^{1}H Nuclear Magnetic Resonance Spectral Detection of the Intermediates involved in the Acid-catalysed Hydrolysis of 2-Substituted 3-Methyl-1,3-oxazolidines

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The hydrolytic decomposition of 2-alkyl- and 2-aryl-substituted 3-methyl-1,3-oxazolidines to 2-methylaminoethanol and appropriate aldehyde has been studied by ^{1}H n.m.r. spectroscopy in deuterioperchloric acid. The time-dependent spectra confirmed that the release of the final products is preceded by an equilibration of the starting material with three different species, *viz.* two geometric isomers of an acyclic cationic Schiff's base and a carbinolamine, which subsequently undergoes the rate-limiting heterolysis to the products.

The course of the hydrolysis of acetals and their analogues, in which one of the oxygen atoms has been replaced by nitrogen, is often followed by u.v. spectroscopy only. Consequently, the rate-limiting stage and the structure of the intermediates involved must be deduced on the basis of indirect kinetic evidence. However convincing this kind of reasoning might be, a direct spectroscopic detection of the intermediates is still desirable.

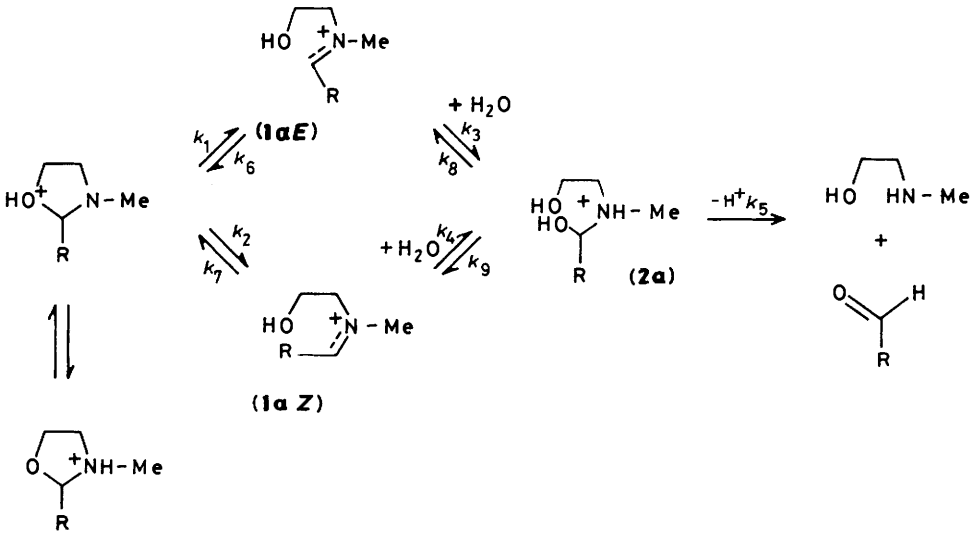
During the course of our studies on the role of Schiff's base intermediates in the hydrolytic decomposition of 2-substituted 3-methyl-1,3-oxazolidines we found that ^{1}H n.m.r. spectroscopy offers a valuable means to get a better insight into the reaction. As a continuation of our previous work[1] we now report on the characterisation of the critical intermediates and the consecutive steps in the hydrolytic decomposition of some 2-substituted 3-methyl-1,3-oxazolidines by the n.m.r. method.

Results and Discussion

2-Substituted 3-alkyl- and 3-aryl-1,3-oxazolidines derived from aromatic carbonyl compounds and appropriate aminoalcohols have been reported to be hydrolysed *via* stable intermediates, very similar to the corresponding acyclic Schiff's bases.[2–4]

We later[1] invoked the same mechanism for the hydrolysis of *N*-methyl-substituted oxazolidines derived from aliphatic aldehydes (Scheme). Consistent with this mechanism, the absorption maximum of the protonated starting material at *ca.* 190 nm (log ε *ca.* 3.4) initially increased and then slowly disappeared with concomitant formation of a weak maximum for the released aldehyde. The u.v. spectrum of the intermediate, (**1a**), closely resembled that of the trifluoromethanesulphonate salt of the acyclic Schiff's base cation, (**1b**). Moreover, the breakdown of (**1a** and **b**) responded in the same manner to changes in the oxonium ion concentration, and exhibited similar entropies of activation, solvent deuterium isotope effects, and salt effects.

