

Limitations on the Acceleration of the Morita-Baylis-Hillman Reaction by Alcohols



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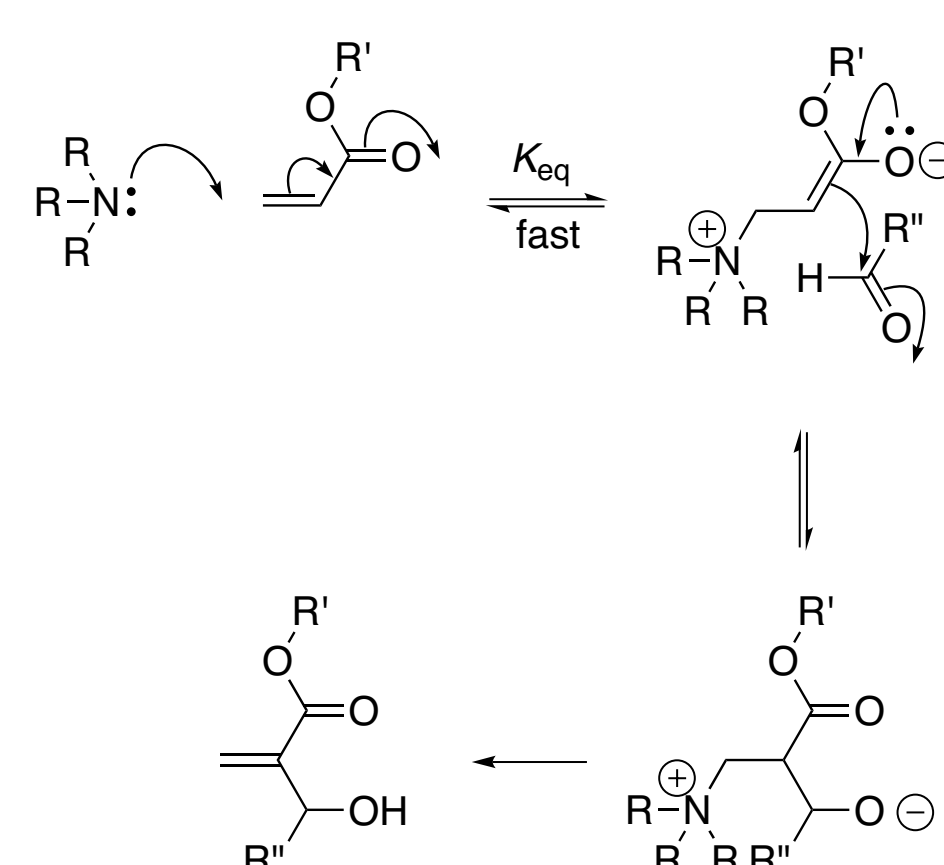


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INTRODUCTION

The Morita-Baylis-Hillman (MBH) reaction^{1,2}

- A useful C—C bond forming reaction between an aldehyde and a Michael acceptor
- Catalyzed by a trialkylamine or trialkylphosphine to give an allylic alcohol.
- First mechanism for the reaction proposed by Hill and Isaacs on the basis of a second order rate law.³
- major steps of the Hill and Isaacs mechanism are given in Scheme 1:

