

## Mechanism of Formation of Schiff Base Complexes. Part 3.† Kinetic Template Effect of Copper(II) in the Condensation Reaction of the Salicylaldehydato-ion with a Polyfunctional Diprimary Amine

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Under suitable experimental conditions the reaction of the salicylaldehydato-ion (sal) with diethylenetriamine (dien) in the presence of copper(II) takes place through a first-order kinetic process. The reactants are envisaged as being first co-ordinated to the copper(II), forming a labile ternary complex; interligand condensation is then supposed to occur within the co-ordination sphere of the metal. In the resulting reaction sequence the metal ion functions as a rudimentary enzyme. The dramatic difference between the activity of an ideal enzyme system, which reduces the order of a reaction by one unit through the rapid formation of a ternary complex, and that of the copper(II) ion, which through an analogous mechanism promotes the reaction of sal and dien, is interpreted on the basis of a perturbation from the optimum reaction geometry of the reactants by the co-ordination of the functional groups to the metal.

Carbonyl addition reactions have been of interest to chemists for many years,<sup>1,2</sup> but relatively little is known regarding the kinetic effect of metal ions on these systems although their mediating effect on Schiff base formation is well recognised.<sup>3</sup> A series of investigations currently underway in our laboratory concerns the influence exerted by metal ions on the mechanism of the condensation reaction of the salicylaldehydato-ion (sal) with primary amines.<sup>4</sup> In this paper we report the results concerning some diprimary amines with particular emphasis on the reaction of sal with diethylenetriamine (dien).

These reactants are pictured to be first co-ordinated to copper(II) forming a labile ternary complex. Interligand condensation is then supposed to occur within the co-ordination sphere of the metal, which presents to the ligands the only opportunity for reaction. In this reaction sequence, the metal ion functions as a rudimentary enzyme.

By reducing the overall reaction from second- to first-order a more favourable entropy of activation should be obtained. Even though the two terms cannot be rigorously separated, it has been proposed<sup>5</sup> that  $T\Delta S$  can be divided into two parts. (i) The first part,  $\Delta S_{tr}$ , may be considered to be involved with transfer to the nucleophile to a position of very close approach to the electrophile; (ii) the second,  $\Delta S_c$ , may be considered to be that involved in the bond-breaking and -forming process:  $T\Delta S = T(\Delta S_{tr} + \Delta S_c)$ .

The term  $\Delta S_{tr}$  should be due to translational and in part rotational entropy factors, while  $\Delta S_c$  should be determined by those kinetic energy terms involved in the formation of the transition state when the ground state corresponds to a very close approach of the reactants. Bruice and Benkovic<sup>5</sup> estimated that in an ideal enzyme system, where the rapid formation of a ternary complex causes the order of a reaction to be reduced by one unit, the entropy gain accounts for a factor of  $10^3$ – $10^4$  favouring the first- over the second-order rate constant observed in the absence of the enzyme. First-order spontaneous processes should then be favoured over higher order reactions provided that the bringing together of reactants cancels  $\Delta S_{tr}$ , so that the entropy of activation is made up of only  $\Delta S_c$ .

On the basis of the previous considerations we have analysed the efficiency of copper(II) in promoting first-order reactions within its co-ordination sphere. The results contain one of the few examples so far reported in the literature concerning the kinetic template effect of metal ions.

† Part 3 is ref. 4b.

### Experimental

**Materials.**—Bis(salicylaldehydato)copper(II) (1), bis(*N*-n-butylsalicylaldiminato)copper(II) (7), and [*NN'*-ethylenebis(salicylideneiminato)]copper(II) (8) complexes were prepared by published methods.<sup>6,7</sup> Salicylaldehyde and the amines were distilled at reduced pressure and stored under nitrogen in the dark. The salicylaldehydato-ion was prepared by neutralization of salicylaldehyde with a standard methanolic solution of NaOMe.

