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NAD(P)H MODELS—XVII[1]

METAL ION CATALYZED REDUCTION OF IMINES BY 3,5-DIETHOXYCARBONYL 2,6-DIMETHYL-1,4-DIHYDROPYRIDINE (HANTZSCH ESTER)

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Abstract The reduction of imines by 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine, an NAD(P)H model, is catalyzed by Mg^{2+} ions Kinetic measurements of the reduction of a series of imines derived from substituted benzaldehydes, show a very small polar substituent effect ($\rho =$ 0 39) The results have been interpreted in terms of a mechanism involving a hydride transfer from the dihydropyridine derivative to an imine-Mg^{2+} ion complex

The biosynthesis of glutamate, tetrahydrobiopterin, tetrahydrofolate and 5,10-methylenetetrahydrofolate involves the NAD(P)H mediated enzymatic reduction of the C N bond Little or no information is available on the mechanistic details of these reactions In general, a hydride[3] transfer—from the reduced pyridine nucleotide coenzyme is assumed, and in case of the glutamate dehydrogenase reaction, catalysis by both, protons and zinc ions has been implicated[4] The postulate of electrophilic catalysis of the hydride-transfer step, in the reduction of the CO group, has received strong support from the X-ray data on lactate dehydrogenase,[5a] alcohol dehydrogenase[5b] and glyceraldehyde-3-phosphate dehydrogenase[5c,d] and from model studies.[6] In order to examine the potential role of electrophiles in the NAD(P)H-mediated enzymatic reduction of the $>$C-N-group, a study of the corresponding model reaction, namely the reduction of imines by 1,4-dihydropyridine derivatives[7] has been undertaken in this laboratory

Although two examples of the reduction of imines with Hantzsch ester have been reported in the literature,[8] these are characterized by drastic reaction conditions (refluxing phenetole) and low yields of the reduction products In contrast, the reduction of imines, in the presence of acids,[9] and of iminium and α,β-unsaturated iminium salts,[11] by 1,4-dihydropyridine derivatives, proceeds smoothly to give high yields of the corresponding amines It was therefore an interesting question whether the reduction of imines by 1,4-dihydropyridines could be catalyzed by Lewis acids, such as metal ions, and, if so, to investigate the role of the electrophilic catalyst We report here the results of Mg^{2+} ion catalysis of the reduction of imines (**1**) with 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester, **2**)

The choice of Mg^{2+} as the catalyst was influenced by the knowledge that Mg ions are (i) widely implicated in biological processes and (ii) capable of forming complexes (with organic ligands) which are soluble in a number of solvents and under a range of reaction conditions

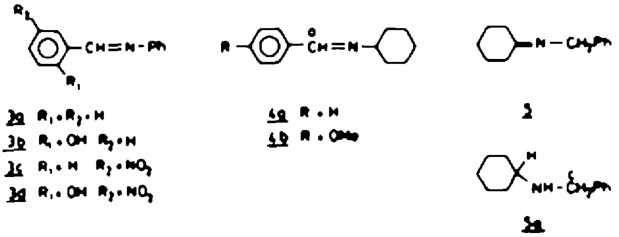
The potential catalytic influence of Mg^{2+} ions was examined by studying the reaction of a series of imines with Hantzsch ester, both in the absence and presence of a Mg salt The imines **3a–d**, **4a–c** and **5**-representing aryl and alkyl substitution at the C and N ends of the imine function—were refluxed with **2**, in THF, with or without $Mg(ClO_4)_2$, till the Hantzsch ester had been consumed (TLC) Upon working up the mixture, the reduction products (amines) were isolated and identified by comparison with authentic samples, which were prepared by $NaBH_4$ reduction of the starting imines (Experimental) The results are presented in Table 1 Comparison of the yields of the isolated amines (Table 1), when considered in conjunction with the time required for the reduction (disappearance of **2**), clearly indicates that in general Mg ions enhance the formation of the reduction products Although, the variable and in some cases modest yields of the isolated amines[12] prevented us from carrying out kinetic studies with these imines, the data in Table 1 suggest that the imines derived from benzaldehydes and anilines (**3a–d**) are intrinsically more reactive than the imines derived from either aliphatic amines (**4a–c**) or an aliphatic carbonyl compound (**5**) In the last mentioned two cases it is noteworthy that no reduction products could be observed in the absence of Mg^{2+} ions