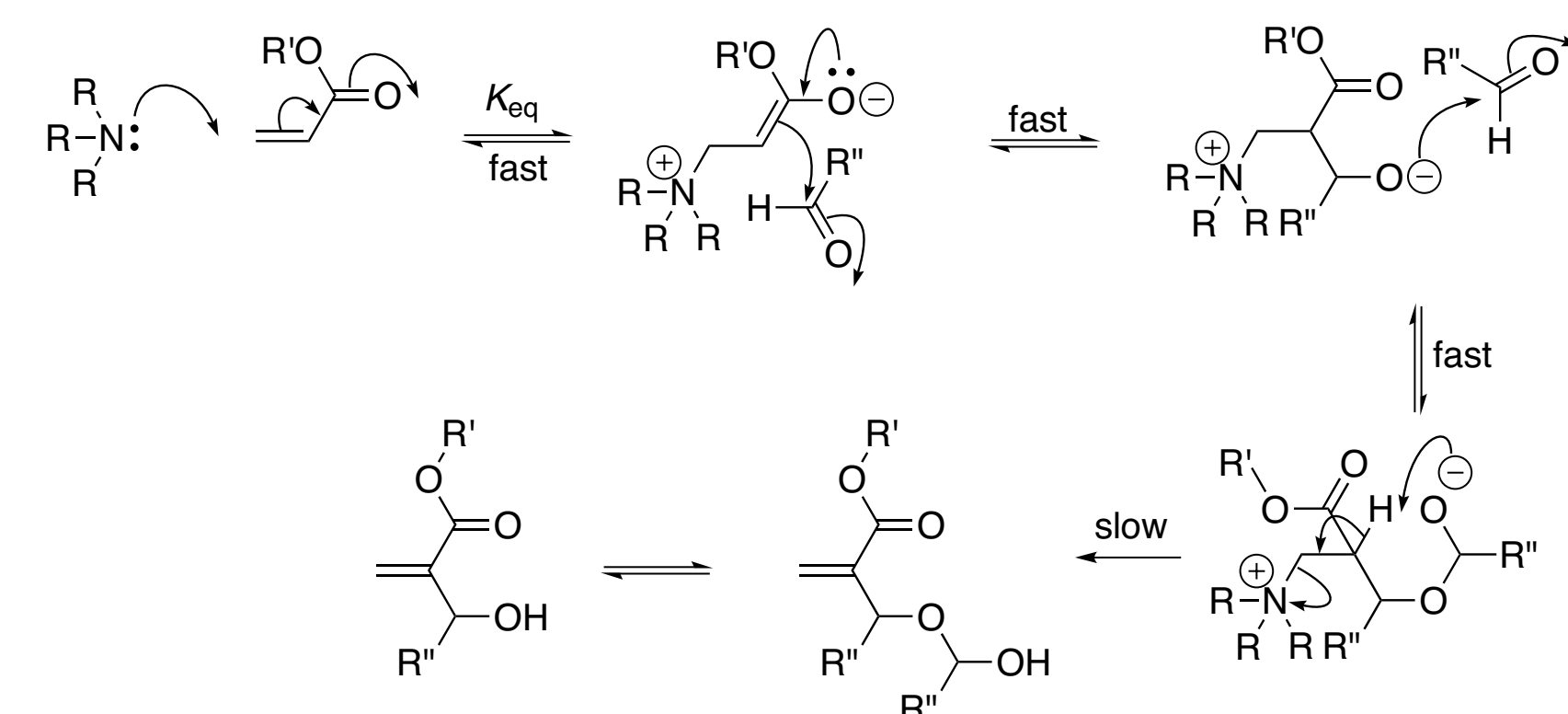


Scheme 1: The Hill and Isaacs Mechanism for the MBH Reaction

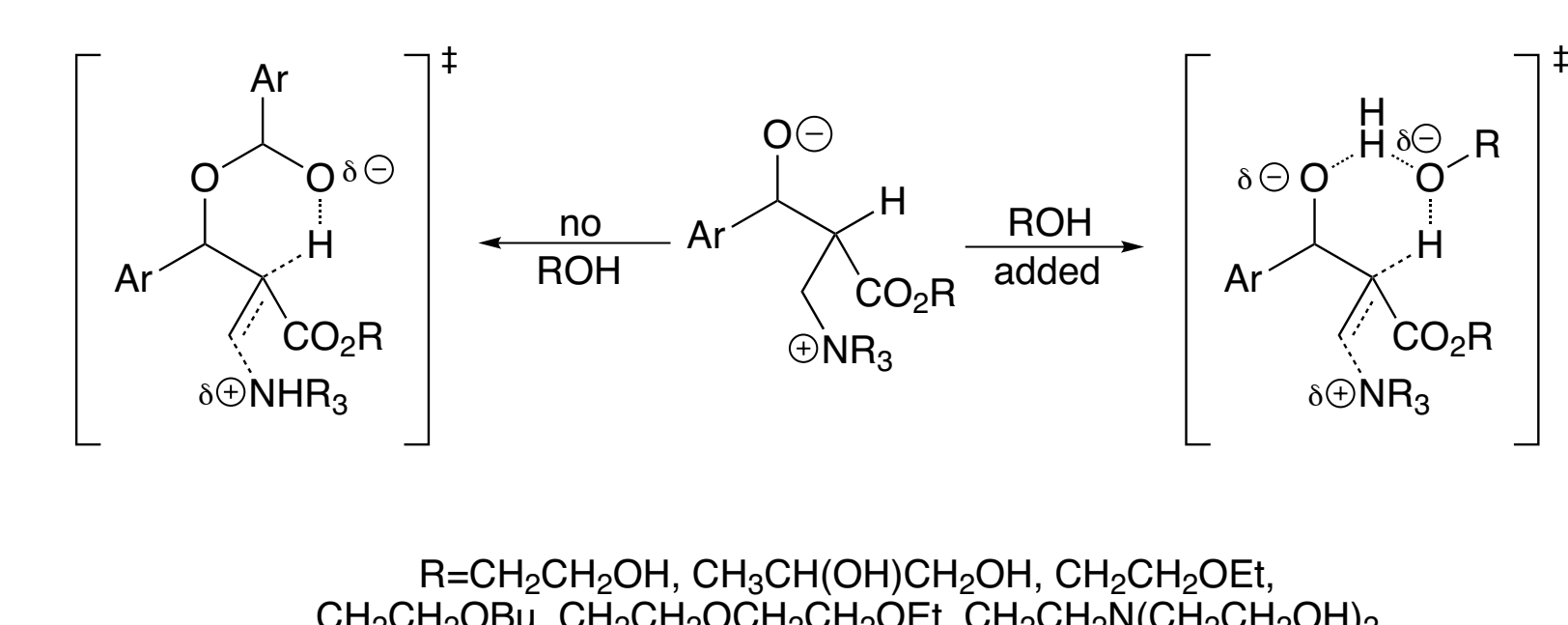
- Mechanism modified on the basis of kinetic and isotope effects studies by McQuade and his group⁴
- Reaction is first order in base, first order in the acrylate, and second order in the aldehyde in aprotic solvents:

$$\text{Rate} = k_{\text{obs}} [\text{Aldehyde}]^2 [\text{Ester}] [\text{Amine}]$$

- Computational studies of Aggarwal and coworkers⁵ have shown that proton transfer is an important part of the reaction pathway.
- This rate law requires a fast reaction with a second molecule of aldehyde to give an adduct that then undergoes intramolecular proton transfer in the slow step of the reaction.



- The addition of protic solvents, especially alcohols, can lead to significant rate enhancement in the reaction.
- The Aggarwal mechanistic proposal suggests that the second molecule of aldehyde may be replaced by the molecule of alcohol.
- This has the advantage of retaining the six-membered transition state for the rate-determining proton transfer step.