**Preparation of (N-salicylidenediethylenetriaminato)copper(II) hexafluorophosphate hydrate (6).** A methanolic solution of dien was added to  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (241 mg) dissolved in a small amount of water. The mixture was allowed to stand for several days at room temperature. A saturated solution of  $\text{KPF}_6$  in water was then added. Slow evaporation of the solvent leads to the formation of dark violet crystals of (6) (Found: C, 30.6; H, 4.2; N, 9.55. Calc. for  $\text{C}_{11}\text{H}_{18}\text{CuF}_6\text{N}_3\text{O}_2\text{P}$ : C, 30.5; H, 4.15; N, 9.7%;  $\nu(\text{OH})$  3 640;  $\nu(\text{NH})$  3 358, 3 315, 3 150br;  $\nu(\text{C}=\text{N})$  (imino) 1 640 vs;  $\nu(\text{PF})$  850vs,  $\text{cm}^{-1}$ ).

**Kinetics.**—Kinetics were performed in 1,2-dichloroethane-methanol (1:1). Solutions of substrate and amines were separately brought to the reaction temperature and then mixed in a thermostatted cell of an OPTICA CF4R or CARY 219 double-beam spectrophotometer. The kinetics were monitored by recording the u.v. region of the spectrum at various times.

The values of pseudo-first-order rate constants ( $k_{\text{obs.}}/s^{-1}$ ), were obtained from the slopes of the plots of  $\log(D_t - D_\infty)$  versus time, where  $D_t$  and  $D_\infty$  are the optical densities of the reaction mixture at time  $t$  and after 5–6 half-lives respectively. The values of  $k_{\text{obs.}}$  are reproducible to better than 5%.

**Kinetics of the reaction of the salicylaldehydato-ion with amines.** These reactions proceed in a single kinetic stage and show isosbestic points at wavelengths ( $\lambda$ ) 335 and 385 nm. Table 1 lists values of  $k_{\text{obs.}}$  at various concentrations of amine. Values of second-order rate constants ( $k_2'/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ), determined as slopes of the linear plots pertaining to these reactions, are also included in Table 1. The final spectra for the reactions with diprimary amines were identical to those of symmetrical Schiff bases independently prepared. Our attempts to prepare Schiff bases of diprimary amines with only one amine group condensed with the salicylaldehydato-ion (mol ratio 1:1) were unsuccessful; in fact, equimolar methanolic solutions of sal and dien led to the formation of mono- and di-imino-derivatives together with small amounts of im-

**Table 1.** Rate constants for the reactions of sal with primary amines at 298 K; [sal] =  $10^{-4}$  mol dm $^{-3}$ 

Amine	$10^3[\text{amine}]/\text{mol dm}^{-3}$	$10^3k_{\text{obs.}}'/\text{s}^{-1}$	$k_2''/\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$
NH <sub>2</sub> Bu <sup>n</sup>	14.0	9.0	0.64
	10.5	6.7	
	7.0	4.6	
	3.5	2.5	
	1.4	1.1	
en	37.5	58.2	1.6
	27.5	43.0	
	17.5	27.6	
	10.1	15.9	
	5.0	8.1	
dien	65.6	112.0	1.7
	45.9	79.0	
	32.8	57.5	
	22.5	40.0	
	13.1	26.7	
	7.6	14.7	

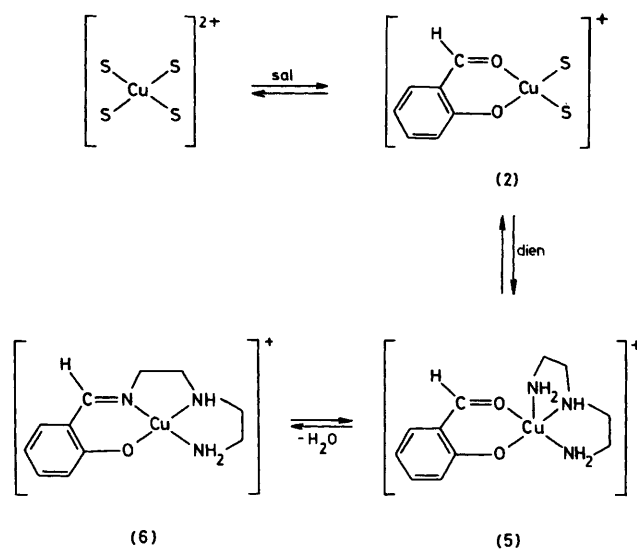
**Table 2.** Rate constants for the second stage of the reactions of [Cu(sal)(S)<sub>2</sub>]<sup>+</sup> (2) with primary amines at 298 K; [(2)] =  $1.5 \times 10^{-4}$  mol dm $^{-3}$ 

