Bis(salicylaldehyde)ethylenedi-iminecobalt(II)-catalysed Oxidation of Aromatic Amines with Oxygen

Francesca Benedini, Guido Galliani, Micaela Nali, Bruno Rindone,* and Stefano Tollari
Dipartimento di Chimica Organica e Industriale dell'Università, Via Venezian 21, 20133 Milano, Italy

N-n-Butylanilines undergo *N*-dealkylation to give a primary amine and butyraldehyde by oxidation with oxygen in the presence of bis(salicylaldehyde)ethylenedi-iminecobalt(II) (Co^{II}salen) as catalyst. High conversions are obtained with high catalyst concentrations and low [substrate]/[catalyst] ratios (*r*). Inspection of the effect of catalyst and substrate concentrations on initial reaction rates (v_{in}) shows poor sensitivity to the electronic effect of the nuclear substituent. Some anilines give azo derivatives at a lower rate in the same conditions.

Much attention has been given to selective oxidations of organic compounds with dioxygenmetal complexes[1] and metal-ion activation of oxygen[2] since these reactions could mimic some biological oxidations.[3,4] Oxidases and oxygenases catalyse oxidation reactions in living organisms.[5] These enzymes contain a transition metal ion which plays an important role in activating molecular oxygen and/or a substrate.[6]

Cobalt(II)–Schiff's base complexes (Co^{II}–SB) behave as oxygen carriers both in organic solvents[7] and in water.[8] Four-co-ordinate Schiff's base complexes of cobalt(II) in the presence of a slight excess of a co-ordinating base form low-spin, five-co-ordinate base adducts.[3] Upon co-ordination of the cobalt(II) complex to dioxygen,[9] partial electron transfer from cobalt to oxygen occurs ranging from 0.1 to 0.8 e^- depending on the ligand field surrounding the cobalt ion.[10] A paramagnetic 1:1 'superoxo complex' is formed, in which an unpaired electron is delocalised on a superoxide-like oxygen [equation (1)]. The spin-pairing model accounts for this.[11] In most cases the superoxo complex is in equilibrium with the diamagnetic 2:1 'μ-peroxo complex' (Scheme 1).

It has been noted that if K_{eq} for the formation of the superoxo complex is small, only the reaction to give this complex is observed and that, since a charge separation is present in the superoxo complex, this is stabilised by the use of polar solvents.[12]

Oxgenated Co^{II}–SB complexes have been used in oxidations of organic substrates such as hindered phenols,[13a,l] quinones,[14] quinone methides,[15] *p*-nitrophenylhydrazones,[16] and sulphides.[17] It has been suggested that the superoxo complex is the active species in these oxidations.[18] This is supposed to act as a hydrogen-atom abstractor, for example from a 2,4,6-trisubstituted phenol giving a phenoxyl radical which is converted into products.[19]

These observations prompted us to study the oxidation of aromatic amines with Co^{II}–SB–O_2 complexes. In fact, aromatic amine oxidation with oxygen and a catalyst could mimic the detoxification of the hepatic cell from nitrogen-containing foreign compounds.[20]

Results

Product Studies.—We oxidised 15 *N*-n-butylanilines (**1**)—(**15**) with oxygen in the presence of the complex bis(salicylaldehyde)ethylenedi-iminecobalt(II) (Co^{II}salen) (**16**). In preliminary product studies the substrate concentration was 10^{-2}M and the catalyst concentration was 10^{-3}M. Hence, the [substrate]/[catalyst] ratio (*r*) was 10. The reaction was performed at reflux temperature in methanol for 24 h under a stream of oxygen. Under these conditions, compound (**2**) gave mostly polymeric material. Then its reaction time was 2 h. The reaction mixtures were analysed by g.l.c.–m.s., then acetylated with acetic anhydride and analysed again by g.l.c.–m.s. In all the experiments only the acetylated starting amine, the acetylated product amine, and butyraldehyde were present. In the case of the amine (**3**), 3% 4,4′-dimethylazobenzene (**23**) was also found. No other product was detected by g.l.c. or by silica gel t.l.c., and in particular products deriving from nuclear methoxylation were not present. In order to obtain reaction yields the acetylated mixture was chromatographed over silica gel and azo derivatives, acetylated starting material, and the product primary acetamide were separately collected and weighed. The results are shown in the Table. The apparent loss of material is attributable to the fact that some material remained bound to the tarry catalyst residue after the reaction. Moreover, impure chromatographic fractions were not considered in yield calculations.