- This model retains the proton transfer as the rate-determining step
- The rate law is changed to to:

$$\text{Rate} = k [\text{Aldehyde}] [\text{Ester}] [\text{Amine}] [\text{Alcohol}]$$

DEVELOPMENT OF KINETIC EXPRESSIONS

Third-order Observed Kinetics

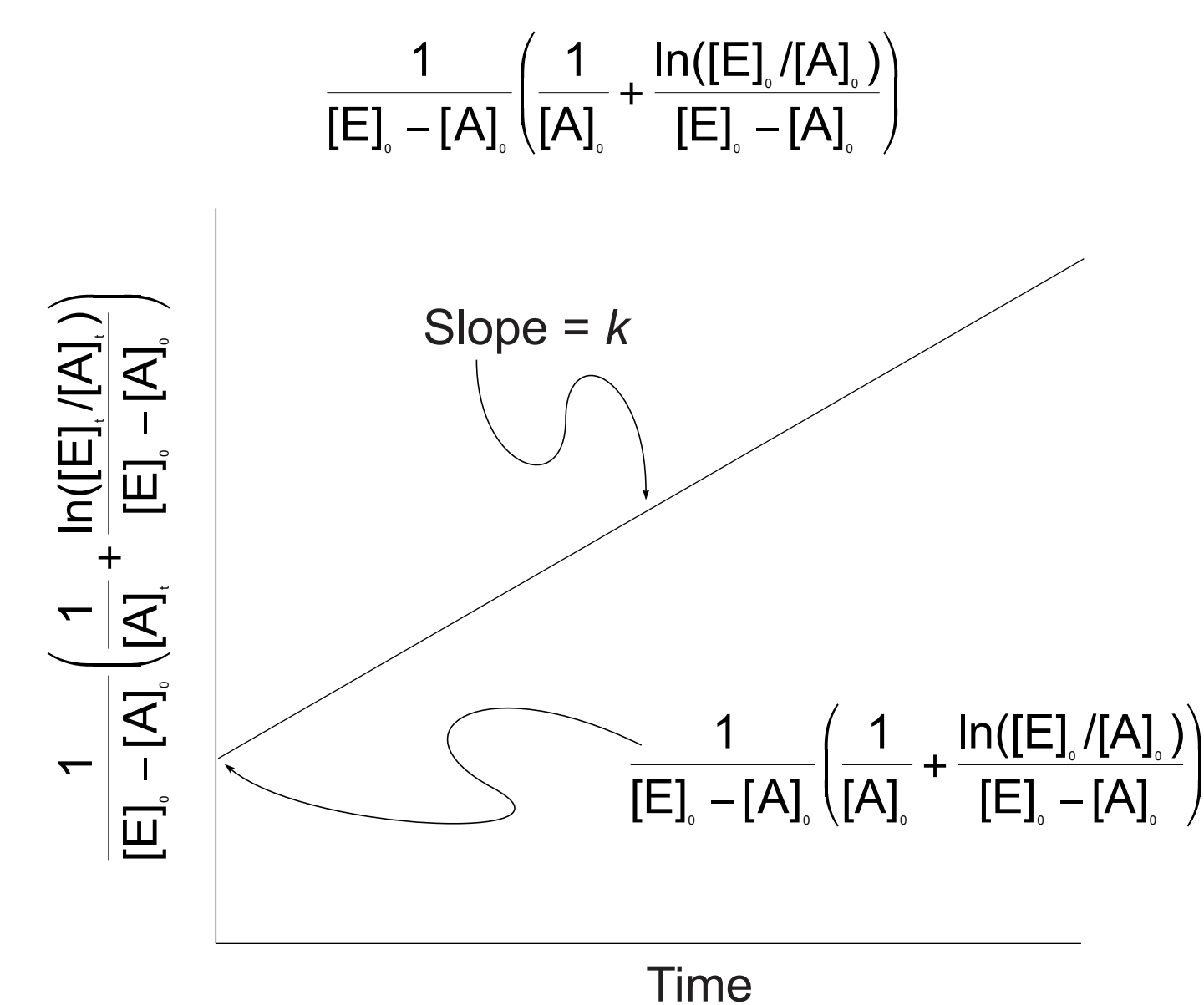
- No zwitterion adduct can be observed by ¹H NMR spectrometry at 400 MHz, but spectra of both starting compounds and the product could be observed
- Equilibrium constant for the formation for the zwitterion is small.
- Reaction becomes effectively zero-order in the amine (DABCO).
- Rate law becomes $\text{Rate} = k_{\text{obs}} [\text{A}]^2 [\text{E}]$
- Under our conditions, acrylate ester is present in excess at the start of each reaction.
- Integrated rate equation for a third order reaction of this type with unequal initial concentrations of the reactants, is of the following form:

$$kt = \frac{1}{[\text{E}] - [\text{A}]} \left(\frac{1}{[\text{A}]} + \frac{\ln([\text{E}]/[\text{A}])}{[\text{E}] - [\text{A}]} \right) - \frac{1}{[\text{E}] - [\text{A}]} \left(\frac{1}{[\text{A}]} + \frac{\ln([\text{E}]/[\text{A}])}{[\text{E}] - [\text{A}]} \right)$$

- This equation leads to the conclusion that plotting

$$\frac{1}{[\text{E}] - [\text{A}]} \left(\frac{1}{[\text{A}]} + \frac{\ln([\text{E}]/[\text{A}])}{[\text{E}] - [\text{A}]} \right)$$

