A Bimolecular Mechanism for Substitution

Sir:

A weight of evidence has accumulated[1,2] supporting the conclusion that, in the activation for substitution in octahedral metal ion complexes, bond breaking is more important than bond making. For complexes which are electron rich but coordinatively unsaturated, there are numerous examples of oxidative addition, and these often appear to proceed with attack by the electrophilic moiety derived from the oxidant on the d electrons of the complex as being rate determining.[3] There is no fundamental reason why mechanisms of the latter type cannot occur with octahedral complexes, but, in contrast to the d^8 square-planar case, net oxidative addition appears to be less likely for an octahedral complex than is oxidative addition followed by elimination. In favorable circumstances, the operation of this kind of mechanism can be expected to lead to substitution, but now, in contrast to the situation obtaining when the entering group is nucleophilic, bond making in the activated complex can be an important component of the activation energetics of the process. We wish to report some results which we believe demonstrate an electrophilic mechanism for substitution.

The ion $Ru(NH_3)_6^{3+}$ is known to undergo substitution very slowly, the halftime for the replacement of NH_3 by H_2O at room temperature and in the dark being the order of days or longer.[4] When NO is added to a solution of $Ru(NH_3)_6^{3+}$, the reaction

$$H^+ + [Ru(NH_3)_6]^{3+} + NO \longrightarrow [Ru(NH_3)_5NO]^{3+} + NH_4^+$$

ensues rapidly and essentially quantitatively.

The product $[Ru(NH_3)_5NO]Br_3$ was identified by the new characteristic infrared absorption bands[5] (in KBr) at 1927 (weak, shoulder), 1913 (strong, sharp), 1358 (weak, sharp), and 845 cm^{-1} (strong), by the visible and uv absorption spectrum (460 $m\mu$, broad, with ϵ 14.4 M^{-1} cm^{-1}; 300 $m\mu$, ϵ 67.2 M^{-1} cm^{-1}), by the fact that the complex behaves like a highly charged cation on an ion-exchange column, and by the microanalysis. *Anal.* Calcd for $[Ru(NH_3)_5NO]Br_3 \cdot H_2O$: N, 17.7; Br, 50.6; H, 3.6. Found: N, 18.0, Br, 49.0; H, 3.8.

Analysis for ammonium ion released to the solution was performed by using indophenol as described elsewhere.[6] Within the error limits of the experiment (±10%), 1 mole of NH_4^+ was liberated per mole of ruthenium(III) hexaammine.

The kinetics of the reaction were studied in both Cl^- and Br^- medium at $\mu \sim 0.1$ with $[H^+] \sim 0.09$ M at 26°. The solution was first deaerated using argon. It was then continually saturated with nitric oxide–argon mixtures and then the deaerated solution of the $Ru(NH_3)_6^{3+}$ was added in small volume relative to that of the reaction medium. Small aliquots of the reaction mixture were withdrawn at various time intervals into fritted funnels so that the reaction could immediately be quenched by a stream of argon. The decay of the $Ru(NH_3)_6^{3+}$ (ϵ 4.67 ± 0.05 × 10^2 M^{-1} cm^{-1} at 275 $m\mu$) was recorded on a Cary 15 spectrophotometer. An isosbestic point was observed at 247 $m\mu$ (ϵ 3.0 ± 0.2 × 10^2 M^{-1} cm^{-1}). The reaction is first order in both nitric oxide and Ru(III) hexaammine. At 26°, $\mu \sim 0.11$, [HCl] 8.8 × 10^{-2} M, $[Ru(NH_3)_6Cl_3]_0$ covering the range 2.3–5.6 × 10^{-3} M, and the nitric oxide–argon gas mixture at atmospheric pressure, but with the NO varying from 30 to 100%, k was found to be 2.0 × 10^{-1} M^{-1} sec^{-1} (mean of five experiments); at $\mu \sim 0.10$, [HBr] 8.6 × 10^{-2} M, $[Ru(NH_3)_6Br_3]_0$ covering the range 0.98–2.2 × 10^{-3} M, and the NO content of the gas varying from 67 to 100%, k was found to be 1.9 × 10^{-1} M^{-1} sec^{-1}. The rate constant as measured by the formation of NH_4^+ agreed with the values above within experimental error.

The rate of release of NH_3 is clearly very much greater in the presence of NO than when NO is absent, and bond making by the entering group is important in the over-all substitution process. A convenient bond-making mechanism is available for the entering group because Ru(III) with a low-spin d^5 electron structure has an unpaired electron which can be engaged by the odd electron of nitric oxide in forming a bond (formally it can be looked at as a bond between Ru(IV) and NO^-), so that a seven-coordinated activated complex, possibly even an intermediate, can be produced in the course of the reaction.