Figure 1 shows the ^{1}H n.m.r. spectrum of (**1b**) in 5 mol dm^{-3} $DClO_4$ at 323 K. By comparison with the respective *N*-methyl chemical shifts of the *E* and *Z* forms of some *N*,3-diarylpropenylideneiminium perchlorates[5] it could be concluded that the *N*-methyl group of (**1b*E***) resonates at a lower field than that of (**1b*Z***). In addition to these *N*-methyl signals a third *N*-methyl signal appeared which seemed to belong to the carbinolamine derivative of (**1b**), (**2b**).[6] The corresponding peak was found in the time-dependent ^{1}H n.m.r. spectrum (Figure 2) of 2-isopropyl-3-methyl-1,3-oxazolidine (**1a**), in accord with the postulated mechanism of hydrolysis.[1,7] The ring *N*-methyl group and the *N*-methyl group of the aminoalcohol were easy to locate by spiking, whereas that of the carbinolamine was assigned by reference to literature data.[6]



Scheme.

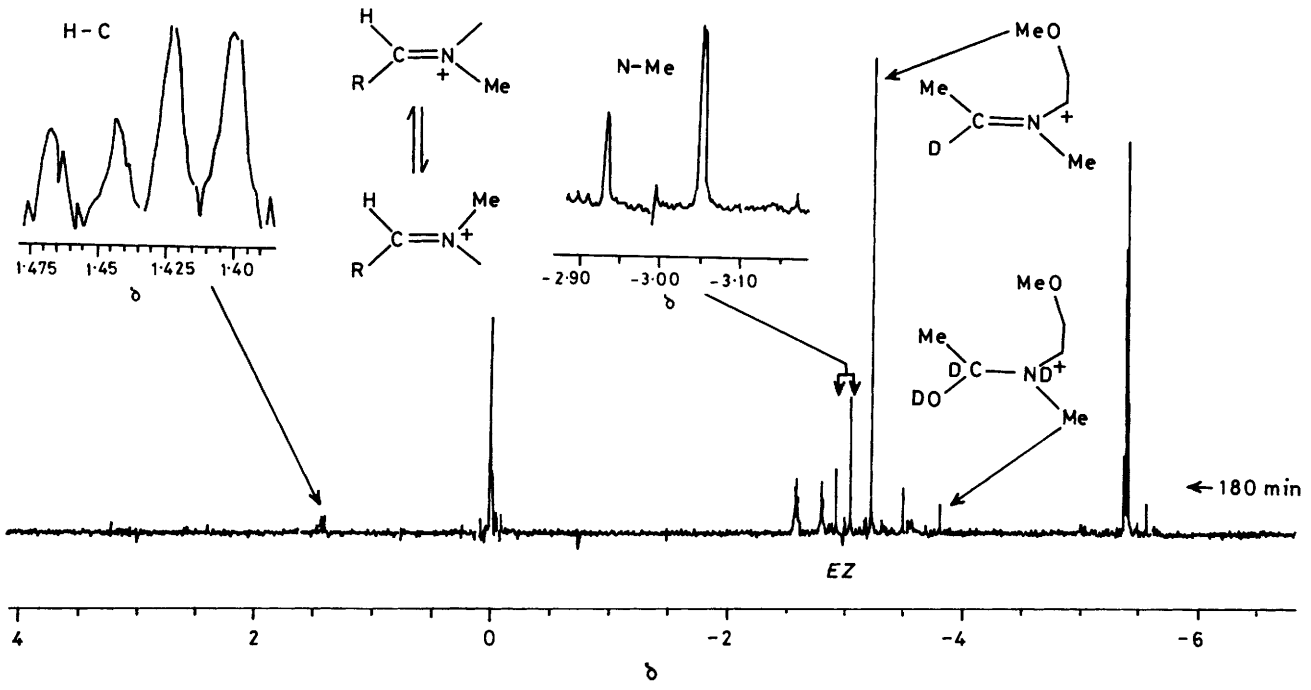


Figure 1. ^{1}H N.m.r. spectrum of the trifluoromethanesulphonate salt of the acyclic Schiff's base cation (**1b**) in 5 mol dm^{-3} deuterioperchloric acid at 323 K. The reference is water (HOD)