- vs. t , one should obtain a straight line with slope k , and y-intercept



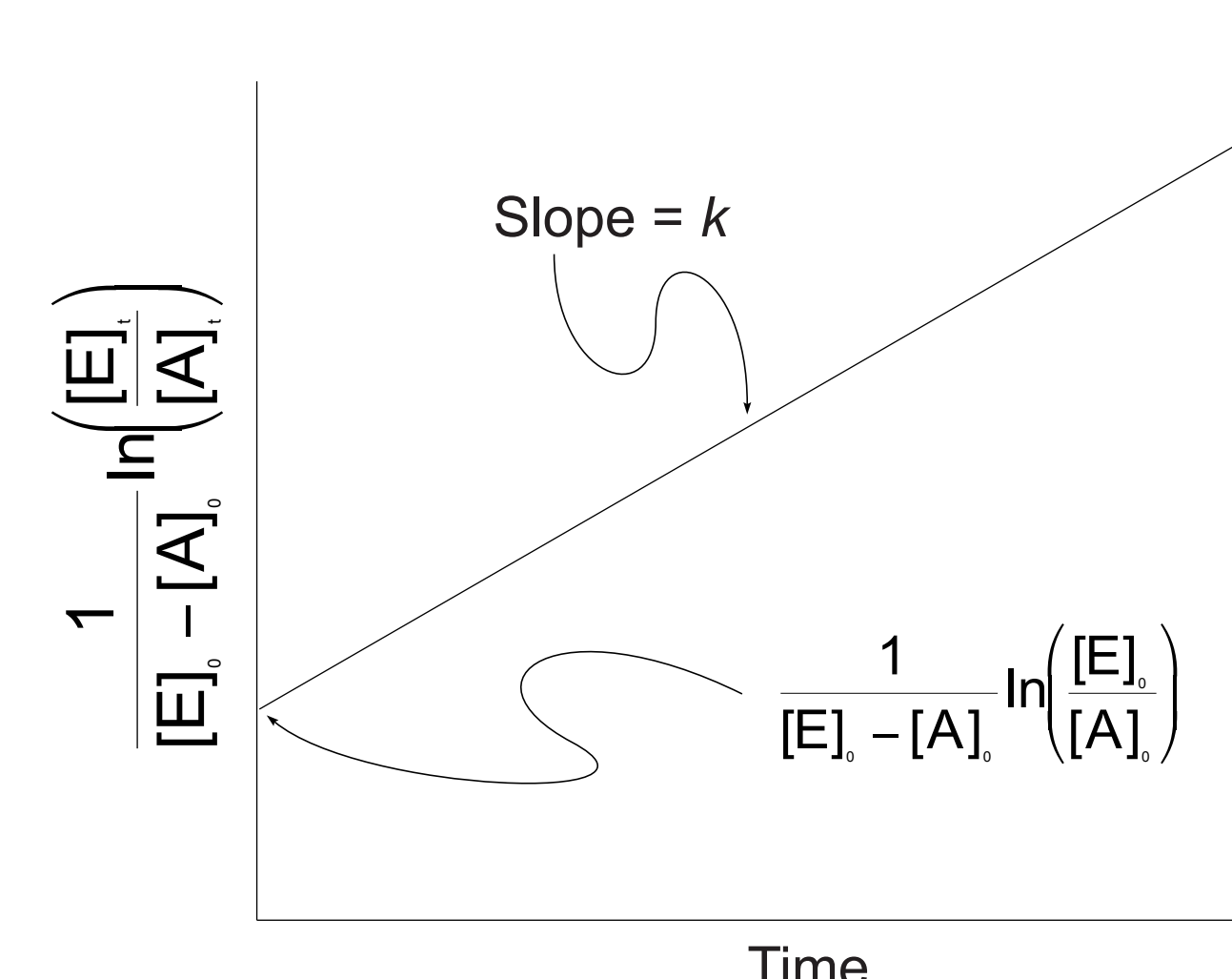
Second-order Observed Kinetics

- The ¹H NMR spectrum of reaction mixtures containing added alcohols gives no signals other than those of the free alcohol.
- The reaction is carried out under zero-order (constant concentration) conditions with respect to the alcohol.
- The reaction becomes second order, with an observed rate law:

$$\text{Rate} = k_{\text{obs}} [\text{A}] [\text{E}]$$

- Integrated rate equation for this type of second-order reaction with unequal initial concentrations of the reactants, is of the form:

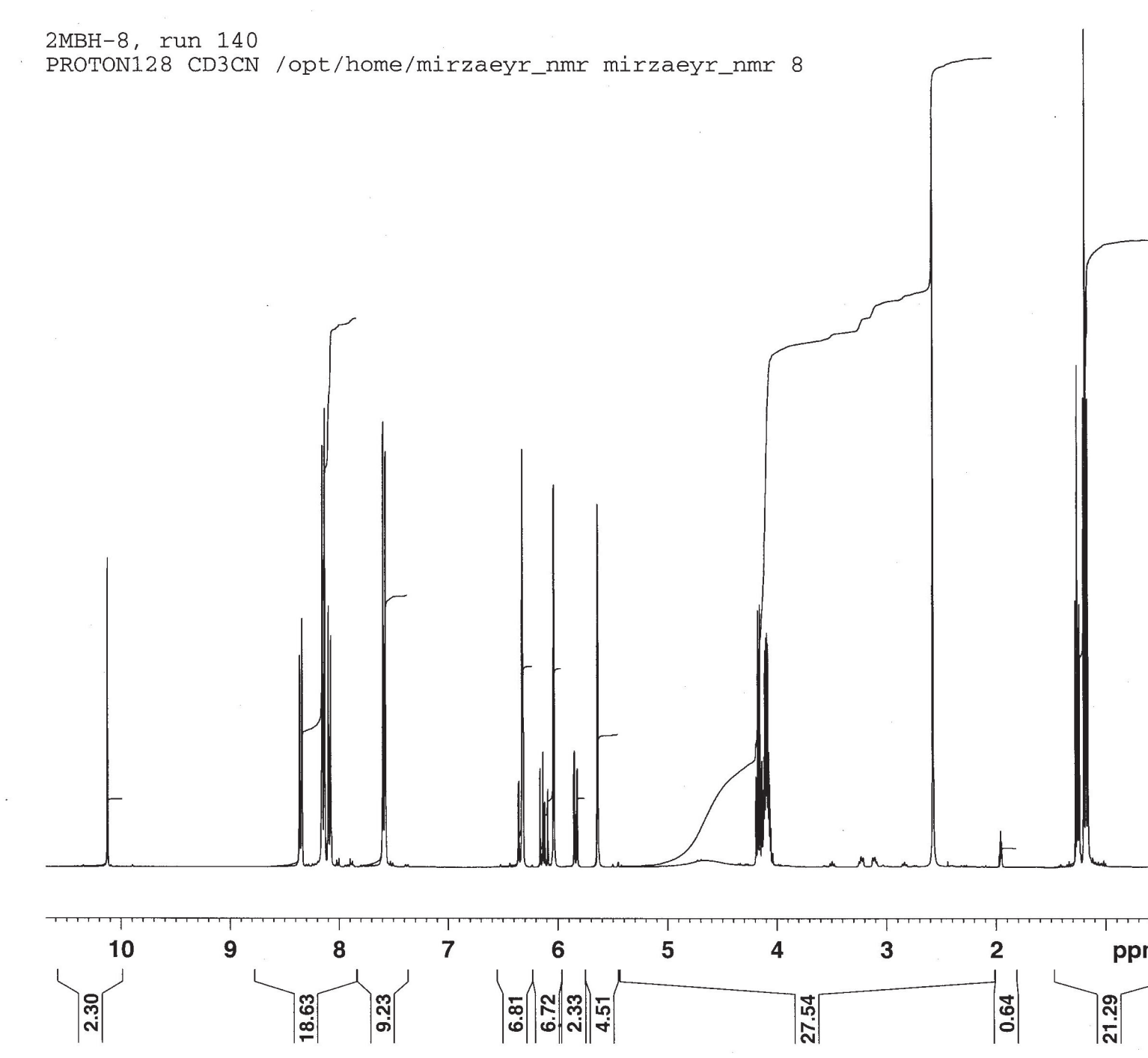
$$kt = \frac{1}{[\text{E}] - [\text{A}]} \left(\frac{1}{[\text{A}]} + \frac{\ln([\text{E}]/[\text{A}])}{[\text{E}] - [\text{A}]} \right) - \frac{1}{[\text{E}] - [\text{A}]} \left(\frac{1}{[\text{A}]} + \frac{\ln([\text{E}]/[\text{A}])}{[\text{E}] - [\text{A}]} \right)$$



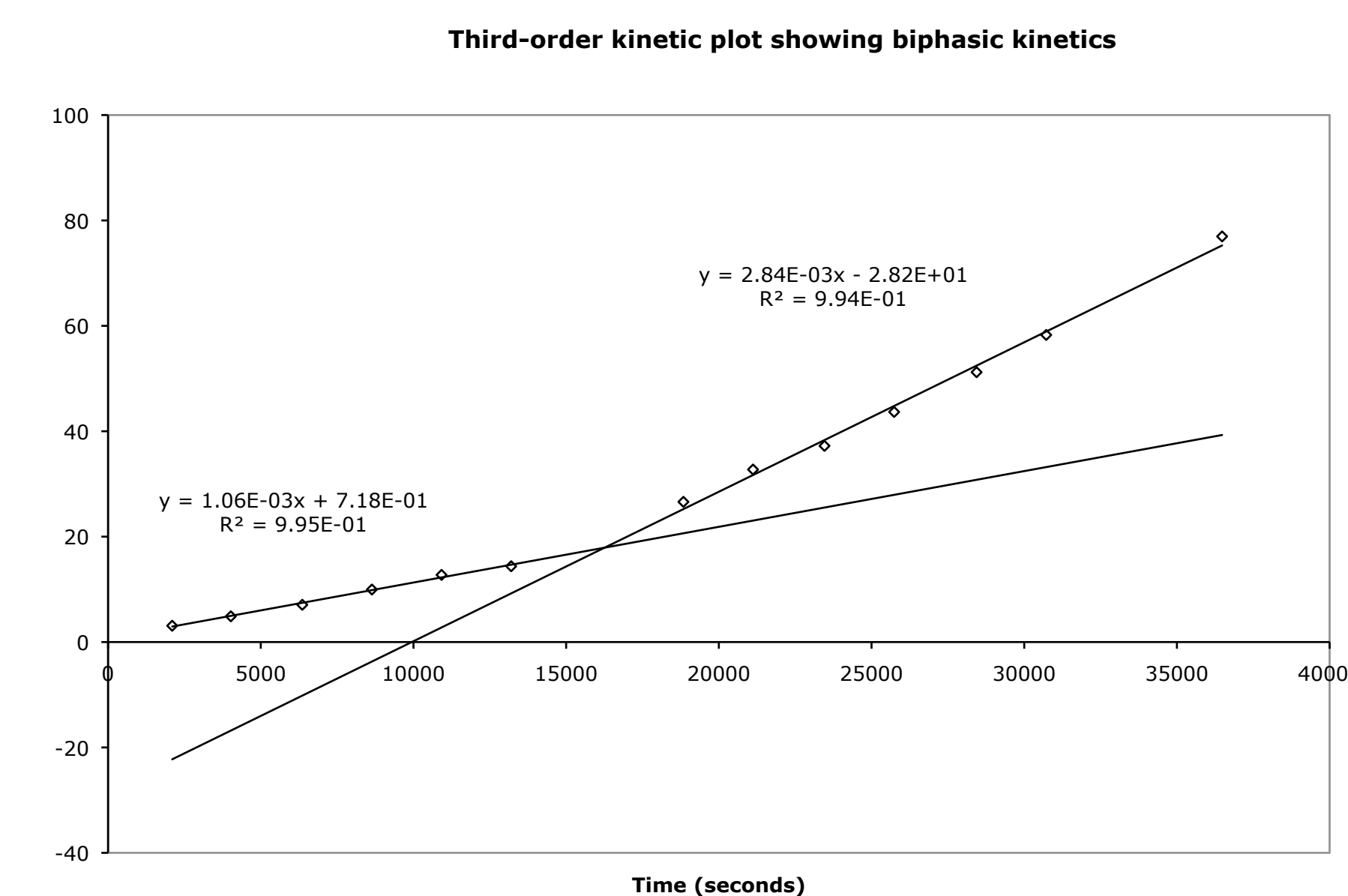
RESULTS: KINETIC EFFECTS OF ADDED GLYCOLS

