
**COMPUTER SIMULATION OF INHIBITOR ACTION ON SINGLET
SUBSTRATE OXIDATION***

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The new mechanism recently proposed for reactions of dioxygen with organic substrates postulates that all reactions of dioxygen are catalyzed by metal ions, sometimes even in trace concentrations. Inhibition in terms of this mechanism is interpreted as being due to the formation of catalytically inactive complexes of catalyst with inhibitor. Kinetic consequences of this mechanism were simulated on a computer as a function of various parameters, and compared with experimental results. It is shown that the new mechanism accounts for all experimentally observed inhibition effects, including those which are considered as proof of a chain mechanism.

The effect of an inhibitor on an oxidation reaction is to decrease the reaction rate, to lengthen the induction period¹, and to reduce the quantum yields². According to the free radical chain mechanism, inhibition is due to the reaction of the inhibitor with propagating radicals, and thus to the breaking of the reaction chains¹. A necessary consequence of this mechanism is the consumption of inhibitor. The recently proposed non-radical mechanism of oxidation^{3,4} implies an interpretation of inhibition along completely different lines.

The mechanism is based on experimental studies of the oxidation of sulphite⁵, benzaldehyde^{6,7}, and ascorbic acid⁸⁻¹¹ by dioxygen. The main conclusions derived from these studies are as follows:

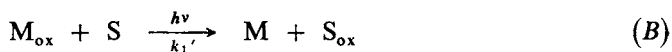
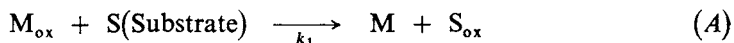
1. All oxidations of singlet substrates by dioxygen, both thermal and photochemical, are catalyzed by transition metal ions, which are present in every real system. Theoretical reasons¹² support the view that in the absolute absence of metal ions the reaction would not proceed at all.
2. The catalysts are metal ions in their lower oxidation states, generated in the system by thermal or photochemical reduction of catalytically inactive precursors in higher oxidation states.
3. The quantum yields of the photochemical reaction depend on the number of the catalytic cycles.

* Part III in the series Cyclic Generation of Catalyst; Part II: Oxid. Commun. 8, 19 (1985/86).

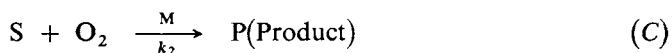
4. In photochemical reactions only the first step, i.e. the catalyst generation, is photochemical. The oxidation proper of the substrate is a thermal catalyzed reaction.

Based on these observations, the following generalized mechanism of singlet substrate oxidation by dioxygen has been proposed.

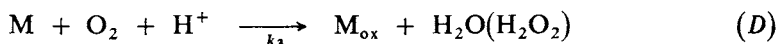
Catalyst generation



Catalyzed oxidation



Catalyst deactivation



Equations (A) and (B) represent, respectively, the thermal and photochemical reductions of a metal in its higher oxidation state, i.e. precursor M_{ox} , to catalyst M. Reaction (C) is the actual catalyzed oxidation, and (D) represents deactivation of the catalyst by reoxidation. As it stands, the mechanism contains two major simplifications: it assumes that the product is unreactive, and disregards the nucleophilic properties of the substrate.

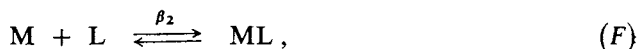
In this mechanism the substrate oxidation is entirely dependent on the catalytic action, and the inhibition is therefore a result of deactivation of the catalyst or its precursor by interaction with the inhibitor, i.e. by the formation of an unreactive complex. It is evident that no inhibitor oxidation is necessary in this case. The formation of catalyst-inhibitor complexes has been considered as the cause of inhibition in some reactions^{13,14}, but in contrast to enzymatic catalysis¹⁵, it has not been accepted as a general principle of inhibition in chemical reactions of dioxygen. Little experimental work has been done on the inhibitor oxidation¹⁶, and its mechanism has never been proven unequivocally.

In formulating the mechanism of inhibited reaction we used, for a start, the following two simplifying assumptions which can be fulfilled in real systems:

a) The complexes of metal ions with inhibitor L are entirely unreactive, i.e. $M_{ox}L$ is not reduced, and ML is catalytically inactive.

b) All equilibria involved are mobile.