Control experiments showed that no reaction occurred when the substrates were treated with oxygen under the same reaction conditions except for the absence of the catalyst or in the presence of the uncomplexed cobalt(II) ion as $CoCl_2$.

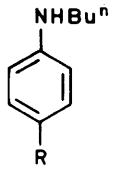
Table. Preparative results in the oxidation of $XC_6H_4NHBu^n$ (10^{-2}M) in methanol with oxygen in the presence of Co^{II}salen (10^{-3}M) at reflux temperature for 24 h (for X = 4-OMe; 2 h)

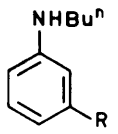
X	Starting material	*N*-Dealkylation (%)
4-OMe	52	21
4-NHAc	52	24
4-OC_6H_5	69	23
4-Me	74	22
4-C_6H_5	56	33
4-F	51	18
H	72	21
4-Cl	55	29
4-NO_2	85	2
3-Me	70	19
3-OMe	51	26
3-C_6H_5	52	31
3-F	53	22
3-Cl	54	28
3-NO_2	78	8

$$L_5\text{–}Co^{II} + O_2 \rightleftharpoons L_5\text{–}Co^{III}(O_2^{-\cdot}) \quad (1)$$

$$L_5\text{–}Co^{III}(O_2^{-\cdot}) + L_5\text{–}Co^{II} \rightleftharpoons L_5\text{–}Co^{II}\text{–}O\text{–}O\text{–}Co^{II}\text{–}L_5 \longleftrightarrow L_5\text{–}Co^{III}\ {}^{-}O\text{–}O^{-}\ Co^{III}\text{–}L_5 \quad (2)$$

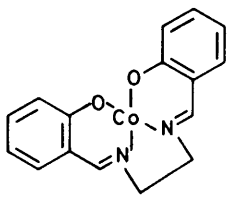
Scheme 1.



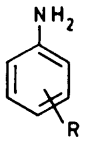


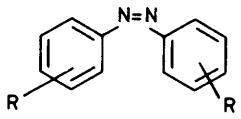
(1) R = H
(2) R = OMe
(3) R = Me
(4) R = NHAc
(5) R = OPh
(6) R = Ph
(7) R = F
(8) R = Cl
(9) R = NO_2

(10) R = OMe
(11) R = Me
(12) R = Ph
(13) R = F
(14) R = Cl
(15) R = NO_2



(16)





(17) R = 4-Me
(18) R = 4-F
(19) R = 4-Ph
(20) R = 4-Cl
(21) R = 2-OH
(22) R = 4-OMe

(23) R = 4-Me
(24) R = 4-F
(25) R = 2-OH

The formation of the azo derivative (**23**) suggested a further oxidation of *p*-toluidine (**17**) formed in the reaction of *N*-n-butyl-*p*-toluidine (**3**). In fact, the oxidation of *p*-toluidine (**17**) and of *p*-fluoroaniline (**18**) (10^{-2}M) in methanol with oxygen for 25 h with *r* 10 gave largely unchanged starting material, together with 11 and 5% of the corresponding azo derivatives (**23**) and (**24**). Under these conditions, *p*-phenylaniline (**19**) and *p*-chloroaniline (**20**) did not react, and *o*-aminophenol (**21**) yielded 61% of the corresponding azo derivative (**25**), together with much polymeric material. This azo derivative was obtained in 44% yield by performing the same reaction at room temperature with *r* 5. These data were obtained after chromatographic separation of the reaction mixtures.

These data suggested that aromatic primary amines are oxidised by this catalytic system at a slower rate than aromatic secondary amines.

The experiments performed with *o*-aminophenol also showed the strong influence of the value of *r* in the reaction. In fact, a good reactivity at room temperature was obtained using a value of *r* lower than that used in the experiment performed in refluxing methanol. Moreover, the formation of polymeric materials was minimised at room temperature.