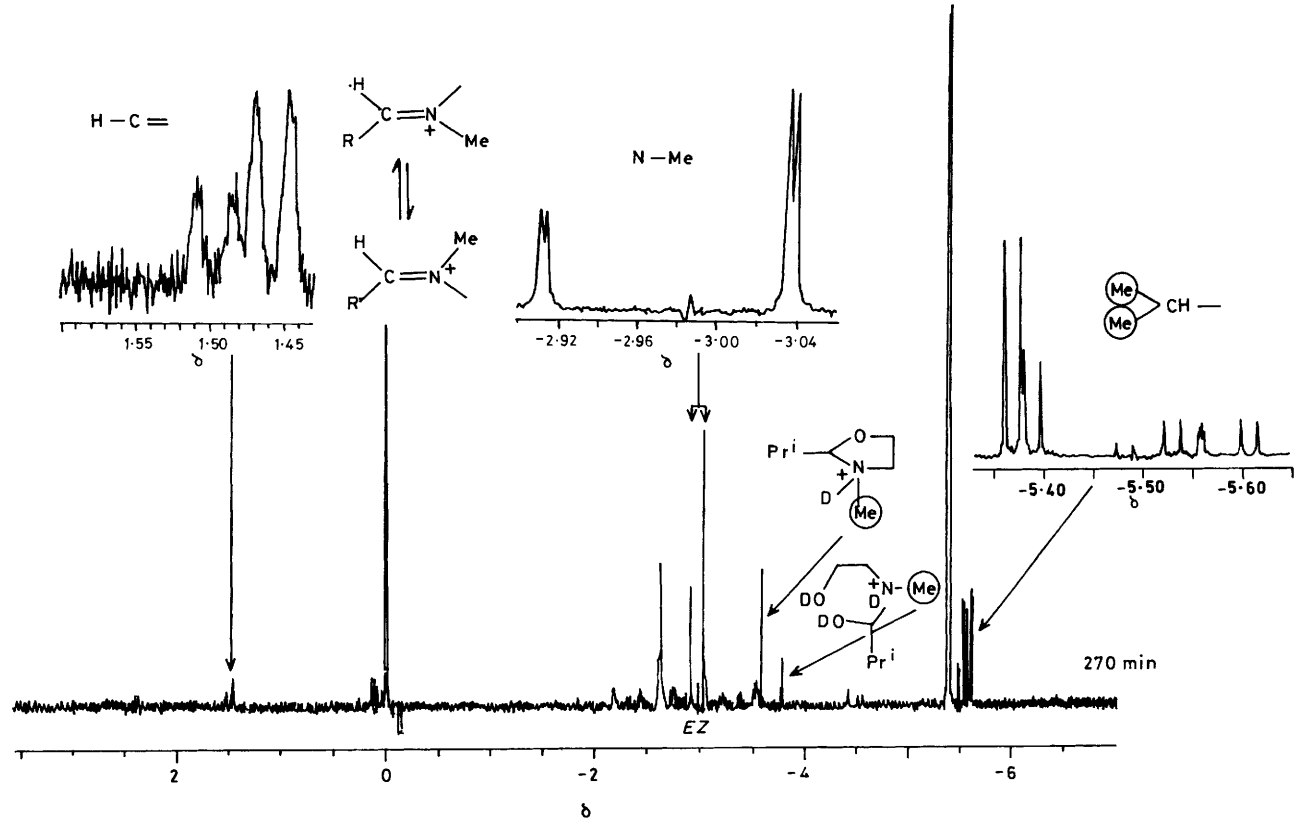


Figure 2. ^{1}H N.m.r. spectrum of 2-isopropyl-3-methyl-1,3-oxazolidine in 5 mol dm^{-3} deuterioperchloric acid at 323 K. The reference is water (HOD)

When the progress of the hydrolysis of 2-isopropyl-3-methyl-1,3-oxazolidine was followed in 5 mol dm^{-3} deuterioperchloric acid, the starting material was observed to be rapidly converted into the *E* isomer of (**1a**), which was subsequently equilibrated with the corresponding *Z* form (**1a*Z***). *E–Z* Isomerisation may take place *via* both the ring form and the carbinolamine species (**2a**), which is present at low steady-state concentration. The time-dependent distribution of these compounds at 303 and 323 K are presented in Figures 3 and 4, respectively. As suggested previously[1] on the basis of u.v. spectroscopic measurements, the decomposition of this pre-equilibrium mixture to the final products, *viz.* isobutyraldehyde and 2-methylaminoethanol, appears to be exceedingly slow under the strongly acidic conditions employed. The n.m.r. spectroscopic detection of the carbinolamine intermediate (**2a**) verifies the suggestion[1] that the breakdown of this species constitutes the rate-limiting step for the formation of the final products.