The action of inhibitor may be represented by the equilibria



where β_1 and β_2 are stability constants; the analytical concentration of catalyst, $[M_a]$, being

$$[M_a] = [M_{ox}] + [M] + [M_{ox}L] + [ML]. \quad (G)$$

On the basis of these relations the actual concentration of catalyst $[M]$ in the reaction system was expressed, and used in further equations. It will be shown that despite the simplifications the proposed model fits with experimental results. And vice versa, experiments stimulated by the results of simulation provide further insight into the mechanism of inhibition.

CALCULATIONS

According to Eqs (A)–(D), the variations in the concentration of substrate and catalyst with time are given by the differential equations

$$-d[S]/dt = k_1[M_{ox}][S] + k_2[M][S][O_2] + I_a\Phi \quad (1)$$

and

$$d[M]/dt = k_1[M_{ox}][S] - k_3[M][O_2] + I_a\Phi, \quad (2)$$

where I_a is the light intensity (in Einstein units) absorbed by the catalyst precursor, M_{ox} , in unit time, $I_a = I_0 \{1 - \exp(-\epsilon l[M_{ox}])\}$, and Φ is the quantum yield of photochemical generation of catalyst (reaction (B)). ϵ is the molar absorption coefficient of the precursor at the wavelength of initiating radiation and l is the thickness of the absorbing layer in cm. For thermal reaction, the third term in Eqs (1) and (2) equals zero. On the assumption that $[L] \gg [M_a]$, the actual concentration of catalyst in the inhibited reaction (Eqs (E)–(G)) is given by

$$[M] = [M_a] - [M_{ox}](1 + \beta_1[L]) / (1 + \beta_2[L]). \quad (3)$$

The rate constants for the individual reactions at 293.15 K were calculated from the Arrhenius equation for chosen values of activation energies. On substitution of these constants in Eqs (1) to (3), the product and catalyst concentrations were evaluated as functions of time. Simultaneous numerical integration of differential Eqs (1) and (2) which have the general form

$$dy/dt = F(x), \quad (4)$$

was performed using the recurrence formula

$$y_n = y_{n-1} + F_{n-1}(x) \{(t_n - t_0)/z\}, \quad (5)$$

where y is the integrated function sought, t is the reaction time, z is the number of integration steps, in our case 100, and $n \in \langle 1, z \rangle$. The computation was performed on a Hewlett-Packard 9 830A desk calculator coupled with a 9 862A plotter. The initial and standard conditions were as follows: $[S]_0 = 1.0 \text{ mol dm}^{-3}$; $[S_{ox}]_0 = 0$; $[M]_0 = 0$; $[M_{ox}]_0 = 1.0 \cdot 10^{-4} \text{ mol dm}^{-3}$; $[M_a] = 1.0 \cdot 10^{-4} \text{ mol dm}^{-3}$; $[O_2] = 1.00 \cdot 10^{-3} \text{ mol dm}^{-3}$. The inhibitor concentration and stability constants were varied over the ranges $5 \cdot 10^{-3}$ to 0.5 mol dm^{-3} and 10 to 10^4 , respectively.

The input values for the photochemical inhibited reaction were as follows: thickness of absorbing layer, $l = 1 \text{ cm}$; light intensity, $I_0 = 3 \cdot 10^{-5}$ and $5 \cdot 10^{-4} \text{ Einstein dm}^{-3} \text{ min}^{-1}$; molar absorption coefficient of absorbing substance, $\epsilon = 1 \cdot 10^3 \text{ l mol}^{-1} \text{ cm}^{-1}$; and quantum yield of photochemical generation of catalyst in the absence of inhibitor, $\Phi = 1$.

A detailed description of the treatment has been given in previous papers^{3,4}.