Amine	$10^3[\text{amine}]/\text{mol dm}^{-3}$	$10^3k_{\text{obs.}}''/\text{s}^{-1}$	$k_2''/\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$
NH <sub>2</sub> Bu <sup>n</sup>	7.75	8.6	1.1
	6.25	7.1	
	4.5	5.4	
	3.1	4.0	
	1.5	1.9	
en	8.0	17.0	2.15
	6.0	12.8	
	4.0	8.4	
	2.0	4.4	
	1.25	2.7	
dien	8.4	18.0	2.2
	6.3	13.9	
	4.2	9.2	
	2.1	5.1	
	1.25	2.8	

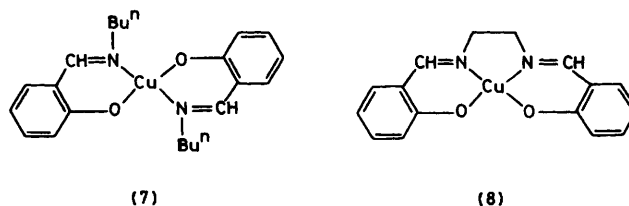
purities. Only in the presence of copper(II), does the reaction of sal and dien lead to the mono-imino-species; therefore the template reaction is a very useful approach to the synthesis of this kind of compound.

**Kinetics of the reactions of [Cu(sal)(S)<sub>2</sub>]<sup>+</sup> (2) [solvent (S) = MeOH-CICH<sub>2</sub>CH<sub>2</sub>Cl (1 : 1)] with amines.** These reactions show a very fast initial stage followed by a slower one. Table 2 lists pseudo-first-order rate constants relative to the slower stage of the process at various concentrations of amines (isosbestic points at 336 and 385 nm). Values of second-order rate constants  $k_2''$ , determined as slopes of the appropriate linear plots, are also reported in Table 2.

The reactions of the solvato-species (2) with an excess of primary amines have been also carried out on a preparative scale under the same conditions reported for the kinetic experiments. The isolated products of the reaction with *n*-butylamine, ethylenediamine (en), and dien are (7), (8), and (6) respectively. Although it is clear that the products of the reaction of (2) with NH<sub>2</sub>Bu<sup>n</sup>, en, and dien are derived from multi-step processes, the kinetic behaviour together with the

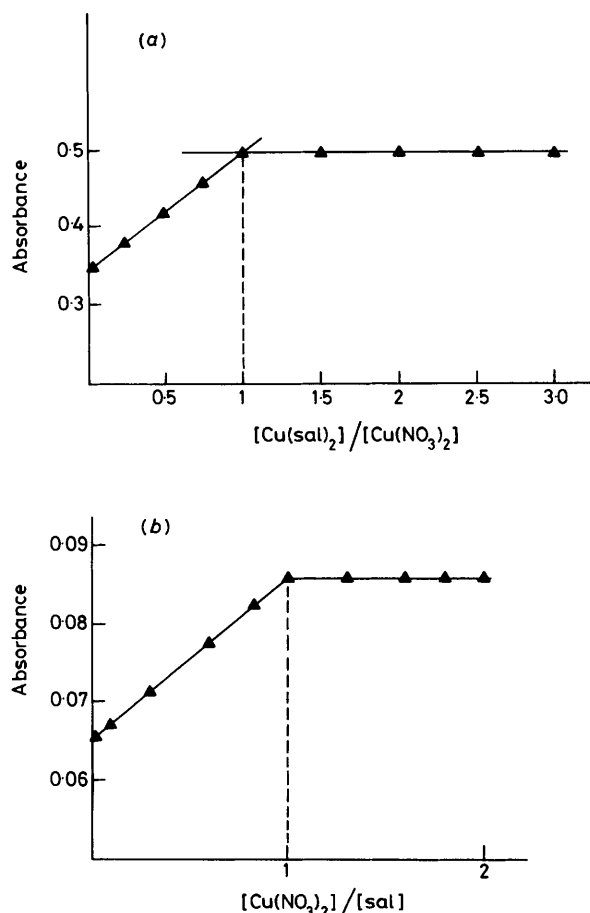
**Scheme 1.** S = solvent (MeOH-CICH<sub>2</sub>CH<sub>2</sub>Cl, 1 : 1)**Table 3.** First-order rate constants for the intramolecular condensation reaction of the ternary complex [Cu(sal)(dien)]<sup>+</sup> (5) at various temperatures and concentrations