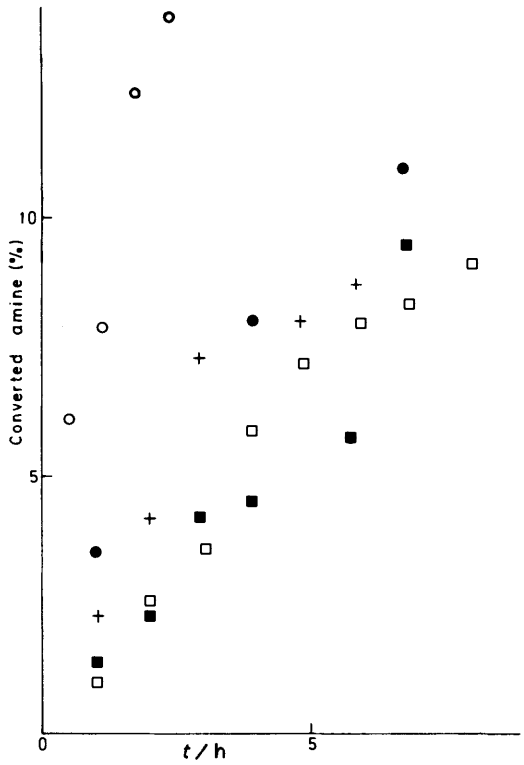


Figure 1. Converted amine (%) against time (h) in the reaction of 4-$XC_6H_4NHBu^n$ (10^{-1}M) with oxygen in refluxing methanol in the presence of Co^{II}salen (10^{-3}M) (*r* 100): ○, X = OMe; ●, X = Me; +, X = F; □, X = OPh; ■, X = Ph

These observations allowed the optimisations of the reaction yield in the *N*-dealkylation of *N*-n-butyl-4-phenylaniline (**6**) and *N*-n-butyl-4-fluoroaniline (**7**) avoiding either extensive resinification or further reaction of the product primary amine. These substrates gave, after 8 h reaction in refluxing methanol, the corresponding primary amines in 69 and 55% yield, respectively, using *r* 5. These data indicate that the reaction shows preparative value.

In most oxidations, the total amount of product produced exceeds the concentration of Co^{II}salen, and this implies a catalytic role for the complex.

Rate Studies.—In order to obtain quantitative data related to the sensitivity of the reaction to the electronic effects deriving from the substrate amine structure, substrates (**2**), (**3**), and (**5**)—(**7**) (10^{-1}M) in methanol were oxidised with oxygen in the presence of catalyst (10^{-3}M) (*r* 100). Samples of the reaction mixture were taken at fixed time intervals and were analysed by g.l.c. The starting amine, butyraldehyde, and the product primary amine were the only products. Their concentration was evaluated against a reference curve (Figure 1).

Poor sensitivity to electronic effects was noted, and no satisfactory correlation between the initial rates (v_{in}) thus obtained and the electronic parameters of the nuclear substituents appeared.

Further experiments were performed with varying concentrations of substrates (**6**) and (**7**) and catalyst, confirming the preparative value of the catalytic oxidation, if the appropriate

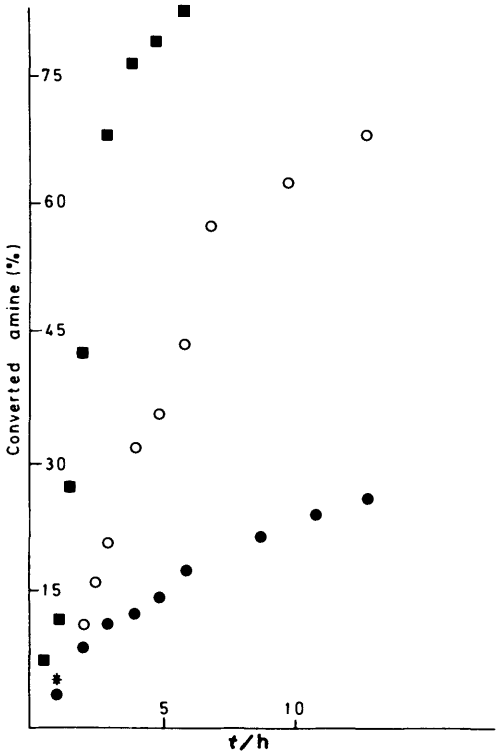


Figure 2. Converted amine (%) against time (h) in the reaction of 4-$PhC_6H_4NHBu^n$ (**6**) (5×10^{-2}M) with oxygen in refluxing methanol in the presence of Co^{II}salen: ■, 10^{-2}M; ○, 5×10^{-3}M; ●, 10^{-3}M

