H), 1.50-1.20 (m, 4 H), 1.17 (d, J = 6.7 Hz, 3 H), 1.12-0.89 (m, 4 H), 0.82 (d, J = 5.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 69.9, 60.0, 50.9, 36.0, 34.0, 33.9, 33.2, 32.8, 25.7, 18.8, 11.8. MS (EI): m/z 168.1503 (M^+), 153, 122, 109, 95, 81, 67, 55, 41. Anal. Calcd for $C_{11}H_{20}O_1$: C, 78.51; H, 11.98. Found: C, 78.67; H, 11.83.

3,4,4aβ,5,6,7,8,8aα-Octahydro-8α-methyl-1β-(phenylthio)-1*H*-2-benzopyran (16). Acetate **11** (51.2 mg, 0.240 mmol, 1.0 equiv) was dissolved in 2 mL of CH_2Cl_2 in a flame-dried flask and cooled to -78 °C under N_2. Thiophenol (32 mg, 0.288 mmol, 1.2 equiv) and BF_3·Et_2O (85 mg, 0.601 mmol, 2.5 equiv) were added via syringe, and the solution was allowed to stir for 15 min. The reaction was quenched with $NaHCO_3$, extracted (3 × 10 mL of CH_2Cl_2), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 1% Et_2O/hexanes) gave the product (59.9 mg, 0.228 mmol, 95%) as a clear oil, which upon standing gave fine white crystals: mp 49.5-50 °C. IR (neat): 3058, 2951, 2923, 2845, 1583, 1478, 1459, 1439, 1374, 1302, 1258, 1077, 1045, 1023, 992, 952, 748, 691 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (m, 2 H), 7.30-7.19 (m, 3 H), 5.53 (d, J = 4.3 Hz, 1 H), 4.31 (ddd, J = 12.2, 11.6, 2.5 Hz, 1 H), 3.69 (ddd, J = 11.6, 3.7, 1.2 Hz, 1 H), 1.72-1.64 (m, 3 H), 1.60-1.48 (m, 3 H), 1.43-1.31 (m, 3 H), 1.10-0.91 (m, 2 H), 0.91 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): *C* 136.0; *CH* 131.4, 128.9, 126.7, 88.6, 52.8, 34.8, 34.2; CH_2 60.41, 35.6, 34.1, 33.6, 25.6; CH_3 18.7; MS (CI, CH_4): m/z 263.1458 (M + H$^+$). Anal. Calcd for $C_{16}H_{22}OS$: C, 73.24; H, 8.46. Found: C, 73.42; H, 8.33.

3,4,4aβ,5,6,7,8,8aα-Octahydro-1β,8α-dimethyl-1*H*-2-benzopyran (15). (Phenylthio)benzopyran **16** (47 mg, 0.177 mmol, 1.0 equiv) was dissolved in 2 mL of THF in a flame-dried flask and cooled to -78 °C. An ~0.2 N solution of lithium di-*tert*-butylbiphenylide in THF at -78 °C was added by cannula into the solution containing **16** until a dark green color persisted (~1.9 mL, 0.372 mmol, 2.1 equiv). The solution was stirred for 10 min, followed by the slow addition of Me_2SO_4 (334 μL, 3.5 mmol, 20 equiv). The solution was stirred an additional 10 min, followed by the addition of 5 mL of saturated NH_4Cl. The mixture was allowed to warm to room temperature, diluted with 15 mL of H_2O, extracted (3 × 10 mL of Et_2O), dried ($MgSO_4$), and concentrated from an ice bath under reduced pressure. Purification by flash chromatography (SiO_2, 2% Et_2O/hexanes) gave 33.2 mg of an inseparable mixture of the axial methylated product **15** (38%) and a protonated side product (61%). Spectroscopic data and the GC retention time for compound **15** matched those of the minor isomer in the reductive decyanation of **13**.