T/K	$10^4[\text{Cu(sal)(S)}_2^+]/\text{mol dm}^{-3}$	$10^4[\text{dien}]/\text{mol dm}^{-3}$	$10^4k_{\text{obs.}}/\text{s}^{-1}$
298	4.4	4.0	1.1
298	2.2	2.0	1.1
298	1.5	1.35	1.1
313	2.2	2.0	3.0
289	2.2	2.0	0.59



presence of isosbestic points in the electronic spectra of the reaction mixtures suggests that the rate-determining step for these processes is always the nucleophilic attack of the amine on the co-ordinated carbonyl of the mixed complexes (3), (4), and (5) respectively (see Results and Discussion, Scheme 2). The isolation of (7), (8), and (6) from the reaction mixtures can be attributed either to a fast rearrangement of the resulting imino-derivatives or to the presence of equilibria which are shifted during the crystallization toward these less soluble species.

**Kinetics of the intramolecular condensation of the ternary complex [Cu(sal)(dien)]<sup>+</sup> (5).** The labile ternary complex (5) is formed *in situ* in a very fast step when equimolar amounts of the solvato-complex (2) and dien are mixed [see Results and Discussion, equation (v)]. The ternary complex (5) is unstable leading to the formation of (6) (Scheme 1) in a single first-order kinetic process (isosbestic points at 335 and 385 nm). In order to prevent the concomitant second-order reaction between non-co-ordinated dien and the ternary complex (5), the amine was always added in a small deficiency with respect



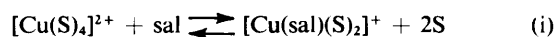
**Figure 1.** Spectrophotometric titrations in methanol-1,2-dichloroethane (1:1) at 298 K: (a) absorbances of solutions of  $[Cu(sal)_2]$  ( $5 \times 10^{-4} \text{ mol dm}^{-3}$ ) containing various amounts of  $Cu(NO_3)_2 \cdot 3H_2O$  ( $\lambda = 395 \text{ nm}$ ); (b) absorbances of solutions of  $Cu(NO_3)_2 \cdot 3H_2O$  ( $1.5 \times 10^{-3} \text{ mol dm}^{-3}$ ) containing various amounts of sal ( $\lambda = 800 \text{ nm}$ )

to the metal ion (*ca.* 10% less) whose concentration was checked for each kinetic run series by atomic absorption measurements.

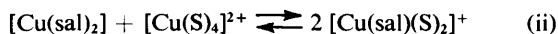
Table 3 lists the first-order rate constants ( $s^{-1}$ ) for the template reaction at various temperatures and ternary complex concentration.

## Results and Discussion

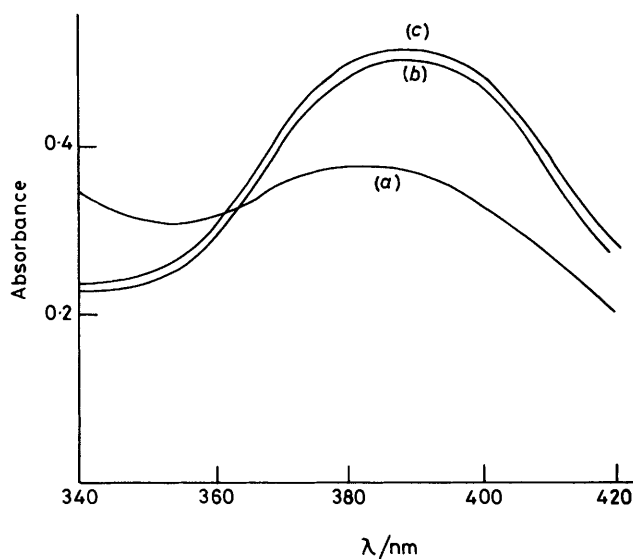
Equimolar solutions of sal and copper(II) lead to a 1:1 complex whose residual co-ordination sites are occupied by molecules of solvent (S), equation (i).