It should be mentioned that decreasing the Mg^{2+} ion concentration by half, in a test case (**5**), did not influence the reaction

Having established that the reduction of the imine group by Hantzsch ester is catalyzed by Mg ions, we

1 **2**

Table 1. Influence of Mg^{2+} ions on the reduction of imines by Hantzsch ester (2). (THF, reflux) $[Imine] = [2] = [Mg^{2+}] = 0.100$ M



Imine	Yield of amine without Mg^{2+} reflux (hr)	(%)	Yield of amine with Mg^{2+} reflux (hr)	(%)
3a	24[a]	25	16	86
3b	[illegible]	[illegible]	16	[illegible]
3c	18	[illegible]	[illegible]	[illegible]
3d	18	[illegible]	[illegible]	[illegible]
4a	90	5	18	66
4b	90	b	90	55
4c	90	b	90	5
5	90	b	90	45

[a] Reduction carried out in phenetole (160°C)

[b] No amine could be detected in these reactions.

sought to examine the mechanism of this catalysis. In this connection, attempts were made to investigate the nature of the interaction between Mg^{2+} and the imines (substrates) or the amines (products). Spectral (NMR) studies to this end were, however, only modestly successful. Addition of $Mg(ClO_4)_2$ to solutions of the imines, in MeCN, gave no observable changes in their UV spectra. Analysis of the ^{1}H-NMR spectra of mixtures of Mg^{2+} and imines was subject to severe limitations due to both, insolubility of $Mg(ClO_4)_2$-imine complexes and line broadening of the chemical shift peaks. Influence of Mg^{2+} ions upon the chemical shifts of characteristic protons in **4a–c**, **5**, and **5a** is described in Table 2. The results suggest a weak coordination of the metal ion with the imines or the amine (**5a**), presumably via the N atom. Comparison of the maximum chemical shift displacements of the benzyl protons in **5** and **5a** suggests that, as expected, the amine complexes more strongly than the corresponding imine. This is in accord with the relative basicities of the nitrogen atom in the two systems.

In Liver alcohol dehydrogenase catalyzed reduction of aromatic aldehydes,[1] it is observed that—in contrast to their reduction with $NaBH_4$—the substituents exert a weak influence upon the rate of the reaction. These results have been explained on the basis of a mechanism which involves the polarization of the CO group by the essential Zn ion at the active site. If Mg ion catalysis of the non-enzymatic reduc-

Table 2. ^{1}H-NMR chemical shifts (δ) of relevant protons in **4a–c**, **5** and **5a**, upon addition of Mg^{2+}, in CD_3CN ([imine] or [amine] = 1.0 M)

Imine : Mg^{2+}	4a (H_a)	4b (H_a)	4c (H_a)	5 ($2H_b$)	5a ($2H_c$)
1 : 0	8.31	8.23	8.40	4.48	3.75
1 : 0.25	8.45	8.35	n.c.	4.66	4.01
1 : 0.50	n.c.	8.38	n.c.	4.59	4.18
1 : 0.75	a	a	a	a	4.18

n.c.: no change

a : accurate chemical shift assignment could not be made due to line broadening.

Table 3. Rates of reduction of imines **6a–f** by Hantzsch ester (**2**) in CH_3CN at 64.1 [Imine] = 0.040 M, [**2**] = 1.00 × 10^{-4} M, [Mg^{2+}] = 0.100 M

Imine	R	k_{obs} min^{-1}	k_H/k_D
6a	H	0.123 ± 0.003	4.28
6b	4-CH_3	0.145 ± 0.011	3.03
6c	4-Cl	0.113 ± 0.005	
6d	4-F	0.109 ± 0.005	3.76
6e	4-NO_2	0.089 ± 0.009	
6f	3-NO_2	0.062 ± 0.007	