RESULTS AND DISCUSSION

Thermal Reaction

For simulation of the inhibitive effect, the values of activation energies E_1 , E_2 , E_3 of non-inhibited reactions (A), (C) and (D) respectively, were chosen so as to yield two types of kinetic curves — sigmoid and convex (see Table I). Experimental counterparts of these curves are found in those for the oxidation of benzaldehyde^{6,7} (sigmoid) and the oxidation of sulphite⁵ and ascorbic acid^{8,9} (convex). The reaction kinetics (product concentration vs time) are characterized by the maximum reaction

TABLE I
Characteristics of kinetic curves for non-inhibited thermal and photochemical reactions

Curve	Shape	E_1 kJ mol ⁻¹	E_2	E_3	Reaction	I_0 einstein dm ⁻³ min ⁻¹	ν mol dm ⁻³ s ⁻¹
A	sigmoid ^a	80	30	65	therm.	0	$1.74 \cdot 10^{-4}$ $T = 30 \text{ min}^c$
		100	30	65	photo.	$3 \cdot 10^{-5}$	$1.70 \cdot 10^{-4}$ $T = 34 \text{ min}^c$
B	convex ^b	72	30	65	therm.	0	$4.21 \cdot 10^{-4}$
		100	30	65	photo.	$5 \cdot 10^{-4}$	$2.12 \cdot 10^{-4}$

^a Sigmoid curve $\nu = \nu_{\max}$; ^b convex curve $\nu = \nu_0$; ^c T induction period.

rate: for sigmoid curves it is the rate, v_{\max} , at the inflection point T whose position defines the length of induction period, while for convex curves it is the initial reaction rate, v_0 . The criterion for inhibition effect is accordingly a change of either v_{\max} or v_0 caused by the presence of inhibitor. Two characteristics of inhibition were simulated: a) dependence on the stability constants of $M_{ox}L$ and ML ; b) dependence on the concentration of inhibitor.

ad a) *The dependence of the reaction kinetics on the stability constants was simulated for three possibilities:*

1) the complex with precursor is more stable than the complex with catalyst, $\beta_1 > \beta_2$;

2) the complex with catalyst is more stable than the complex with precursor, $\beta_1 < \beta_2$; and

3) both complexes are of comparable stability $\beta_1 = \beta_2$.

A survey of the cases is given in Table II. Typical kinetics for cases 1) and 2) of convex curves are portrayed in Fig. 1. As the stability constant increases, the reaction rate diminishes in each case, while the induction period decreases if the precursor is complexed predominantly, and increases if catalyst is complexed predominantly. The inhibitive effect is more pronounced when the catalyst is complexed. In cases where the precursor is complexed, the inhibitive effect is small, especially when the rate of the reduction (A) is high.

ad b) *The dependence of the magnitude of the inhibitive effect on the inhibitor concentration c_L was simulated for the same two types of curves as in the preceding paragraph, using the following values of stability constants:*

$$\begin{array}{ll} \beta_1 = 100, \beta_2 = 1 & \beta_1 = 5\,000, \beta_2 = 1 \\ \beta_1 = 1, \beta_2 = 100 & \text{and } \beta_1 = 1, \beta_2 = 5\,000 . \\ \beta_1 = \beta_2 = 100 & \beta_1 = \beta_2 = 5\,000 \end{array}$$

TABLE II
Characteristics of simulated sets of curves

Set of curves	Stability constants	
	β_1	β_2
1 $\beta_1 > \beta_2$	$10-10^4$	1
2 $\beta_1 < \beta_2$	1	$10-10^4$
3 $\beta_1 = \beta_2$	$10-10^4$	$10-10^4$

Changes in the kinetics of inhibited reaction are illustrated in Fig. 2. In all the cases, the maximum reaction rate decreases with increasing concentration of inhibitor.