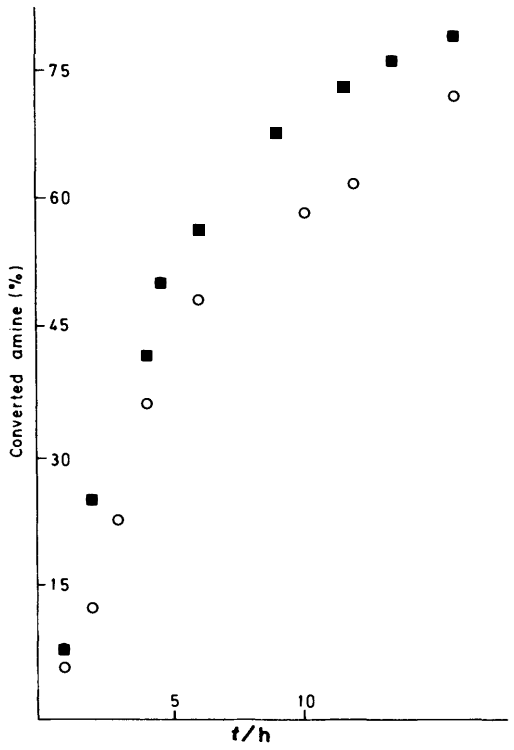


Figure 3. Converted amine (%) against time (h) in the reaction of 4-$FC_6H_4NHBu^n$ (**7**) (5×10^{-2}M) with oxygen in refluxing methanol in the presence of Co^{II}salen: ■, 10^{-2}M; ○, 5×10^{-3}M

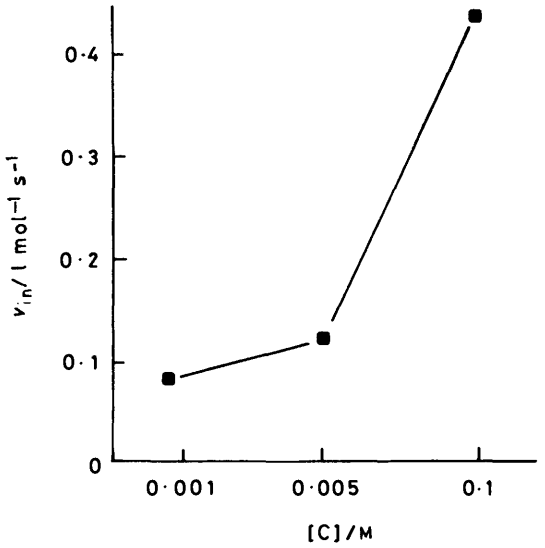


Figure 4. v_{in} against catalyst concentration [C] in the oxidation of 4-$PhC_6H_4NHBu^n$ (**6**) (5×10^{-2}M) with oxygen in refluxing methanol in the presence of Co^{II}salen

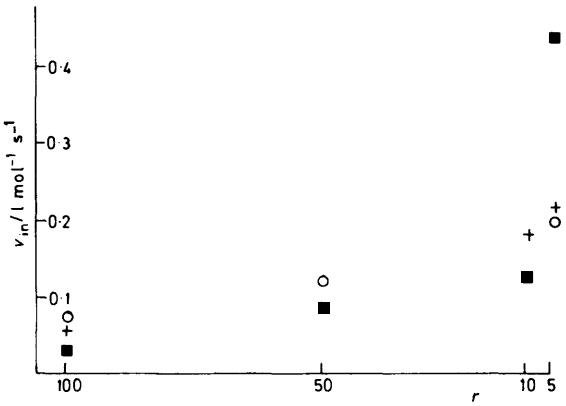


Figure 5. v_{in} against r in the oxidation of 4-$XC_6H_4NHBu^n$ with oxygen in refluxing methanol in the presence of Co^{II}salen: ■, X = Ph; ○, X = OMe; +, X = F

catalyst concentration and r value is used (Figures 2 and 3). In the oxidation of (**2**), v_{in} was approximately linearly related to the concentration of the substrate.

A non-linear dependence of the initial rate (v_{in}) of the oxidation of 5×10^{-2}M (**6**) from the concentration of the catalyst is shown in Figure 4.

A roughly linear dependence of v_{in} on r over a wide interval ranging from r 5 to 100 for different concentrations of substrates (**2**), (**6**), and (**7**) and catalyst is shown in Figure 5.