The *N*-methyl and 1-H protons of the *E* and *Z* isomers of the acyclic cationic Schiff's base intermediates of 2-phenyl-3-methyl-1,3-oxazolidine (Figure 5) resonate in reverse order compared with those of the 2-isopropyl derivative. This is understandable since the phenyl group appreciably shields the *N*-methyl group in the *E* isomer (**3*E***) whereas practically no shielding can be observed if the phenyl group is replaced by an alkyl group [*e.g.* (**Ib*E***) and (**1a*E***)], as verified by Bjørgø *et al.* with *E–Z* isomers.[8]

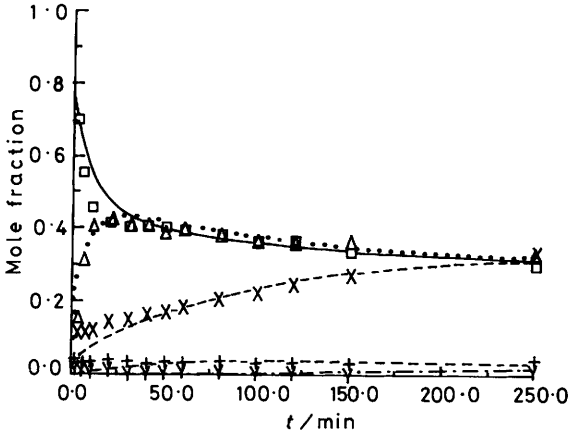


Figure 3. The mole fractions of 2-isopropyl-3-methyl-1,3-oxazolidine, Schiff's base intermediates, carbinolamine, and aminoalcohol as a function of time in 5 mol dm^{-3} deuterioperchloric acid at 303 K. Ring form (□), carbinolamine (+), *E*-isomer of intermediate (△), *Z*-isomer of intermediate (X); and the aminoalcohol (Y) (k_1 8 × 10^{-4}, k_2 1 × 10^{-3}, k_3 4 × 10^{-5}, k_4 0, k_5 4 × 10^{-5}, k_6 8 × 10^{-4}, k_7 1 × 10^{-3}, k_8 9 × 10^{-3}, and k_9 0 s^{-1}, obtained by the Runge–Kutta method)

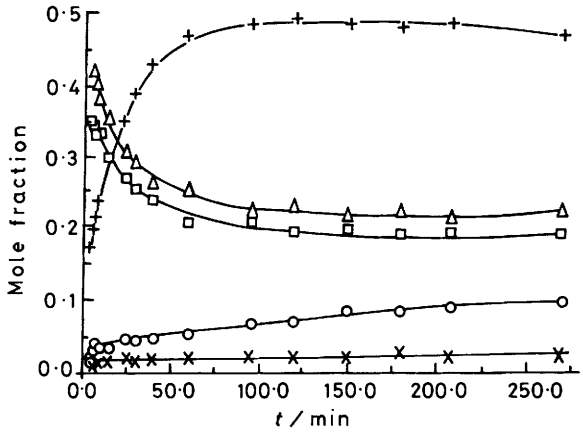


Figure 4. Mole fractions of 2-isopropyl-3-methyl-1,3-oxazolidine, Schiff's base intermediates, carbinolamine, and aminoalcohol as a function of time in 5 mol dm^{-3} deuterioperchloric acid at 323 K. Ring form (□), carbinolamine (○), *E*-isomer of intermediate (△), *Z*-isomer of intermediate (+), aminoalcohol (X)