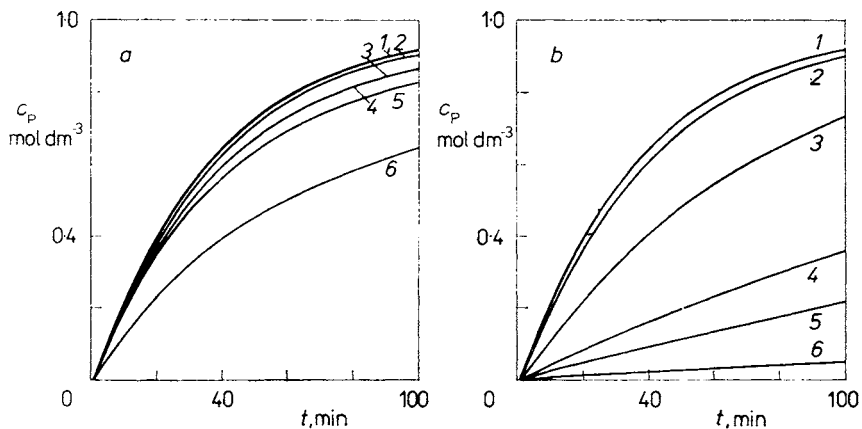


FIG. 1

Kinetics of thermal reaction for various values of stability constants of complexes with inhibitor (L). Type B curve; inhibitor concentration $c_L = 0.01 \text{ mol dm}^{-3}$; a) precursor inhibition, $\beta_2 = 1$; 1 non-inhibited reaction; β_1 : 2 10; 3 100; 4 500; 5 1 000; 6 5 000; b) catalyst inhibition, $\beta_1 = 1$; 1 non-inhibited reaction; β_2 : 2 10; 3 100; 4 500; 5 1 000; 6 5 000.

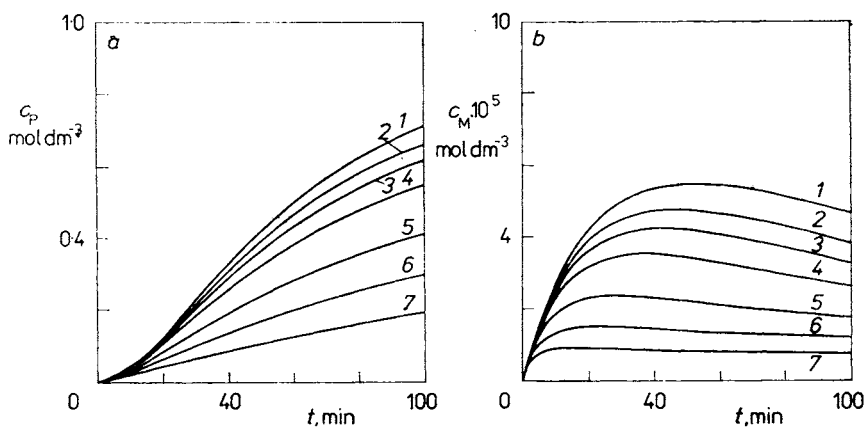


FIG. 2

Kinetics of thermal reaction at various inhibitor concentrations (c_L). Type A curve; precursor inhibition, $\beta_1 = 100$, $\beta_2 = 1$; 1 non-inhibited reaction; c_L : 2 0.005; 3 0.01; 4 0.02; 5 0.05; 6 0.1; 7 0.2 mol dm^{-3} . a) dependence of product concentration (c_P) vs time b) dependence of catalyst concentration (c_M) vs time

A plot of the reciprocals $1/v_{\max}$ or $1/v_0$ against c_L is linear over a range covering two orders of magnitude (Fig. 3). The linear dependence has been observed for many inhibited reactions and has been interpreted in terms of the radical chain mechanism. The effect of inhibitor is again greater if a complex with catalyst is formed preferen-

TABLE III
Variation of the length of induction period T with inhibitor concentration

Inhibitor concentration mol dm^{-3}	Induction period T , min					
	thermal reaction			photochem. reaction		
	1	2	3	1	2	3
0	30	30	30	34	34	34
0.005	28	35	34	33	40	40
0.01	28	40	38	32	45	44
0.02	26	47	44	30	53	51
0.05	22	60	56	26	67	—
0.1	18	71	67	21	78	—
0.2	14	75	79	16	85	—

Type A curve: 1 $\beta_1 = 100, \beta_2 = 1$; 2 $\beta_1 = 1, \beta_2 = 100$; 3 $\beta_1 = \beta_2 = 100$.