The increase of v_{in} obtained with decreasing values of r even if the concentration of the substrates is high suggests that maximum catalytic efficiency is obtained with a combination of low values of r and high concentrations of the catalyst. No simple kinetic expression could be obtained from these data.

Discussion

The mechanism of the oxidation of phenolic compounds and of *p*-nitrophenylhydrazones with Co^{II}–SB–O_2 complexes has been suggested to occur through hydrogen abstraction from the X–H group (X = O, N) effected by the superoxo complex L_5–$Co^{III}(O_2^{-\bullet})$. A steady-state approximation for the con-

centration of the superoxo complex was applied since its concentration was estimated to be very low.[13f]

In the case of aromatic secondary amines the equilibrium formation of the five-co-ordinate complex [equation (3)], of the superoxo complex [equation (4)], and of the μ-peroxo complex [equation (5)][21] may be thought to occur *via* the intervention of the substrate amine itself as the basic ligand necessary for the co-ordination of oxygen to cobalt (Scheme 2).

The formation of the μ-peroxo complex [equation (5)], although discouraged by the polarity of the solvent, is likely to occur, but does not cause inactivation of the catalyst since it has been pointed out that μ-peroxo species undergo either slow heterolytic dissociation leading to mononuclear Co^{III} species or fast decomposition to Co^{II} species with reductive elimination of oxygen,[22] thus restoring the Co^{II}–SB complex. In fact, a Co^{II}–SB catalyst has been demonstrated to be able to perform *ca.* 70 turnovers in the oxidation of hindered phenols before being inactivated by oxidation of the organic ligand.[13a]

The Co^{II}salen-catalysed oxidation of aromatic amines with oxygen is slower than the above reported oxidation of phenols under comparable conditions. Moreover, the higher temperatures required for the oxidation of aromatic amines increase the influence of the competing oxidation of the organic ligand with the resulting inactivation of the catalyst, lowering the catalytic efficiency of the whole process.

The *N*-dealkylation of an aromatic amine has been reported[23] to occur when an arylalkylamine or a dialkylarylamine is oxidised to an aminiumyl radical (**27**) which undergoes fast loss of a proton from the carbon α to nitrogen to give a carbon radical (**28**). This is further oxidised to a cation (**29**), which solvolyses to the *N*-dealkylated product and an aldehyde. This mechanism is shown in Scheme 3 for an aromatic secondary amine. *N*-Dealkylation could also derive from the direct formation of the radical (**28**) through hydrogen-atom abstraction. This was noted for the oxidation of some *NN*-dimethylanilines with the reagent Fe^{II}–H_2O_2.[24]

In this case it can be suggested that the superoxo complex converts the substrate into a radical by hydrogen abstraction. This radical could be either the amino radical (**26**) or the α-arylalkylamino radical (**28**). Reactions with this as the rate-determining step exhibited low sensitivity to electronic effects,[25] as shown by this Co^{II}–SB-catalysed oxidation. Both radicals are in acid–base equilibrium with the aminiumyl radical (**27**), thus explaining the analogy with oxidation reactions occurring *via* this intermediate.[23] This equilibrium is likely to occur in reaction conditions containing the Co^{III} species with Lewis acid character. A further facile oxidation step could give rise to the cation (**29**). This oxidations occurs readily with Cu^{2+} or Fe^{3+},[26] and is then likely to occur with these Co^{III} species.

The hydroperoxocobalt(III) species (**30**) arising from the hydrogen transfer has been suggested[13a] to regenerate the five-co-ordinate complex and to give the hydroperoxyl radical $HO_2^{\bullet}$ which rapidly disproportionates to hydrogen peroxide and oxygen.

Preliminary e.s.r. data obtained from the system containing *p*-anisidine, Co^{II}salen, and oxygen suggest the intermediate formation of an amino radical.[27]

Studies are in progress in order to elucidate the kinetics of the activation and the regeneration steps which are correlated with the catalytic activity of Co^{II}salen in this reaction.

$$Co^{II}salen + Ar\text{–}NH\text{–}CH_2\text{–}Pr \rightleftharpoons (Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{II}salen \quad (3)$$

$$(Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{II}salen + O_2 \rightleftharpoons (Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{III}salen(O_2^{-\bullet}) \quad (4)$$