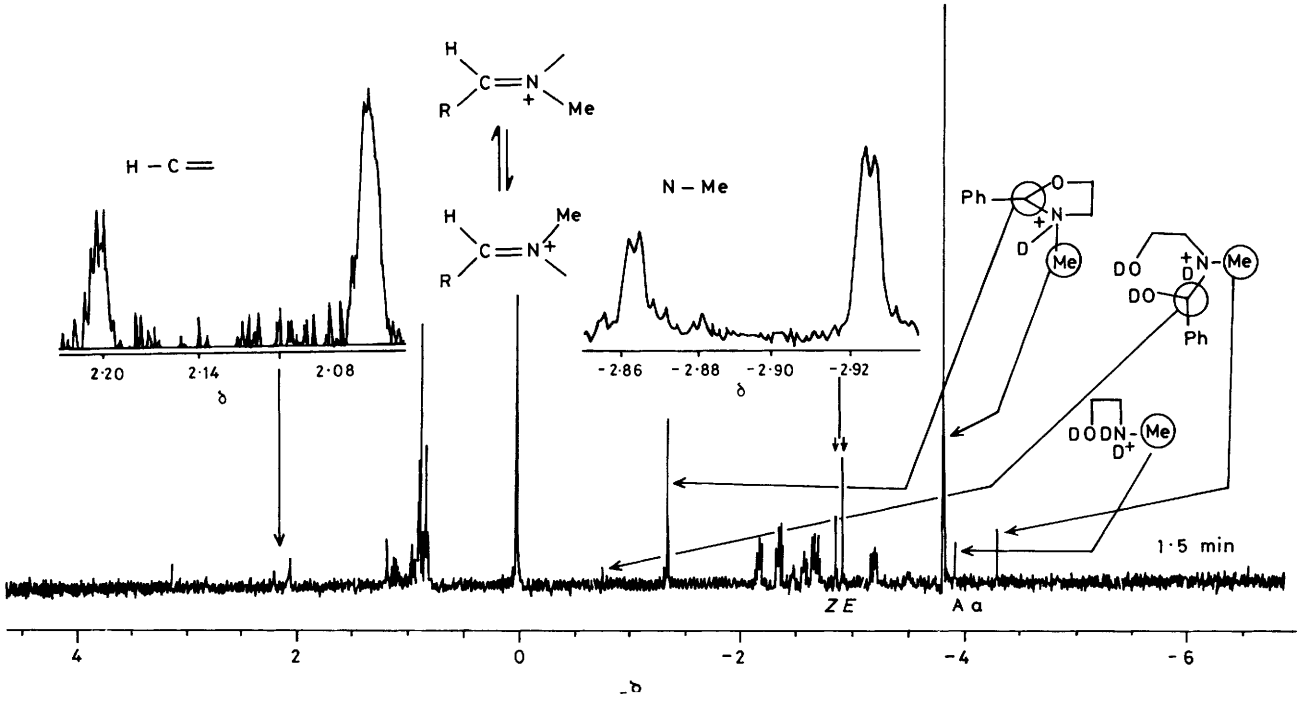
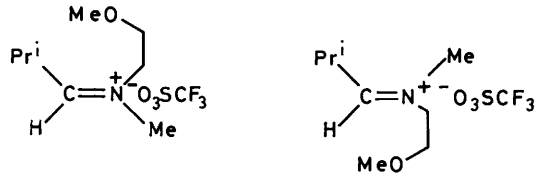
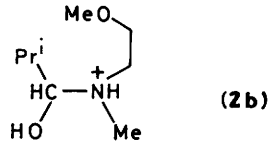
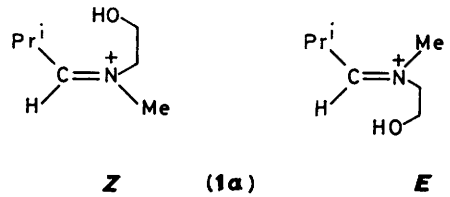
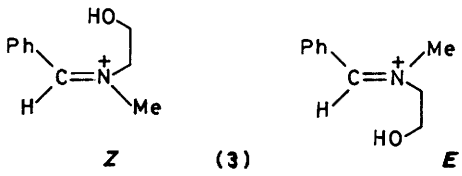


Figure 5. ^{1}H N.m.r. spectrum of the 2-phenyl-3-methyl-1,3-oxazolidine in 5 mol dm^{-3} deuterioperchloric acid at 303 K. The reference is water (HOD)









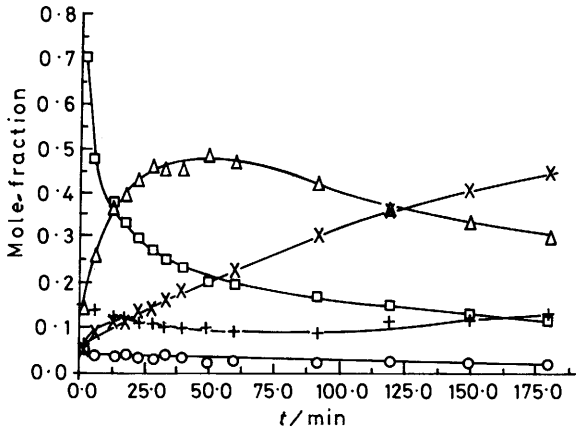


Figure 6. The mole fractions of 2-phenyl-3-methyl-1,3-oxazolidine, Schiff's base intermediates, carbinolamine, and aminoalcohol as a function of time in 5 mol dm^{-3} at 303 K. Ring form (□), carbinolamine (○), *E*-isomer of intermediate (△), *Z*-isomer of intermediate (+), aminoalcohol (X)