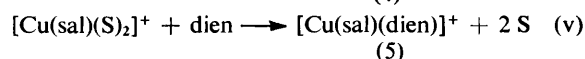
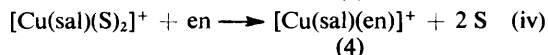
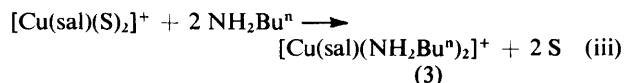
Our spectrophotometric titrations confirmed that (2) is by far the most important species present in equimolar solutions of sal and copper(II) in the mixed solvent we have used (MeOH- $ClCH_2CH_2Cl$ , 1:1). The solvato-complex (2) is also quantitatively formed when nitrates of copper(II) are stoichiometrically added to bis(salicylaldehydato)copper(II) (1) (Figures 1 and 2) *via*  $[Cu(S)_4]^{2+}$ , equation (ii).



Stoichiometric amounts of primary amines can easily displace the solvent from the solvato-complex (2) in a fast stage according to equations (iii), (iv), and (v).



**Figure 2.** Electronic spectra of (a) solutions of  $[Cu(sal)_2]$  ( $1.5 \times 10^{-4} \text{ mol dm}^{-3}$ ), (b) solutions of  $[Cu(sal)_2]$  ( $1.5 \times 10^{-4} \text{ mol dm}^{-3}$ ) containing equimolar amounts of  $Cu(NO_3)_2 \cdot 3H_2O$ , and (c) solutions of  $[Cu(sal)_2]$  ( $1.5 \times 10^{-4} \text{ mol dm}^{-3}$ ) containing an excess of  $Cu(NO_3)_2 \cdot 3H_2O$  ( $6.0 \times 10^{-4} \text{ mol dm}^{-3}$ )



These reactions are too fast for an exact valuation, even for stopped-flow methods; however, our experiments demonstrated that their values of  $t_{1/2}$  are less than  $10^{-3} \text{ s}$ . These reaction rates, and spectral changes in the *d-d* transition region, are in good agreement with substitution of the molecules of solvation by ligands with nitrogen-donor atoms in square-planar copper(II) complexes.<sup>8,9</sup> Comparative analysis of the spectra also suggests the formation of five-co-ordinate species when the tridentate dien is stoichiometrically added to the solvato-species (2) (Figure 3).

While no change can be detected in the electronic spectra of solutions of (3) and (4), in the absence of further amounts of non-co-ordinated amine, reactions with good isosbestic points take place in the analogous solutions of (5). In the latter case the nature of the product and the kinetic law of the reaction, typical for a first-order process, strongly suggest that the spectral changes reflect the intramolecular condensation between the two reactants within the co-ordination sphere. The proposed mechanism for the global reaction is depicted in Scheme 1, which particularly emphasises the 'match-making' role played by the metal during the course of the reaction.

According to Scheme 1 the metal ion principally serves to lower the order of reaction from second-order observed between the free ligands, to a first-order reaction occurring within a mixed complex with one amino-nitrogen loosely bound to the metal.

Therefore we could follow the same condensation between sal and dien as a bimolecular process in the absence of copper(II) and as a monomolecular process in the presence of copper(II).

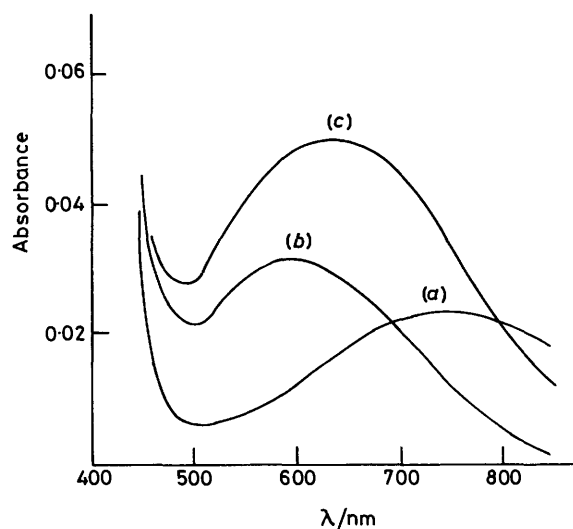
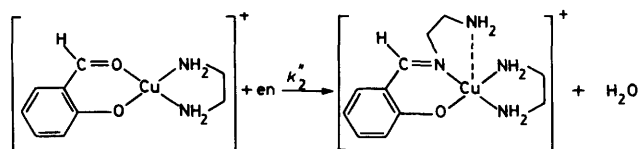