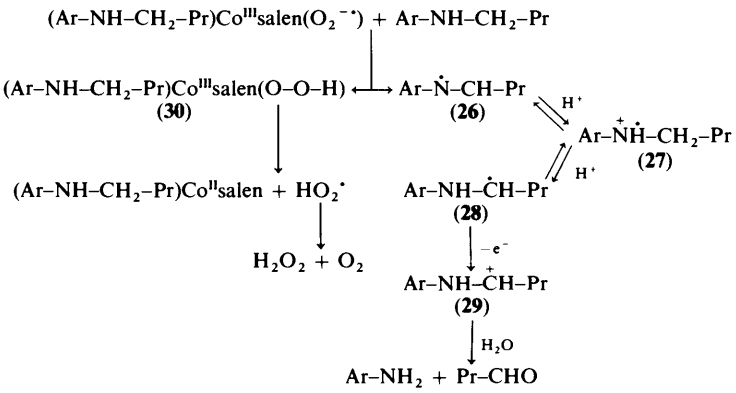
$$(Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{III}salen(O_2^{-\bullet}) + (Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{II}salen \rightleftharpoons (Ar\text{–}NH\text{–}CH_2\text{–}Pr)Co^{II}salen\text{–}O\text{–}O\text{–}Co^{II}salen(Ar\text{–}NH\text{–}NH_2\text{–}Pr) \quad (5)$$

Scheme 2.

Experimental

G.l.c.–m.s. was performed with a Varian Mat 1120 instrument equipped with a 2.5% SE 30 on Chromosorb W glass column. Quantitative g.l.c. measurements were performed using a Varian VISTA 6000 instrument equipped with a 2.5 m × 0.3 in glass column filled with 2.5% SE 30 on Chromosorb W, carrier gas nitrogen 30 ml min^{-1}, injection temperature 250 °C, column temperature 100—220 °C, flame ionisation detector temperature 250 °C, and integrating the peaks with a Varian 4270 instrument by comparison with reference mixtures. Co^{II}salen was from Merck.

Preparation of N-*n-Butylanilines.*—A 10^{-1}M solution of the appropriate aniline in benzene was added to an equimolecular amount of butyric anhydride and refluxed for 2 h. The resulting solution was evaporated under reduced pressure and the residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution, then with water, dried (Na_2SO_4), and evaporated under reduced pressure. The amide thus obtained was dissolved in dry tetrahydrofuran up to a 10^{-1}M final concentration, and an equimolecular amount of lithium aluminium hydride was added and the mixture was refluxed for 24 h. Excess of hydride was eliminated, the suspension was washed with saturated aqueous ammonium



Scheme 3.

chloride solution, then with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a residue which was dissolved in chloroform and chromatographed over silica gel (*R* 100) eluting with chloroform to obtain the *N*-n-butylaniline in pure state.

Oxidation of the Substrates.—A methanol solution (100 ml) of the substrate amine and Co^{II}salen at the appropriate concentrations was refluxed under an oxygen stream. After the appropriate period, the mixture was analysed by g.l.c.–m.s., then the solvent was evaporated under reduced pressure, and the residue was treated with acetic anhydride (2 ml) and left overnight at room temperature. The resulting solution was evaporated to dryness under reduced pressure and the residue was again analysed by g.l.c.–m.s. For preparative purposes, the residue was chromatographed over silica gel G (Merck; 0.05—0.2) (*R* 100) eluting with chloroform (100 ml) and 7:3 chloroform–ethyl acetate (50 ml fractions). The first eluant eluted the azo derivative, the second eluant eluted the acetamide. The fractions were assayed by silica gel t.l.c. eluting with chloroform and fractions containing the same component were collected, evaporated under reduced pressure, and weighed. In control experiments, the reactions were performed in the absence of the catalyst or $CoCl_2$ was used instead of Co^{II}salen.

Kinetic Experiments.—A methanol solution (100 ml) containing the required amount of substrate and catalyst was taken at reflux temperature under a stream of oxygen and samples therefrom were taken at time intervals and monitored by gas chromatography.

v_{in} was obtained by calculating the slope at zero time from a curve showing the amounts of converted amine against time.

Acknowledgements

We thank the Italian C.N.R. (Progetto Chimica Fine e Secondaria) for financial support.