The time-dependent mole fractions of the molecular species involved in the hydrolytic decomposition of 2-phenyl-3-methyl-1,3-oxazolidine (Figure 6) in 5 mol dm^{-3} $DClO_4$ at 303 K qualitatively resemble those observed with the isopropyl derivative (Figure 3). However, the consecutive steps are less clearly distinguishable, the release of the 2-methylaminoethanol already beginning at the early stage of the reaction. Obviously the rate difference between the initial formation of the acyclic cationic Schiff's base and the breakdown of this intermediate is less pronounced than with the 2-alkyl derivatives.[1] The preceding observation that 2-methylaminoethanol is markedly released already at the very early stage of the hydrolysis of 2-phenyl-3-methyl-1,3-oxazolidine (Figure 6) does not support a 40-fold rate difference[2] between the formation of the open-chain intermediate and that of the final products.

The ^{1}H n.m.r. experiments confirmed that in dilute acid solutions (0.1 mol dm^{-3} $DClO_4$) the formation of the Schiff's base intermediates (**1a**) and (**3**) occurred instantaneously and the only measurable reaction was the formation of the final products, aldehyde and aminoalcohol, in accord with the conclusions based on u.v. spectroscopic results.[1,2] The composition of the pre-equilibrium mixture remained constant during the whole kinetic run, the mole fractions of the starting material, (**1a***E*), (**1a***Z*), and (**2a**) being 0.5, 0.15, 0.3, and 0.05, respectively. Accordingly, the rate constants reported earlier[1] for the opening of the 1,3-oxazolidine ring are actually the sums of the rate constants for opening and reclosure reactions. The values of the rate constants for the opening reaction are thus about half those given. Correspondingly, the rate constants reported for the breakdown of the acyclic intermediate are too small. The real rate constants are probably almost twice as large as the observed constants.

In summary, ^{1}H n.m.r. spectroscopy offers a convenient tool to follow the course of the hydrolytic decomposition of 2-substituted 3-methyl-1,3-oxazolidines. The results confirm the mechanistic deductions made earlier on the basis of u.v. spectroscopic measurements,[1,2] including the postulate[1] of pre-equilibrium formation of a carbinolamine which in the rate-limiting stage produces 2-methylaminoethanol and the corresponding aldehyde from the Schiff's base intermediate. 2-Phenyl substitution, however, changes the relative stabilities of the different reactive species which, especially in moderately concentrated acid, makes complete distinction between the formation and the decomposition of the Schiff's base intermediates difficult.

Experimental

2-Isopropyl- and 2-phenyl-3-methyl-1,3-oxazolidines were prepared by mixing equal amounts of appropriate aldehyde and 2-methylaminoethanol in benzene and then removing water by azeotropic distillation.[9,10] ^{1}H N.m.r. spectra were taken for $DClO_4$–D_2O solutions using a JEOL GX-400 instrument. The substrate concentration was *ca.* 0.6% by volume. In one representative case (Figure 3) the time-dependent product distribution was simulated by a numerical integration technique using the Runge–Kutta algorithm.[11] The simulation was based on equations (1)—(5) where y_1 = [(ring form)], y_2 = [(**1a***E*)], y_3 = [(**1a***Z*)], y_4 = [(**2a**)], y_5 = [(product)], and $x = t$. The rate constants and the enumeration of the compounds refer to the Scheme.

$$dy_1/dx = k_6y_2 + k_7y_3 - (k_1 + k_2)y_1 \quad (1)$$

$$dy_2/dx = k_1y_1 + k_8y_4 - (k_6 + k_3)y_2 \quad (2)$$

$$dy_3/dx = k_2y_1 + k_9y_4 - (k_7 + k_4)y_3 \quad (3)$$

$$dy_4/dx = k_3y_2 + k_4y_3 - (k_5 + k_8 + k_9)y_4 \quad (4)$$

$$dy_5/dx = k_5y_4 \quad (5)$$

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