Acknowledgment. Support has been provided by the Minnesota Supercomputer Institute, the McKnight Land-Grant Professorship Program, and the National Science Foundation Presidential Young Investigator Program. Additional support was provided by the Eastman Kodak Company and Eli Lilly and Company as a 1991 Lilly Grantee. We thank Dr. Michael J. Frisch of Lorentzian Inc. for carrying out the UMP2 calculations on **22ax** and **22eq**.

Note Added in Proof. The stereochemical outcome of dissolving metal reductions on cyclic and acyclic ketones has recently been examined by ab initio methods: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656-1661.

Supplementary Material Available: Geometries of 6-31G* unconstrained minima for **17ax, 17eq, 17ts, 18ax, 18eq, 21c, 21b, 22ax**, and **22eq** (12 pages). Ordering information is given on any current masthead page.

Imidazole Buffer-Catalyzed Cleavage and Isomerization Reactions of Dinucleotides: The Proposed Mechanism Is Incompatible with the Kinetic Measurements

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Abstract: It is shown that the mechanism and the kinetic model proposed for the imidazole-catalyzed cleavage and isomerization reactions of dinucleotides (Breslow, R.; Huang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 9621. Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 4473) are incompatible with the kinetic measurements.

The difficulties in proceeding from kinetic measurements to mechanistic elucidation have been discussed extensively.[1] Errors and ambiguities in mechanistic interpretations are not uncommon.[2] A case in point relates to recent studies on dinucleotides. To account for their kinetic measurements of the cleavage and isomerization reactions of 3',5''-uridylyluridine (3',5''-UpU), of its 2',5'' isomer (2',5''-UpU), and of 3',5''-adenyladenine, Breslow and co-workers (AB,[3] BH[4]) proposed a mechanism and a kinetic model. Recently, Menger[5] noted several shortcomings in Breslow's papers but did not take issue with the discrepancies between the functional dependences measured experimentally and those predicted by the proposed mechanism. The purpose of the present contribution is to point out that Breslow's proposed mechanism is incompatible with some of the observed functional dependences, that the kinetic model does not reproduce the reported rate constants, and that the proposed reactions of the postulated intermediate common to cleavage and isomerization are inconsistent with the kinetic measurements.

The rate of cleavage was found to have a "clean" first-order dependence upon total imidazole concentration and a bell-shaped dependence upon state of protonation.[6] The rate of isomerization was reported to "show no deviation from linearity in buffer concentration" and to be "near-linear" in state of protonation.[7] For each set of measurements at variable total buffer concentration but constant state of protonation, the measured pseudo-first-order rate constants were treated by linear least-squares to obtain the buffer-independent contributions at each value of the state of protonation. The extrapolated contributions at zero buffer con-

(1) (a) See for example: Lewis, E. S.; Bunnett, J. F. In *Techniques of Chemistry*, 3rd ed.; Lewis, E. S., Ed.; Wiley-Interscience: New York, 1974; Vol. VI, Chapters 1 and 8. (b) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.

(2) (a) Haim, A. *Inorg. Chem.* **1966**, *5*, 2081. (b) Haim, A. *J. Phys. Chem.* **1979**, *11*, 339. (c) Seaman, G. C.; Haim, A. *J. Am. Chem. Soc.* **1984**, *106*, 1319. (d) Haim, A. *Int. J. Chem. Kinet.* in press.

(3) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 4473.

(4) Breslow, R.; Huang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 9621.

(5) Menger, F. M. *J. Org. Chem.* **1991**, *56*, 6251.

(6) We adopt the definition that state of protonation is $[ImH^+]/[Im]_t$: Breslow, R.; Labelle, M. *J. Am. Chem. Soc.* **1986**, *108*, 2655.