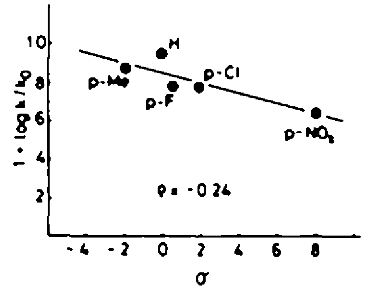


Fig. 1. Hammett plot for the reduction of $ArCH{-}NCH_2CH_2{-}C_5H_4N$ (**2**) by Hantzsch ester

tion of imines involves an analogous polarization of the imine function via metal coordination of the N—it would be expected that the reaction display a relative insensitivity to substituent effects.[14] An orientation study of several imines, designed to examine this aspect, indicated that the series of imines of general structure **6** (Table 3) was suitable for this purpose. Reduction of **6a–f** with Hantzsch ester (**2**), in THF, in the presence of $Mg(ClO_4)_2 \cdot (C_2H_5OH)_4$,[15] gave mixtures consisting of only oxidized **2** and the product amines (TLC). From these mixtures the latter amines (**7a–f**) could be isolated in 75–85% yield. The observed pseudo first order rate constants for the reduction of **6a–f** were measured by following the rate of disappearance of the Hantzsch ester. The results are summarized in Table 3. Also included in the latter are kinetic isotope effects for the reduction of **6a**, **6b** and **6d**. The results indicate that the reduction rate is not appreciably influenced by substituents; the maximum variation, that between **6a** and **6f**, being a factor of less than 3. Significantly, the rate decreases with the electron withdrawing character of the substituents and a Hammett plot (Fig. 1) gives a negative ρ value of −0.39. It is noteworthy, that in analogous reactions Mg ions retard the reduction of thiopivalophenone,[16] hexachloroacetone,[17] N-methylacridinium ion[18] and benzoylpyridine.[19]

DISCUSSION

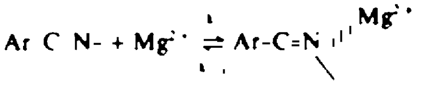
The results of the present study, plus the limited lit. reports,[8] indicate, that while Schiff's bases derived from benzaldehydes and aniline can be reduced, under severe conditions, by 1,4-dihydropyridine derivatives; in an analogous reaction, the imines, in general, are unaffected. The catalytic influence of acids on the reaction has been recognized[9] and N-alkylation of the imine group[10] has been shown to greatly facilitate its reduction. The latter may be regarded as the extreme form of electrophilic catalysis, where the electrophile is covalently linked to the substrate. The data presented in Table 1 demonstrate that, whereas, as expected, an intramolecular proton-donating substituent or a strong electron withdrawing group promotes the reduction reaction (compare **3a** with **3b**, **3c** and **3d**), addition of Mg ion results, in each case, in a distinct catalytic influence upon this process. This is reflected in the time required for complete oxidation of the Hantzsch ester, considered together with the yields of the isolated reduction products.

^1H NMR spectra of mixtures of imines and Mg^{2+} ions (Table 2) suggest that a weak complexation between the substrate and the metal ions may account for the small but definite chemical displacements of the characteristic protons. The difference between maximum δ-value displacements of the benzyl methylene protons in **5** and **5a** significantly point to a stronger complexation of Mg^{2+} ion with the amine, than with the imine. This is in line with the catalytic effect of the metal ions, since a relatively stronger complexation of the imine in the transition state,[20] than with the starting material,[21] would be expected to enhance the reduction process. The narrow range of Mg ion concentrations within which the ^1H NMR spectral studies of imine/amine-Mg^{2+} mixtures were possible, do not allow a specific description of the structure of the complexes. However, the curve of Mg^{2+}–**5a**, which points to a maximum chemical shift displacement at 0.5 equivs of Mg^{2+} ions, suggests a stoichiometry of 2:1 in the amine (**5a**)–Mg^{2+} complex.

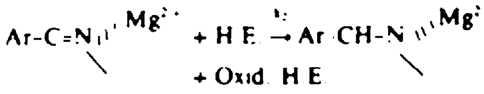
Two questions are of primary interest in connection with the metal-catalyzed reduction of imines. These are: (i) does the reduction proceed via single-step hydride transfer or a multiple-step process[22] and (ii) does the formal hydride transfer occur from the "free" dihydropyridine to the complexed substrate, or from the metal-complexed dihydropyridine to the free substrate.[19-21] Whereas the catalytic role of metal ions in the NADH-model mediated reduction of carbonyl compounds has been the subject of several investigations, only two communications, emerging from the current programme, describe the analogous metal-ion catalyzed reduction of imines.[4a,b] While the discussion of the hydride vs multiple-step mechanism of reduction with NADH-models continues,[22-24a] recent results on both, enzymatic[24b] and nonenzymatic[24c-f] reductions strongly favour the hydride transfer mechanism. It is also significant that the Mg^{2+} ion mediated reduction of N-methylacridinium salt has been interpreted in terms of a simple one-step hydride transfer.[18] In the present study the primary kinetic isotope effect points to the transfer of the H-nucleus in the rate-determining step (Table 3) and the overall results are consistent with a one-step process.

