac{2}{17}$	$\frac{-3}{17}$	$4k_1$	$\frac{3}{5}k_1$	$\frac{-1}{4}$	$\frac{3}{8}$	$2k_2$	$\frac{1}{5}k_2$
4	1	0	0	$5k$	k	$\frac{1}{13}$	$\frac{-3}{13}$	$4k_1$	$\frac{3}{4}k_1$	0	1	k_2	$2k_1$
12	3	0	0	$15k$	k	$\frac{3}{157}$	$\frac{-11}{157}$	$12k_1$	$\frac{11}{14}k_1$	$\frac{-1}{20}$	$\frac{6}{20}$	$3k_2$	$\frac{1}{7}k_2$

[a] α and β are the fractions of total H remaining at any time after exchange with D, for the inequivalent amine-H sites 1 and 2, respectively. [b] m and n are the numbers of equivalent protons in α and β sites, respectively. [c] k_1 and k_2 are the actual specific exchange rates for the α and β protons; x and y are the apparent specific rates.

$$d\beta/dt = \left\{\frac{(4k_1 + 3k_2)(4k_2 + 3k_1)}{7(k_1 + k_2)}\right\}\alpha - \left\{\frac{19k_2^2 + 32k_1k_2 + 12k_1^2}{7(k_1 + k_2)}\right\}\beta \tag{32}$$

$$\alpha = p\ \exp(-4(k_1 + k_2)t) + (1-p)\exp\left(-\frac{3k_1^2 + 8k_1k_2 + 3k_2^2}{7(k_1 + k_2)}t\right) \tag{33}$$

$$\beta = q\ \exp(-4(k_1 + k_2)t) + (1-q)\exp\left(-\frac{3k_1^2 + 8k_1k_2 + 3k_2^2}{7(k_1 + k_2)}t\right) \tag{34}$$

where

$$p = (4k_1 + 3k_2)(k_1 - k_2)/(25k_1^2 + 48k_1k_2 + 25k_2^2)$$

$$q = -(3k_1 + 4k_2)(k_1 - k_2)/(25k_1^2 + 48k_1k_2 + 25k_1^2)$$

Because of the symmetry we need only consider the two limiting cases, $k_1 = k_2$ and $k_1 \gg k_2$:

$k_1 = k_2$

$$\alpha = 0\ \exp(-8k_1t) + 1\ \exp(-k_1t) \tag{35}$$

$$\beta = 0\ \exp(-8k_1t) + 1\ \exp(-k_1t) \tag{36}$$

$k_1 \gg k_2$

$$\alpha = (4/25)\exp(-4k_1t) + (21/25)\exp(-3k_1t/7) \tag{37}$$

$$\beta = (-3/25)\exp(-4k_1t) + (28/25)\exp(-3k_1t/7) \tag{38}$$

Clearly a two-exponential rate law is followed for each site, except in the limit $k_1/k_2 \to 1$. Moreover, the exponents differ by more than the critical factor of two, and the pre-exponential factors for the smaller exponent are always dominant. Therefore conventional rate plots $\ln\alpha$ *versus* t, $\ln\beta$ *versus* t are predicted to be curved*. Moreover, and the key result, each should have later-time linear sections of identical slope (k_1 to $3k_1/7$), *i.e.* apparently equal exchange rates. It must be concluded that the effect of rapid conjugate base equilibration is to level the apparent exchange rates, as previously suggested, and contrary to the conclusions of Balt and Gamelkoorn [1]. Also, since these rates are experimentally different [1], it is clear that rapid conjugate base equilibration is not operative for the *trans*-Co(en)$_2$AX^{n+} complexes in NH$_3$(*l*).

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*We have confirmed the curvature 'experimentally' by constructing standard rate plots similar to those shown in Fig. 1 and using synthetically generated data.

We now turn briefly to other multi-proton exchange processes and draw on previously reported exchange data [3] to construct a general case for negligible rates of conjugate base equilibration in cobalt(III) amine complexes.

For the 2-site exchange systems nH_α, H_β, two-exponential rate laws also arise (Table I)[†]. However, for complexes which bear a unique proton that happens to be the more rapidly exchanged ($k_2 \gg k_1$), the consequence of rapid conjugate base equilibration is not experimentally detectable. As for the H_α, H_β example, the same simple first-order rate laws operate; $k_\alpha(\text{obs.}) = k_\alpha$ and $k_\beta(\text{obs.}) = 2k_\beta$ (Table I). In contrast, the situation $k_1 \gg k_2$ leads to the prediction of levelled exchange rates. In practice, the unique proton in aminecobalt(III) complexes is usually, if not always, that which is exchanged more rapidly [3, 4], and therefore the question of conjugate base equilibration is unsettled for these particular systems.