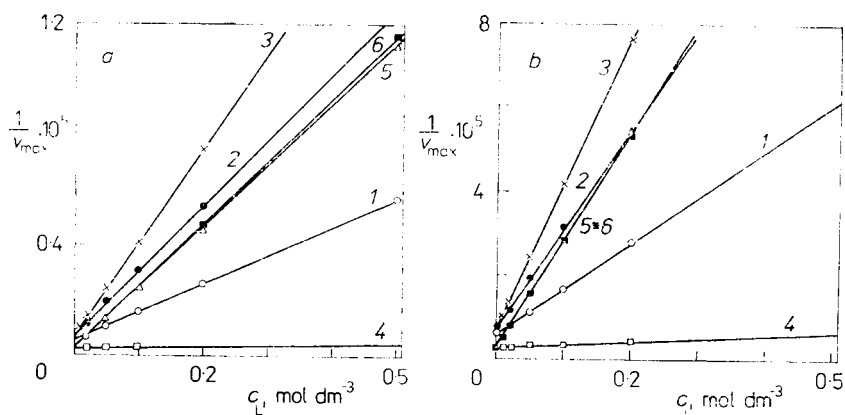


FIG. 3

Reciprocal reaction rate as a function of inhibitor concentration (c_L). a) Thermal reaction; type A curve, $v = v_{\max}$: 1 $\beta_1 = 100, \beta_2 = 1$; 2 $\beta_1 = 1, \beta_2 = 100$; 3 $\beta_1 = \beta_2 = 100$; type B curve, $v_{\max} = v_0$: 4 $\beta_1 = 100, \beta_2 = 1$; 5 $\beta_1 = 1, \beta_2 = 100$; 6 $\beta_1 = \beta_2 = 100$; b) photochemical reaction; type A curve, $v = v_{\max}$: 1 $\beta_1 = 100, \beta_2 = 1$; 2 $\beta_1 = 1, \beta_2 = 100$; 3 $\beta_1 = \beta_2 = 100$; type B curve, $v_{\max} = v_0$: 4 $\beta_1 = 100, \beta_2 = 1$; 5 $\beta_1 = 1, \beta_2 = 100$; 6 $\beta_1 = \beta_2 = 100$

tially. As the concentration of inhibitor is increased, the induction period increases if the catalyst is complexed, and decreases if the precursor is complexed predominantly (Table III). The prolongation of the induction period with increasing inhibitor concentration has been ascribed without exception to the oxidation of inhibitor and accepted as a criterion for the radical chain mechanism.

Photochemical Reaction

The effect of initiating radiation on the rate of oxidation is observable only if the rate of photoinitiated generation of catalyst is comparable with, or higher than, the rate of thermal generation. Thus, if the activation energy, E_1 , of thermal reaction is high, the photoinitiated reaction predominates, its rate depending on the intensity of initiating radiation. The effect of inhibitor was simulated for two kinetic curves of sigmoid and convex types. The characteristics of non-inhibited reaction are given in Table I. As a first approximation, we assume that there is no interference of the inhibitor with the photochemical process, for example by quenching of the excited state or by internal filtration of the initiating radiation. The inhibition is caused, as in the thermal reaction, by the formation of complexes of inhibitor with catalyst and/or its precursor. Once again, the inhibitive effect was characterized by changes in the reaction rate (v_0 , v_{\max}) and in the length of the induction period. The following dependences of the reaction kinetics were simulated: *a*) dependence on the stability constants of $M_{ox}L$ and ML ; *b*) dependence on the inhibitor concentration; *c*) dependence of the quantum yield of photochemical reaction on inhibitor concentration.

ad a) The dependence of the reaction kinetics on the stability constants was simulated for the same conditions as quoted in Table II. The inhibitor-induced changes in the reaction rate and the induction period are analogous to those found for the thermal reaction.

ad b) The dependence of the magnitude of the inhibitive effect on the inhibitor concentration is illustrated in Fig. 4. For each of the cases simulated, the plot of $1/v_{\max}$ or $1/v_0$ vs inhibitor concentration is linear (Fig. 3). As evident from Table III, the effect of inhibitor on the induction period in the photochemical reaction is the same as in the thermal reaction.

ad c) The dependence of the quantum yield of the photochemical reaction on the inhibitor concentration is documented in Table IV. The quantum yield decreases with increasing concentration of inhibitor; the effect is more distinct if the catalyst is complexed with inhibitor. In terms of the chain mechanism, the decrease in the quantum yield is explained by a shortening of the chain length due to the reaction of radicals with inhibitor², which unavoidably means consumption of the inhibitor. Though the proposed mechanism of cyclic generation of catalyst does not involve any chemical change of inhibitor, it is capable of reproducing such behaviour.