Observed Kinetics: No Added Alcohol

- Kinetics were followed by ¹H NMR spectroscopy in CD₃CN.
- Solutions were approximately 0.6 M ethyl acrylate, 0.6 M p-nitrobenzaldehyde, and 0.6 M DABCO.
- The spectrum shows sufficient resolution of resonances to allow ¹H NMR spectroscopy to be used to monitor the reaction kinetics.



- Plots based on the third-order equation show excellent linearity for the first four hours
- The effects of autocatalysis⁶ become evident in the form of curvature (or at least a change in slope) of the plot after approximately four hours.



- Results of these kinetic studies are reported in Table 1 as the fourth-order (k_4) and apparent second-order (k_2) rate constants.

Table 1. Rate Constants (First 4 h) for the MBH Reaction of p-Nitrobenzaldehyde (A) and Ethyl Acrylate (E) in CD₃CN with Catalysis by DABCO

[A] ₀	[E] ₀	k ₄ (M ⁴ s ⁻¹)	R ²	k ₂ (M ² s ⁻¹)	R ²
0.602	0.693	6.4 × 10 ⁻⁴	0.995	2.2 × 10 ⁻⁴	0.996
0.615	0.385	5.4 × 10 ⁻⁴	0.994	2.4 × 10 ⁻⁴	0.997
0.623	0.172	5.2 × 10 ⁻⁴	0.995	2.6 × 10 ⁻⁴	0.993
0.060	0.775	6.3 × 10 ⁻⁴	0.987	3.3 × 10 ⁻⁵	0.992

Reaction conditions: Solutions were prepared by mixing 0.50 mL of (1.0 M aldehyde + 1.0 M DABCO) or (0.1 M aldehyde + 1.0 M DABCO) in CD₃CN with 0.25 mL of CD₃CN. The reaction was started by the addition of neat ethyl acrylate to the tube by syringe and rapidly mixing (vortex mixer). Initial concentrations of all species were related to the concentration of DABCO by means of the ¹H NMR integration.

Observed Kinetics: Alcohol Added

- Addition of either ethylene glycol or triethanolamine accelerates the reaction
- Addition of glycols changes reaction kinetics from pseudo-third order to pseudo-second order.
- Pseudo-second order rate constants for the MBH reaction in CD₃CN in the presence of ethylene glycol and triethanolamine are gathered in Table 2.

Table 2. Rate Constants (First 4 h) for the MBH Reaction of p-Nitrobenzaldehyde and Ethyl Acrylate in CD₃CN with Catalysis by DABCO in the Presence of Ethylene Glycol (EG) and Triethanolamine (TEA)

alcohol	[ROH]	k ₂ (M ² s ⁻¹)	R ²
EG	0.10	2.70 × 10 ⁻⁴	0.995
EG	0.18	2.83 × 10 ⁻⁴	0.998
EG	0.50	3.24 × 10 ⁻⁴	0.998
EG	1.02	3.90 × 10 ⁻⁴	0.999
TEA	0.10	2.92 × 10 ⁻⁴	0.999
TEA	0.21	3.12 × 10 ⁻⁴	0.994
TEA	0.44	3.51 × 10 ⁻⁴	0.997
TEA	0.83	4.31 × 10 ⁻⁴	0.968

Reaction conditions: Solutions were prepared by mixing 0.50 mL of (1.0 M aldehyde + 1.0 M DABCO) in CD₃CN with the requisite volume of 2.0 M alcohol in CD₃CN and sufficient CD₃CN to make a total volume of 0.75 mL. The reaction was started by the addition of 0.070 g of neat ethyl acrylate to the tube by syringe and rapidly mixing (vortex mixer). Initial concentrations of all species were related to the concentration of DABCO by means of the ¹H NMR integration.