(7) (a) For the experiments with no imidazolium chloride added, the rate decreases with increasing imidazole concentration. (b) In one instance, the change in rate with buffer is not linear: for $[Im]/[ImH^+] = 0$, the values of the pseudo-first-order rate constants are 0.19, 1.13, and 0.91 ($\times 10^{-3}$ h^{-1}) at buffer concentrations of 0.8, 1.3, and 2.0 M, respectively.[4]

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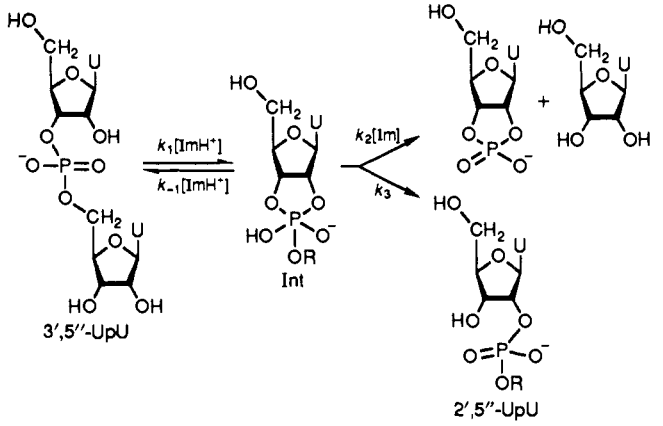
Scheme I. Breslow's Mechanism for the Imidazole-Catalyzed Cleavage and Isomerization Reactions of Dinucleotides



centration were subtracted from the observed rate constants and the resulting values (hereinafter referred to as corrected rate constants) were taken to represent the buffer-dependent rate constants.[3,4] It has been shown[5] that, if, as claimed[3,4] the buffer-independent and buffer-dependent pathways proceed via the same intermediate, the correction is inappropriate because the two pathways are in a competitive rather than an additive relationship.[8] Under these circumstances, the corrected rate constants would be an inaccurate measure of the catalyzed pathways. At this point, however, we accept the correction at face value and analyze Breslow's own interpretation of the corrected rate constants on the basis of his proposed mechanism and kinetic model. We will return later to the measured (uncorrected) rate constants.

Breslow's Interpretation of the Corrected Rate Constants

The mechanism, Scheme I, proposed to account for the observed functional dependences of the corrected rate constants features a bifunctional pathway with a phosphorane intermediate at steady state. The rate equations (eqs 1 and 2) derived from Scheme I

$$\text{rate of cleavage} = \frac{k_1k_2[\text{UpU}][\text{Im}][\text{ImH}^+]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3} \quad (1)$$

$$\text{rate of isomerization} = \frac{k_1k_3[\text{UpU}][\text{ImH}^+]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3} \quad (2)$$

are incompatible with the first-order buffer dependences observed for *both* cleavage and isomerization. In order to simplify the following analysis, we define $f = [\text{ImH}^+]/[\text{Im}]_t$ and recast eqs 1 and 2 as eqs 3 and 4. For cleavage to be first order in total

$$\text{rate of cleavage} = \frac{k_1k_2[\text{UpU}](1-f)f[\text{Im}]_t^2}{k_{-1}f[\text{Im}]_t + k_2(1-f)[\text{Im}]_t + k_3} \quad (3)$$

$$\text{rate of isomerization} = \frac{k_1k_3[\text{UpU}]f[\text{Im}]_t}{k_{-1}f[\text{Im}]_t + k_2(1-f)[\text{Im}]_t + k_3} \quad (4)$$

imidazole, it is necessary that $k_{-1}f[\text{Im}]_t + k_2(1-f)[\text{Im}]_t \gg k_3$. If this inequality is valid in eq 3, it must also be valid in eq 4. But then, the rate of isomerization would be zeroth order[9] in buffer,[10] a prediction in variance with the observed first-order