Figure 3. Electronic spectra in methanol-1,2-dichloroethane (1 : 1) of (a)  $[\text{Cu}(\text{sal})(\text{S})_2]^+$  ( $3 \times 10^{-4} \text{ mol dm}^{-3}$ ), (b)  $[\text{Cu}(\text{sal})(\text{S})_2]^+$  ( $3 \times 10^{-4} \text{ mol dm}^{-3}$ ) with an equimolar amount of en, and (c)  $[\text{Cu}(\text{sal})(\text{S})_2]^+$  ( $3 \times 10^{-4} \text{ mol dm}^{-3}$ ) with an equimolar amount of dien



Scheme 2.

The stability of the square-planar derivatives (3) and (4), in contrast with the reactivity of the five-co-ordinate species (5), can be interpreted on the basis of their different crystal-field stabilisation energies. Ligand-field effects, in fact, should cause a much more rigid metal-ligand geometry in the square-planar complexes than in the five-co-ordinate species. This means that ligand-field effects cause the reactants to remain separated by being bound to co-ordination sites of precise geometry only in the case of square-planar complexes. Conversely the five-co-ordinate complex (5) is expected to provide, through a highly dynamic situation in which various metal-donor-atom bonds are frequently broken and reformed in chelate rings, a much larger concentration of electron pair close to the carbonyl group. Interestingly, the ternary complexes (3), (4), and (5) react with an excess of amine by similar second-order kinetic processes.

The experimental kinetic results for these reactions (Table 2) fit the same kinetic law that we have found for the reaction of free sal and amine, equation (vi). The reported second-order

$$k_{\text{obs.}}'' = k_2''[\text{amine}] \quad (\text{vi})$$

rate constants show that the condensation of sal co-ordinated to copper(II) in a positively charged complex is about two times faster than the corresponding condensation of the free salicylaldehyde-ion. Inductive effects favouring the nucleophilic attack should be mainly responsible for the observed behaviour (general acid catalysis). Scheme 2 depicts the proposed rate-determining step for the second-order reaction of (4) with an excess of en; similar pathways can be envisaged as rate-determining steps for the reaction of (3) and (5) with an excess of  $\text{NH}_2\text{Bu}^a$  and dien, respectively.

Table 4. Activation parameters for (a) the bimolecular condensation reaction of sal with dien, and (b) the copper(II) template condensation reaction

	$\Delta H^\ddagger/$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger/J$ $\text{K}^{-1} \text{ mol}^{-1}$
(a) sal + dien	24.6	-159.3
(b) $[\text{Cu}(\text{sal})(\text{S})_2]^+ + \text{dien}$	48.5	-158.4

From Tables 1 and 2 it is also evident that diprimary amines react twice as fast as primary amines. The statistical effect which of course favours the former by a factor of two perfectly accounts for this difference. Therefore it seems that the reaction rate of multidentate ligands cannot be accelerated by a previous fast co-ordination to the metal of an amino-group through a sort of anchimeric-assistance mechanism. Rather, the co-ordination to the metal of one or more nitrogen atoms makes the lone pair of the residual nitrogen less available for the electrophilic attack of the carbonyl, both for the electrophilic competition of the metal and for the reduced nucleophilicity of these residual nitrogen atoms.<sup>10</sup>

In keeping with the kinetic results, activation parameters indicate that a lower activation energy path is presented to bimolecular condensations. In fact, on proceeding from first- to second-order reactions, the expected higher enthalpy of activation is not compensated by those translational and rotational entropy factors which a monomolecular process should cancel out (Table 4).

It seems likely that the lack of a more favourable entropy of activation for the template reaction is the result of compensatory effects between  $\Delta S_{\text{tr.}}$  and  $\Delta S_e$ . Therefore in this template reaction a lower  $T\Delta S_{\text{tr.}}$  matches a larger  $T\Delta S_e$  as a result of perturbation from the optimum reaction geometry by the co-ordination of the functional groups to the metal. This perturbation can be clearly envisaged by (i) the necessity of a perpendicular alignment between the terminal nitrogen lone pair and the  $sp^2$  hybrid carbon during the nucleophilic attack; (ii) the intramolecular strain introduced by the condensation reaction between the co-ordinated ligands.

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