With respect to the second question, the rates of reduction of the imines **6a–f** throw light upon the mechanism of the catalytic process. The data in Table 3 show that the rate of reduction is relatively insensitive to substituents in the aromatic moiety and the observed trend indicates a lowering of the rate with electron-withdrawing substituents.

Whereas activation of the imine function by metal coordination of the N would be expected to suppress the influence of aryl substituents on the reduction reaction, the negative, albeit low ρ-value, of the Hammett plot points to the development of a very slight (if any) positive charge, in the transition state.[25] A two-step mechanism involving metal-complexation of the imine, followed by hydride transfer from the Hantzsch ester to the complexed imine, [eqs (i) and (ii)] allows a satisfactory rationalization of these results.


(i)

$$\mathrm{Ar{-}C{=}N{-}} + Mg^{2+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Ar{-}C{=}N}\cdots Mg^{2+} \qquad (i)$$


(ii)

$$\mathrm{Ar{-}C{=}N}\cdots Mg^{2+} + \mathrm{H.E.} \xrightarrow{k_2} \mathrm{Ar{\cdot}CH{-}N}\cdots Mg^{2+} + \mathrm{Oxid.\ H.E.} \qquad (ii)$$

The observed ρ value is composed of the sum of ρ values of the two steps. If k_{obs} is the observed rate constant, k_1/k_{-1} the equilibrium constant of the first step and k_2 the rate constant of the second step, then:

$$k_{obs} = \frac{k_1}{1 + k_{-1}}\, Ck_2 \quad \text{where C is a constant.}$$

If constants for the imine **6a** are denoted by suffix "0", then

$$(k/k_0)_{obs} = \frac{(k_1/1 + k_{-1})}{(k_{1\,obs}/1 + k_{-1\,obs})}\cdot\frac{Ck_2}{Ck_{2\,obs}} = \frac{k_1}{k_{1\,obs}}\cdot\frac{1 + k_{-1\,obs}}{1 + k_{-1}}\cdot\frac{k_2}{k_{2\,obs}}$$

$$\log (k/k_0)_{obs} = \log \frac{k_1}{k_{1\,obs}} + \log \frac{1 + k_{-1\,obs}}{1 + k_{-1}} + \log \frac{k_2}{k_{2\,obs}}$$

if $k_{-1}, k_{-1\,obs} \gg 1$ (equilibria are established rapidly)

$$\log (k/k_{obs}) = \log \frac{k_1}{k_{1\,obs}} - \log \frac{k_{-1}}{k_{-1\,obs}} + \log \frac{k_2}{k_{2\,obs}}$$

$$(\rho\sigma)_{obs} = (\rho\sigma)_{complexation} - (\rho\sigma)_{decomplexation} + (\rho\sigma)_{reduction}$$

Assuming σ is the same for all reactions

$$\rho_{obs} = (\rho_{complex} - \rho_{decomplex}) + \rho_{reduc} = \rho_1 + \rho_2$$

It is obvious that polar effects of substituents in eqns (i) and (ii) would have opposite effects and the relative magnitudes of ρ_1 and ρ_2 would determine whether the observed ρ would be positive or negative. The ρ value of -0.39 indicates that the transition state hardly possesses a polar character. In fact, ρ values of this magnitude are found for cyclic transition states, such as for the Claisen-rearrangement of p-substituted cinnamyl p-tolyl ethers.[26] The significance of the low negative ρ value in the reduction of imines lies in the fact that it makes the two-step reaction an obligatory mechanism. Furthermore, this obligatory mechanism has to involve the reduction of a metal-ion complexed imine moiety by the free Hantzsch ester.