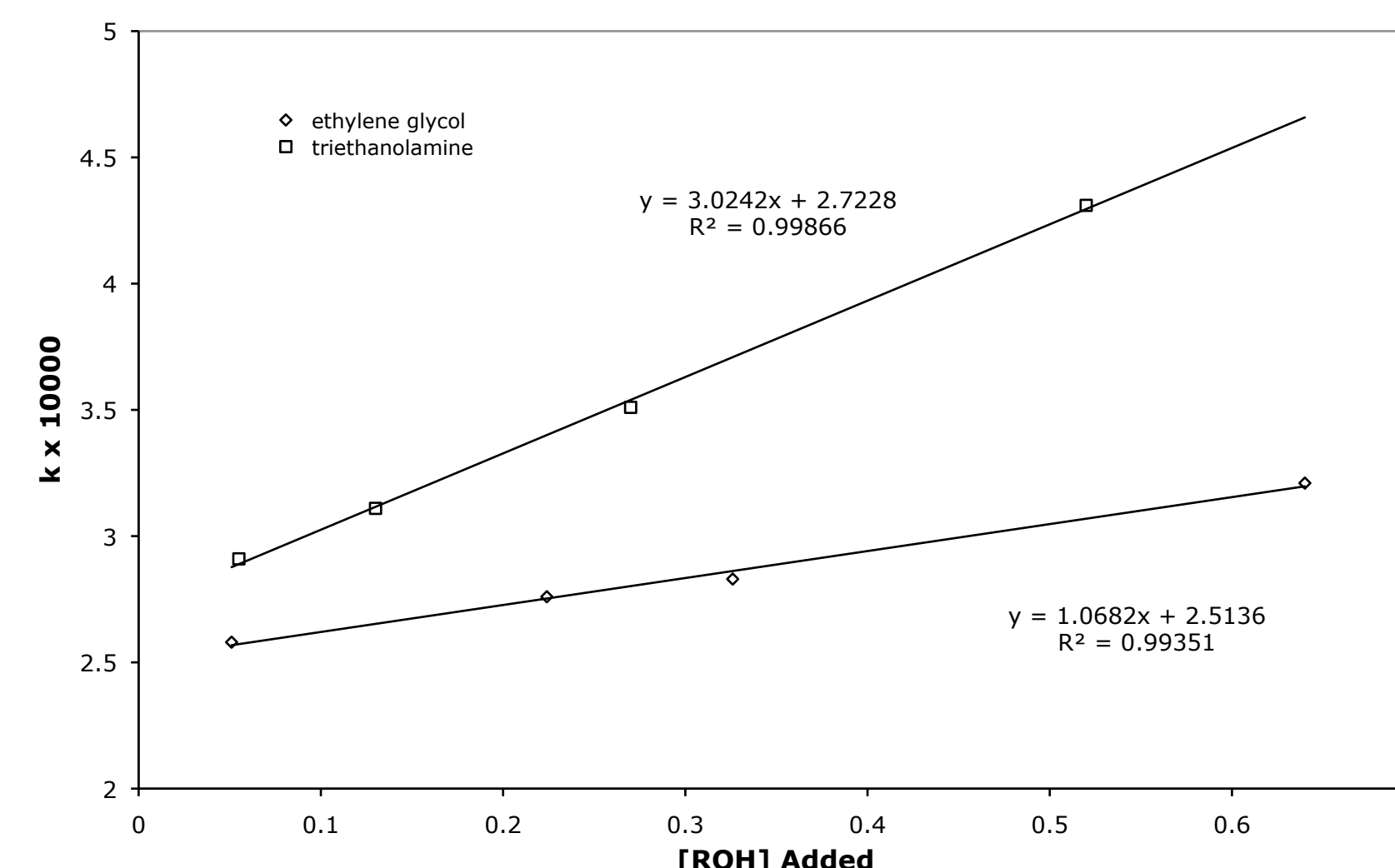
- Propylene glycol, ethyl cellosolve, butyl cellosolve, and diethylene glycol monoethyl ether all accelerate the reaction.
- We have observed excellent pseudo-second order kinetics when these alcohols are added.
- These alcohols were chosen to maintain the overall polarity of the alcohol (especially near the hydroxyl group) within a reasonably narrow range.
- The pseudo-second order rate constants (k_2), and the pseudo-third order rate constants (k_3 , adjusted for the alcohol concentration) are gathered in Table 3.

Table 3. Pseudo-second- and third-order Rate Constants for MBH Reaction with Added Alcohols

Alcohol	[ROH]	k ₂ (M ² s ⁻¹) (R ²)	k ₃ (M ³ s ⁻¹)
BuOCH ₂ CH ₂ OH	0.52 M	2.4 × 10 ⁻⁴ 0.998	4.6 × 10 ⁻⁴
EtO(CH ₂ CH ₂ O) ₂ H	0.58 M	2.5 × 10 ⁻⁴ 0.999	4.3 × 10 ⁻⁴
EtOCH ₂ CH ₂ OH	0.53 M	2.9 × 10 ⁻⁴ 0.996	5.5 × 10 ⁻⁴
HOCH ₂ CH ₂ OH	0.61 M	3.9 × 10 ⁻⁴ 0.999	6.4 × 10 ⁻⁴
HOCH ₂ CH(OH)CH ₃	0.52 M	2.8 × 10 ⁻⁴ 0.999	5.4 × 10 ⁻⁴
(HOCH ₂ CH ₂) ₃ N	0.50 M	4.3 × 10 ⁻⁴ 0.999	8.6 × 10 ⁻⁴

Reaction conditions: Solutions were prepared as described in the footnote to Table 2 using 250 μL of 2.0 M solutions of the alcohol.