CONCLUSIONS

The proposed mechanism of inhibition is based on the concept that all oxidations of singlet substrates by dioxygen are catalyzed by metal ions and that the inhibition is caused by the formation of unreactive complexes of catalyst with inhibitor, which

TABLE IV
Variation in quantum yield of inhibited photochemical reaction with inhibitor concentration

Inhibitor concentration mol dm^{-3}	Quantum yield		
	1	2	3
0	229	229	229
0.005	214	181	171
0.01	201	150	136
0.02	179	114	96
0.05	134	69	51
0.1	94	45	29
0.2	59	29	15
0.5	28	17	—

Type A curve: 1 $\beta_1 = 100, \beta_2 = 1$; 2 $\beta_1 = 1, \beta_2 = 100$; 3 $\beta_1 = \beta_2 = 100$.

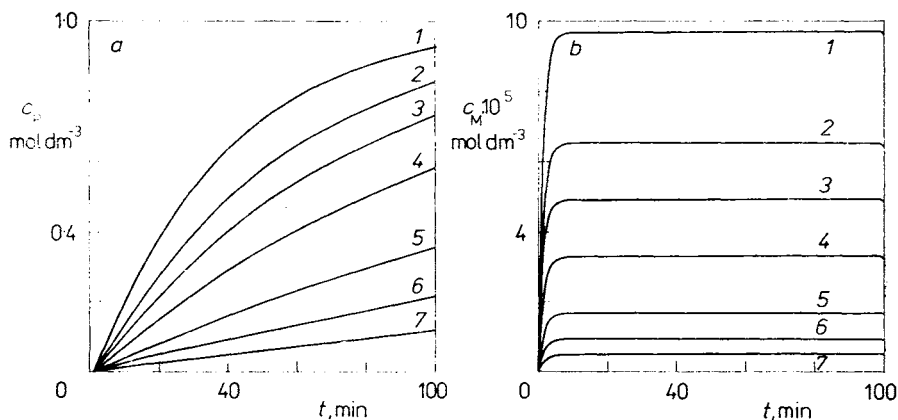


FIG. 4

Kinetics of photochemical reaction at various inhibitor concentrations (c_L). Type B curve, catalyst inhibition, $\beta_1 = 1, \beta_2 = 100$; 1 non-inhibited reaction; c_L : 2 0.005; 3 0.001; 4 0.02; 5 0.05; 6 0.1; 7 0.2 mol dm^{-3} . a) dependence of product concentration (c_p) vs time, b) dependence of catalyst concentration (c_M) vs time

accordingly need not undergo oxidation. The proposed mechanism of inhibition has the following consequences:

The reaction rates of both the thermal and photochemical reactions decrease with increasing stability constants of the complexes and the concentration of inhibitor. The reciprocal reaction rate is a linear function of the inhibitor concentration. The inhibitive effect is greater when catalyst is complexed in preference to precursor complexation.

The effect of inhibitor is the same in both thermal and photochemical reactions.

The quantum yield of photochemical reaction decreases with increasing concentration of inhibitor.

Despite the simplifying assumptions used in the simulation, good agreement between the results simulated and obtained experimentally was found in a number of cases. A greater inhibitive effect due to the complexation of catalyst than to complexation of precursor has been observed in the oxidation of ascorbic acid catalyzed by cuprous ions and inhibited by polyamines^{8,9}. An increase of the induction period without inhibitor oxidation has been demonstrated in benzaldehyde oxidation inhibited by 2-propanol¹⁶. A reduction in the quantum yield with increasing concentration of complexing agents acting as inhibitors has been found in the photochemical and photosensitized oxidation of sulphite catalyzed by ferric ions and inhibited by EDTA (refs^{5,17}). These experimental findings are incompatible with the concept of radical chain mechanism.

It is noteworthy that simulation of the proposed mechanism reproduces phenomena typical of inhibition and generally regarded as experimental criteria of radical chain mechanism, namely (i) the linear dependence of $1/v$ on the inhibitor concentration, (ii) the increase of the induction period with increasing inhibitor concentration, (iii) the decrease in the quantum yield with increasing inhibitor concentration, (iv) equality of inhibitive effects in the thermal and photochemical reactions. It is clear that these phenomena can be consequences of a completely different mechanism and therefore cannot be regarded as proof of the radical chain mechanism.

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