In connection with the present study it is interesting to note that the Mg ion catalyzed reduction of substituted α, α, α,-trifluoroacetophenones exhibits a substitution dependency with a reactivity constant of $\rho = 1.29$.[23e] Although the latter value can, in principle, be accounted for by a mechanism such as the one proposed for the reduction of the imines, it is, however, not in disagreement with the alternative mechanistic proposal involving a hydride transfer from a metal complexed NAD(P)H model. In conclusion it can be stated that Mg ions catalyze the reduction of imines by Hantzsch ester and that the mechanism of catalysis involves the polarization of the C=N bond by complexation of the imine N with metal ions.

EXPERIMENTAL

Materials. Analytical grade (Merck) MeCN, employed as a solvent, was stored over mol sieves 3 Å. For kinetic measurements the solvent was distilled over P_2O_5. Hantzsch ester **2**,[27] **3a**,[28] **4a**,[27] **4b**,[10] **4c**,[10] **5**[29] and magnesiumhexkisethanol perchlorate[11] were synthesized according to lit. procedures.

Imines **3b–d**

General procedure. A mixture of stoichiometric amounts of aniline and the substituted benzaldehyde in EtOH (2 ml/gm of reactants) was stirred overnight at room temp. The crystalline product thus formed was filtered off and recrystallized from dry EtOH to give the pure imine. Characteristic data is presented in Table 4.

Imines **6a–f**

General procedure. A mixture of stoichiometric amounts of 2-(2-aminoethyl)pyridine and the substituted benzaldehydes in ether (5 ml/gm of reactants) was stirred overnight at room temp. The imines **6a**, **6c** and **6d** were isolated and purified by separating the ether layer from the water (product during the reaction), evaporating the ether and distilling (short-path) the residue. The fraction which came over at 140–160 (10^{-2} torr) was collected. In case of imines **6b**, **6e** and **6f** an ether insoluble product was formed at the end of the reaction which was filtered off and recrystallized from dry EtOH to give the pure imines (Table 4).

Table 4. Characteristic data on imines (**3a–d**, **6a–f**)

Imine	Yield	m.p./b.p.	δ ($CDCl_3$) <u>CH</u>=N-
<u>3b</u>	85%	52-53°	8.38 s
<u>3c</u>	87%	68-69°	8.42 s
<u>3d</u>	79%	135°	8.70 s
<u>6a</u>	95%	150°/.01 mm	8.20 s
<u>6b</u>	93%	62-63°	8.27 s
<u>6c</u>	88%	54-55°	8.24 s
<u>6d</u>	85%	29-30°	8.12 s
<u>6e</u>	92%	107-108°	8.26 s
<u>6f</u>	95%	83-84°	8.38 s

Reduction of imines—by sodium borohydride

General procedure. A mixture of the imine (2 mmol) and $NaBH_4$ (equal amount in weight) in EtOH water (95:5; in case of **3a–d** and **6a–f**) or MeOH (in case of **4a–c**) was stirred overnight at room temp. The mixture was diluted with water or allowed to react with dil HCl (10%), followed by 10% Na_2CO_3 (till pH 10–11), and extracted with $CHCl_3$. The $CHCl_3$ soln was filtered through a $CHCl_3$-wetted filter paper and evaporated to yield the corresponding amines (**5a**, **7a–f**, **8a–d**, **9a–c**) as oils. Yields varied from 60–95%, except in the case of the amine from **3d**, where a low yield (40%) was observed due to difficulty in extraction of the product from the water layer (Table 5).

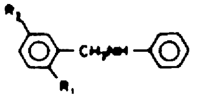
Reduction of imines with Hantzsch ester (**2**)

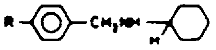
A soln of the imine (2 mmole) and **2** (2 mmole) in THF was flushed with dry N_2 prior to refluxing and then heated to reflux under N_2, till the Hantzsch ester had been consumed (TLC). The mixture was subsequently worked up as follows.

Amines **5a**, **9a,b**. After evaporation of the THF, a 1 M NaOH was added (pH 10–11) and the mixture extracted with ether. The organic layer was separated, dried over Na_2SO_4. Evaporation of the ether yielded mixtures of the amines (**5a**, **9a**, **b**) and oxidized Hantzsch ester which were analyzed by ^1H NMR spectroscopy.