Effects of Ethylene Glycol and Triethanolamine on the Pseudo-Second Order Rate Constants for the MBH Reaction



RESULTS AND CONCLUSIONS

- Triethanolamine is not an effective catalyst for the MBH reaction when used alone.
- Observed reaction kinetics are third-order for the first four hours in the absence of added alcohols:

$$\text{Rate} = k_{\text{obs}} [\text{A}]^2 [\text{E}]$$

- Effects of autocatalysis by the product begin to appear after approximately 4 hours under our reaction conditions.
- Added alcohols change the observed kinetics of the reaction to second-order:

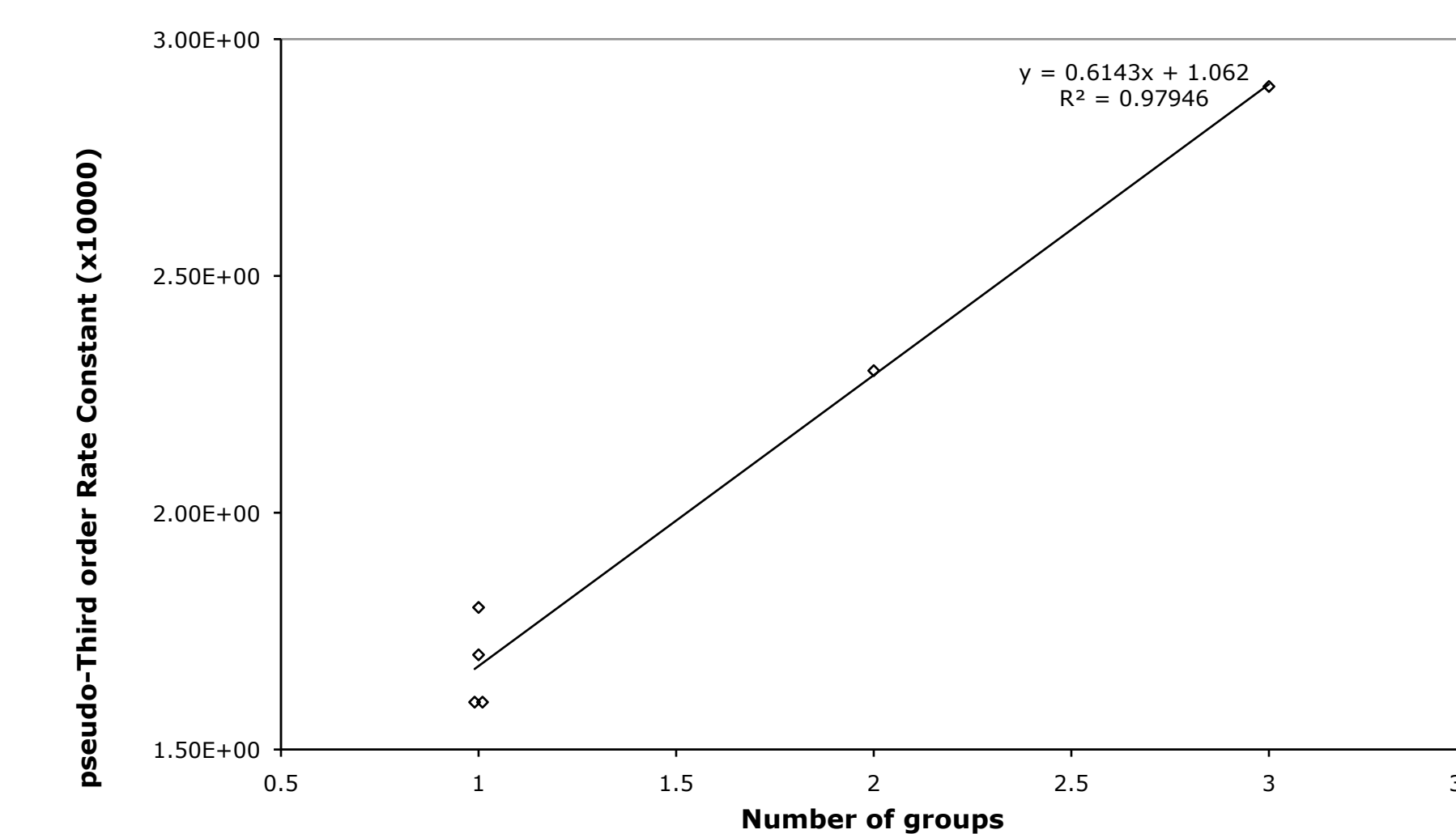
$$\text{Rate} = k_{\text{obs}} [\text{A}] [\text{E}]$$

- Observed pseudo-second-order rate constant is dependent on alcohol concentration
- Effects of added alcohols on the magnitude of the rate constant are modest, at best.
- The rate constants for the six alcohols studied to obey a reasonable linear relationship with the number, n , of hydroxymethyl groups in the alcohol:

$$k = 0.6 \times 10^{-n} + 1.1 \times 10^{-5} \quad (R^2 = 0.955)$$

- The rate constants do not correlate well with the number of hydroxyl groups in the alcohol or the polarity of the alcohol.
- This limits the effectiveness of alcohols as rate-enhancers for the amine-catalyzed MBH reaction

Correlation of Rate Constants with Number of Hydroxymethyl Groups



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