References

1 Proceedings of the First International Symposium on Oxygen Activation and Selective Oxidation Catalysis by Transition Metals, *J. Mol. Catal.*, 1980, **7**.
2 T. G. Spiro, 'Metal Ion Activation of Dioxygen,' Wiley, New York, 1980.
3 F. Basolo. B. M. Hoffmann, and J. A. Ibers, *Acc. Chem. Res.*, 1975, **8**, 384.
4 R. D. Jones, D. A. Summerville, and F. Basolo, *Chem. Rev.*, 1979, **79**, 139.
5 T. Matsuura, *Tetrahedron*, 1977, **33**, 2869.
6 O. Hayaishi, 'Molecular Mechanism of Oxygen Activation,' Academic Press, New York, 1972.
7 L. H. Vogt, Jr., H. M. Faigenbaum, and S. E. Wiberley, *Chem. Rev.*, 1963, **63**, 269.
8 A. E. Martell, *Acc. Chem. Res.*, 1982, **15**, 155.
9 R. S. Drago, *Inorg. Chem.*, 1979, **18**, 1408.
10 B. S. Tovrog, D. J. Kitko, and R. S. Drago, *J. Am. Chem. Soc.*, 1976, **98**, 5144.
11 B. B. Corden and R. S. Drago, *Acc. Chem. Res.*, 1980, **13**, 353.
12 D. V. Stynes, H. C. Stynes, J. A. Ibers, and B. R. James, *J. Am. Chem. Soc.*, 1973, **95**, 1142.
13 (*a*) A. Zombeck, R. S. Drago, B. C. Corden, and J. H. Gaul, *J. Am. Chem. Soc.*, 1981, **103**, 7580; (*b*) M. Matsumoto and K. Kuroda, *Tetrahedron Lett.*, 1981, **22**, 4437; (*c*) A. M. McKillop and S. J. Ray, *Synthesis*, 1977, 847; (*d*) T. J. Fullerton and S. P. Ahern, *Tetrahedron Lett.*, 1976, 139; (*e*) A. Nishinaga, Y. Watanabe, and T. Matsuura, *ibid.*, 1974, 1291; A. Nishinaga, H. Tomita, and T. Matsuura, (*f*) *ibid.*, 1979, 2893; (*g*) 1980, 1261; (*h*) p. 2833; A. Nishinaga, T. Shimizu, and T. Matsuura, (*i*) *ibid.*, p. 1265; (*j*) 1981, 5293.
14 A. Nishinaga, H. Tomita, and T. Matsuura, *Tetrahedron Lett.*, 1980, **21**, 4853.
15 A. Nishinaga, H. Tomita, Y. Tarumi, and T. Matsuura, *Tetrahedron Lett.*, 1980, **21**, 4849.
16 A. Nishinaga, H. Tomita, M. Oda, and T. Matsuura, *Tetrahedron Lett.*, 1982, **23**, 339.
17 T. Numata, Y. Watanabe, and S. Oae, *Tetrahedron Lett.*, 1978, 4933.
18 V. M. Kothari and J. J. Tazurma, *J. Catal.*, 1976, **41**, 180.
19 A. Nishinaga, K. Nishizawa, H. Tomita, and T. Matsurra, *J. Am. Chem. Soc.*, 1977, **99**, 1287.
20 J. W. Bridges, J. W. Gorrod, and D. V. Parke, 'Biological Oxidations of Nitrogen in Organic Molecules,' Taylor and Francis, London, 1972.
21 R. G. Wilkins, *Adv. Chem. Ser. No 100*, 1971, 111.
22 S. Fallab, P. H. Hunold, M. Maeder, and P. R. Mitchell, *J. Chem. Soc., Chem. Commun.*, 1981, 469; R. P. Hanzlik and D. Williamson, *J. Am. Chem. Soc.*, 1976, **98**, 6570.
23 G. Galliani, B. Rindone, and P. L. Beltrame, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1803; G. Galliani and B. Rindone, *J. Chem. Res.*, 1980 (*S*) 178; (*M*) 2524.
24 G. Galliani and B. Rindone, *Gazz. Chim. Ital.*, 1983, **113**, 207.
25 J. R. Lindsay Smith, International Symposium on Activation of Dioxygen Species and Homogeneous Catalytic Oxidations, Galzignano, 1984.
26 F. Minisci, personal communication.
27 F. Morazzoni and F. Porta, unpublished work.

Received 25*th June* 1984; *Paper* 4/1093