On the basis of present evidence, admittedly still limited in extent, bond breaking in the activated complex is not as important a component. Thus, when $Ru(NH_3)_5Br^{2+}$ is the reactant, k for the consumption of the reactant is observed to be 0.7 M^{-1} sec^{-1}, and $Ru(NH_3)_5NO^{3+}$ and $Ru(NH_3)_4NO(Br)^{2+}$ are both formed (and in roughly equal amounts). Thus, release of NH_3 is approximately as rapid as the release of Br^-, in striking contrast to the rates of release when H_2O is the entering group.

In principle, the intermediate $Ru(NH_3)_6NO^{3+}$ can also be formed by the addition of NO^+ to $Ru(NH_3)_6^{2+}$, and a report of the preparation of $Ru(NH_3)_5NO^{3+}$ by the action of HCl and $NaNO_2$ on $Ru(NH_3)_6Cl_2$ appears in the literature.[7] We have done some additional experiments with this system, but its diagnosis is still incomplete. On making up a mixture of 1.4 × 10^{-2} M HCl, 1.2 × 10^{-1} M $NaNO_2$, and 1.2 × 10^{-3} M $Ru(NH_3)_6^{2+}$ (chloride medium), there is an immediate rapid reaction, as judged by the decrease in extinction at the maximum for $Ru(NH_3)_6^{2+}$ (275 $m\mu$, ϵ 6.2 ± 0.2 × 10^2 M^{-1} cm^{-1}) followed by a much slower change. Examination by infrared spectroscopy of the solid collected a few minutes after mixing shows that the peak at 1230 cm^{-1} characteristic of $Ru(NH_3)_6^{2+}$ is absent. The immediate reaction may be the oxidation of $Ru(NH_3)_6^{2+}$ to $Ru(NH_3)_6^{3+}$ by HNO_2 and, following this, slower formation of $Ru(NH_3)_5NO^{3+}$ by the action of NO on $Ru(NH_3)_6^{3+}$ as shown above. At most, 20% of the Ru(II) hexaammine is converted to

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(1) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1967, pp 124–246.

(2) M. Eigen and R. G. Wilkins in "Mechanisms of Inorganic Reactions," Advances in Chemistry Series, No. 49, American Chemical Society, Washington, D. C., 1965, Chapter 3.

(3) (a) P. B. Chock and J. Halpern, *J. Am. Chem. Soc.*, **88**, 3511 (1966); (b) J. P. Collman and W. R. Roper, *Advan. Organometal. Chem.*, in press.

(4) Using a solution of 1.88 × 10^{-3} M $Ru(NH_3)_6Cl_3$ and 8.75 × 10^{-2} M HCl stored in the dark at 26°, only 5% (determined by uv spectral changes) of the ruthenium(III) hexaammine was converted into $[Ru(NH_3)_5Cl]Cl_2$ over a period of 2 months.

(5) (a) E. E. Mercer, W. A. McAllister, and J. R. Durig, *Inorg. Chem.*, **5**, 1881 (1966); (b) M. B. Fairly and R. J. Irving, *Spectrochim. Acta*, **22**, 359 (1966).

(6) P. C. Ford, J. R. Kuempel, and H. Taube, *Inorg. Chem.*, **7**, 1976 (1968).

(7) F. M. Lever and A. R. Powell, Special Publication No. 13, The Chemical Society, London, 1959, p 135.

$Ru(NH_3)_5NO^{3+}$ during the initial phase of the reaction. If HNO_2 and $Ru(NH_3)_6^{2+}$ form the same intermediate as $Ru(NH_3)_6^{3+}$ and NO, we must conclude that the usual fate of the intermediate is decomposition to $Ru(NH_3)_6^{3+}$ and NO, rather than formation of $Ru(NH_3)_5NO^{3+}$.

The ion $Ru(NH_3)_5NO^{3+}$ is also formed from $Ru(NH_3)_5OH_2^{3+}$ with NO. The reaction is of a rapidity comparable to that of $Ru(NH_3)_5Br^{2+}$ or $Ru(NH_3)_6^{3+}$ as the starting materials. The rate of formation of $Os(NH_3)_5NO^{3+}$ (the NO stretching band of $[Os(NH_3)_5NO](ClO_4)_3$ in KBr is split: weak at 1895; strong, sharp at 1875 cm^{-1}) from $Os(NH_3)_5OH_2^{3+}$ and NO seems to be even somewhat greater.