Amines **7a–f**. After cooling the mixture to room temp.

Table 5. Characteristic NMR ($CDCl_3$) data on amines (**5a**, **7a–f**, **8a–d** and **9a–c**)





8a $R_1 = R_2 = H$
8b $R_1 = OH$, $R_2 = H$
8c $R_1 = H$, $R_2 = NO_2$
8d $R_1 = OH$, $R_2 = NO_2$

5a $R = H$
9a $R = OMe$
9b $R = NO_2$

Amine	δ Ar<u>CH</u>$_2$ ($CDCl_3$)	Amine	δ Ar<u>CH</u>$_2$	δ Arom. (H)
<u>8a</u>	4.37 s	<u>5a</u>	3.81 s	7.08-7.45 m
<u>8b</u>	4.25	<u>9a</u>	3.75 s[a]	6.83, 7.25 (A_2B_2, J=9)
<u>8c</u>	4.40 s	<u>9b</u>	3.94 s	7.52, 7.64 (A_2B_2, J=8)
<u>8d</u>	4.52 s			

[a] The OMe signal overlaps that of the CH_2.

Amine	δ N<u>H</u>	δ Pyr <u>CH</u>$_2$<u>CH</u>$_2$ N	δ N-<u>CH</u>$_2$Ar
<u>7a</u>	2.07	2.98	3.78
<u>7b</u>	2.38	3.08	3.82
<u>7c</u>	2.09	3.05	3.85
<u>7d</u>	2.20	2.99	3.75
<u>7e</u>	2.18	3.00	3.90
<u>7f</u>	2.12	3.09	3.98

about 10 g silica (per mmole of imine) were added and the resulting slurry was evaporated to dryness The residue was brought on a silica column and eluted consecutively with diethyl ether (150–200 ml), and MeOH (100–150 ml) The ether layer contained the oxidized Hantzsch ester and traces of 2 The MeOH fraction was evaporated to dryness, the residue dissolved in 30 ml CHCl$_3$ plus 20 ml 25% ammonia (per mmole of starting imine) The water layer was extracted with CHCl$_3$ (3 ×), the combined extracts dried by filtering through a CHCl$_3$-wetter filter paper and the solvent removed by evaporation, whereupon the product amines were obtained The purity was checked by comparison with the authentic samples (IR, ^{1}H NMR and TLC)

^{1}H NMR *spectral measurements of imine/amine*-Mg^{2+} *mixtures* NMR spectra were recorded of 1.0 M solns of **4a–c**, **5** and amine **5a** in CD$_3$CN, containing varying amounts of Mg(ClO$_4$)$_2$(EtOH)$_6$ The signal corresponding to CHD$_2$CN, which is present in small amounts in deuterated acetonitrile, was fixed at 1.90 ppm (relative to TMS) and employed as reference for the measurements Since no change in the spectrum was observed when a sample containing 1.0 M of **5** and 0.5 M of Mg(ClO$_4$)$_2$(EtOH)$_6$, in CD$_3$CN, was diluted to twice the original volume with CD$_3$CN, it was assumed that varying the ethanol concentration did not significantly affect the chemical shifts

Kinetic measurements To 7 ml of dry, argon-flushed MeCN, in a 10 ml measuring flask was added 0.40 ml of a 1 M soln of one of the imines (**6a–f**) and 1.00 ml of 1 M Mg(ClO$_4$)$_2$ and the volume made up to 10 ml with dry MeCN Both, the reference and the measuring cells were filled, under argon, with 2.5 ml of the latter mixture, and the cells placed in a thermostated (64.1° ± 0.1°) cell holder of a Cary-17 UV spectrometer After waiting (± 30 min) till the cell-contents had reached 64.1°, 10 μl of a soln containing 0.02 M Hantzsch ester (2) (in MeCN), containing about 0.2 M Mg(ClO$_4$)$_2$ in order to increase the solubility of 2 was injected into the measuring cell The extinction at 370 nm (in the case of **6e** and **6f** at 395 nm) was followed for at least three half-lives Subsequently, a second portion of 2 10 μl) was added to the measuring cell and the extinction followed once again This was repeated However, no significant change in of the half-lives was observed for 3–4 injections Pseudo first order rates were calculated from the extinction data (Table 3)

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