Finally we consider the more general nH_α, mH_β systems ($n, m > 1$). The well-studied $(NH_3)_5CoX^{n+}$ complexes (in both D_2O and $ND_3(l)$) are examples. Reference to Table I shows that levelled exchange rates are expected if either $k_1 \gg k_2$ or $k_2 \gg k_1$, and two-exponential rate laws operate. Experimentally, $k_\alpha(\text{obs.})$ and $k_\beta(\text{obs.})$ are very different for most X groups [12], and clearly rapid conjugate base equilibration cannot be occurring.

In passing, we allude to an important problem in the mechanism of the well-studied base hydrolysis reaction [3, 4] and which is related to relative rates of H/D exchange at inequivalent coordinated metal amine centres. Because the pK_α values of these centres exceed fourteen and are therefore not directly measurable in water, H-exchange rates have been used to assess relative acidities. Notwithstanding some contention in the underlying assumption of this approach [3, 4], it has been argued that the relative values of k_{ex} directly reflect the relative populations of the several possible complexes bearing a deprotonated amine centre. For example, $(NH_3)_5CoCl^{2+}$ exchanges the NH protons *trans* to Cl^- approximately 60-fold faster than that *cis* to Cl^- [12], implying that *trans*-$Co(NH_3)_4(NH_2)Cl^+$ is more abundant than *cis*-$Co(NH_3)_4(NH_2)Cl^+$ by a similar margin. We have already seen that the Principle of Microscopic Reversibility requires that rapid and direct interconversion between the *cis*- and *trans*-conjugate bases be inconsequential (eqn. (29)), negating suggestions to the contrary [13], but the problem rests simply with the experimental values for $k_{ex}(cis)$ and $k_{ex}(trans)$ used in the calculation. The actual relative population is given as follows*

$$[\textit{trans}\text{-}Co(NH_3)_4(NH_2)Cl^+]/[\textit{cis}\text{-}Co(NH_3)_4(NH_2)Cl^+] = \frac{3k_{ex}(\textit{trans})}{12k_{ex}(\textit{cis})} \tag{39}$$

This correction for the numbers of equivalent protons in the two sites leads to a ratio of only 15, not 60 as thought previously [11]. Similar arguments apply in earlier cases where there has been this oversight, necessitating re-thinking of the problem [3, 4] of the relative reactivities of alternative conjugate base species as opposed to their relative abundances.

Conclusions

The question of rapid conjugate base equilibration is a problem of interest in its own right, and we have examined its consequences for the kinetics of proton exchange in aminemetal complexes. In deriving the expected rate laws under conditions of rapid conjugate base equilibration[†], the specific numbers of equivalent protons in each inequivalent site need be taken into account; the implications for the H_α, H_β system for example, are not the same as for $2H_\alpha$, $2H_\beta$ or $4H_\alpha$, $4H_\beta$ systems. For many but not all H-exchange systems, we have shown that it is possible to experimentally detect rapid conjugate base equilibration, either as curved rate plots or, more convincingly, by the observation of levelled exchange rates. Presently there is no evidence for its occurrence in aminemetal systems. Furthermore we have established, for a limited number of systems, that there is definitely negligible scrambling of the deprotonated amine centre amongst inequivalent sites.

Acknowledgements

The author is grateful to Dr. B. C. Freasier for assistance with the program REDUCE which led to exact solutions to the complex rate equations. Thanks are also due to Mr. M. Newnham who drew the figures.

[†] These calculations are trivial but tedious. Sample calculations are available on request from the author.

*With the assumption (refs. 3, 4) $k_{-1} = k_{-2}$, this follows directly from eqn. (29), noting that, as alluded to in the first paragraph of this section, $12k_{ex}(cis) = k_1$, and similarly $3k_{ex}(trans) = k_2$. Also, [CB1] + [CB4] = [*cis*-$Co(NH_3)_4(NH_2)Cl^+$], and [CB2] + [CB3] = [*trans*-$Co(NH_3)_4(NH_2)Cl^+$].

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