When $Fe(CN)_6^{3-}$ in excess acid is treated with NO, the yellow solution slowly begins to turn brown. At the end of 24 hr, the solution is red-brown. Upon addition of S^{2-} ion, the solution immediately turns violet. This result is consistent with that of Schwarzkopf,[8] who claimed that he obtained nitroprusside on bubbling ferri- or ferrocyanide solutions with nitric oxide.

Further work is in progress on these and related reactions of ruthenium and osmium.

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[8] P. Schwarzkopf, *Abhandl. Deut. Naturw., Med. Ver. Böhmen*, **3**, 1 (1911); *Chem. Abst.*, **8**, 1106 (1914).

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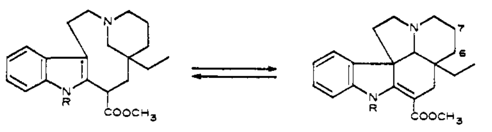
Studies on Indole Alkaloid Biosynthesis. II[1]

Sir:

In a previous communication[1] we reported some of our results relating to the later stages of indole alkaloid biosynthesis. In particular it was suggested that the transannular cyclization of nine-membered ring intermediates as had been previously postulated[2] was probably not a biosynthetically significant reaction in the Aspidosperma and Iboga series. This communication describes further results which strongly support such a suggestion, at least in the Aspidosperma alkaloids, and which in addition yield novel information about the later steps in the biosynthesis of these alkaloids.

In the hope of obtaining more distinctly positive results to those reported previously[1] we have studied a completely different approach to this problem. It is clear that the transannular cyclization process as illustrated in the conversion of the alkaloid vincadine (I) to vincadifformine (II), a reaction easily accomplished in the laboratory,[3] is only one of a number of alternative pathways in the plant elaboration of Aspidosperma alkaloids. An equally attractive and plausible scheme could invoke the reverse process, namely the ring opening of the pentacyclic system to yield the nine-membered ring alkaloids (*i.e.*, II → I).[4] This latter process would imply that Aspidosperma alkaloids of type II are biosynthetic precursors of type I. In order to obtain information on the relationship, if any, between these alternatives we have initiated some studies in *Vinca minor* L., a plant which possesses a wonderful array of Aspidosperma alkaloids.[5]



I, R = H
III, R = CH₃

II, R = H
IV, R = CH₃
VII, R = H; 6,7-double bond

A detailed investigation involving the incorporation of DL-tryptophan-3-^{14}C into *V. minor* L. over different time intervals was undertaken, and some of the results are summarized in Table I. The method involved incorporation of a solution of the amino acid in 0.1 *N* acetic acid containing a few drops of methanol, and after the appropriate time the isolation of the alkaloids was carried out by chromatographic techniques. In each time interval reported the experiment was repeated at least twice. There was surprisingly good agreement between the results obtained in the individual experiments, and Table I gives the average values obtained in these studies. For the purposes of this discussion, the *total* per cent incorporation into the nine-membered ring alkaloids, vincadine (I) and vincaminoreine (III), and their respective cyclic relatives, vincadifformine (II) and minovine (IV), is presented. The fourth column in Table I shows the relative ratio of activities between these two groups.

Table I. Results of Incorporation of DL-Tryptophan-3^{14}C into *Vinca minor* L. at Various Time Intervals

	Total % incorporation		
Time	Vincadine (I) + vincaminoreine (III) (*A*)	Vincadifformine (II) + minovine (IV) (*B*)	*B*/*A*
4 hr	0.003	0.057	19
1 day	0.015	0.24	16
2 days	0.010	0.21	21
4 days	0.010	0.22	22
7 days	0.009	0.13	14
14 days	0.003	0.06	20

A critical analysis of these results reveals several interesting features. These are: (1) activity in the alkaloids is noted even after a short exposure of 4 hr, (2) the activity in the pentacyclic alkaloids (II and IV) is consistently higher than in the nine-membered ring system, and (3) the relative ratio of activities (*B*/*A*) is *remarkably similar* over the time interval, 4 hr–2 weeks. This latter finding is certainly the most important in terms of providing information about the later stages of Aspidosperma alkaloid biosynthesis. The lack of any tendency for the ratio *B*/*A* to progressively increase or decrease with time speaks strongly against any direct biosynthetic relationship between the two groups of alkaloids. In other words, the previous suggestion[1]

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[1] Part I: J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, V. R. Nelson, and D. C. Wigfield, *J. Am. Chem. Soc.*, **90**, 3566 (1968).

[2] E. Wenkert, *ibid.*, **84**, 98 (1962).

[3] J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *ibid.*, **90**, 3891 (1968).

[4] We have recently shown that such a ring-opening process can readily occur in the laboratory.

[5] J. Mokry and I. Kompis, *Lloydia*, **27**, 428 (1964).