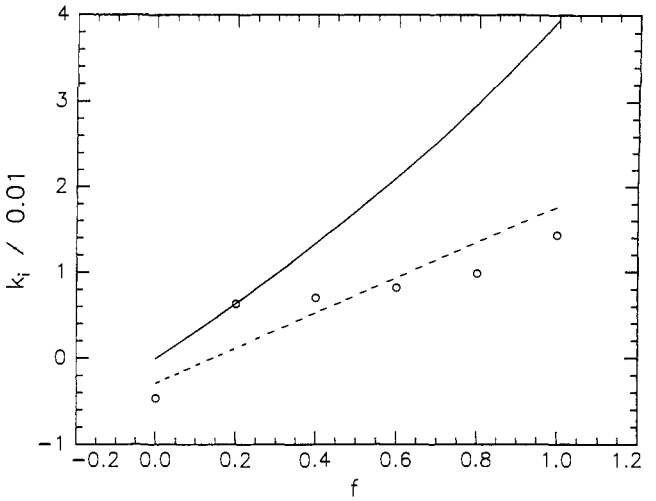


Figure 1. Corrected pseudo-first-order rate constants[13] for isomerization of 3',5''-UpU to 2',5''-UpU vs fraction of protonation of imidazole. Total imidazole concentration is 1.3 M. Circles, experimental points reported in Figure 7B of ref 3. Dashed line, curve calculated by AB with the parameters in Table I of ref 3. Solid line, curve recalculated in the present work with the same parameters.

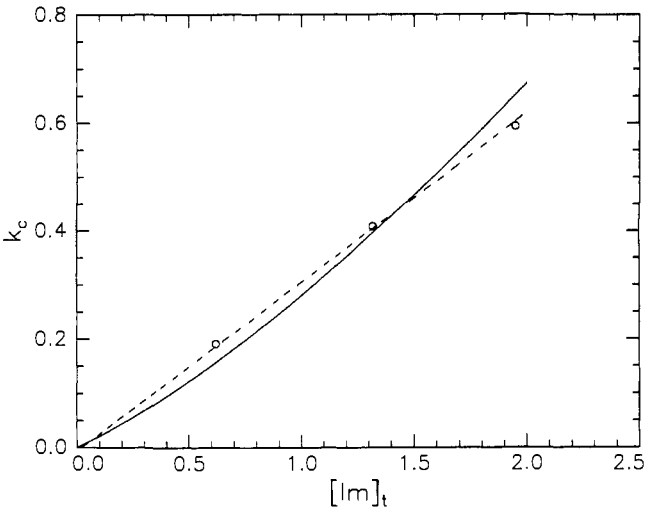


Figure 2. Corrected pseudo-first-order rate constants[13] for cleavage of 3',5''-UpU vs imidazole concentration. $[\text{ImH}^+]/[\text{Im}]_t = 0.4$. Circles, experimental points reported in Figure 1B of ref 3. Dashed line, curve calculated by AB with the parameters in Table I of ref 3. Solid line, curve recalculated in the present work with the same parameters.

dependence. In physical terms, the deficiency of Scheme I is seen by considering the competitive reactions of the postulated intermediate. The first-order dependence for cleavage requires that the fate of the intermediate be, principally, return to reactant or forward progress to cleavage product, with little contribution from isomerization. In contrast, the first-order dependence for isomerization requires that the dominant reaction of the intermediate be isomerization rather than cleavage and return to reactant. The required relative rates of reaction of the intermediate are contradictory for cleavage and for isomerization, and therefore the postulate of a common intermediate that undergoes partition as in Scheme I is inconsistent with the experimental findings. Additional results incongruent with the proposed mechanism relate to the reported[4] inhibition of isomerization by imidazole. The decrease in the rate of isomerization with an increase in [Im] at constant [ImH$^+$] was taken[4] to provide evidence for a common intermediate and was rationalized algebraically by the presence of the k_2 term in the denominator of eq 2 (and also eq 4). But if the k_2 term is sufficiently important to cause inhibition by imidazole, then isomerization cannot be first order in total imidazole nor in state of protonation, as found experimentally.

(8) The inappropriate correction, if the measurements are taken at face value, may be the origin[5] of the reported[4] negative rate constants. But see also footnotes 23–25.

(9) This may explain why AB stated that "the interpretation of the catalysis of isomerization by imidazolium ion is not simple".

(10) Alternatively, if the buffer dependence of isomerization is taken to be linear in buffer as reported, then from eq 4 the inequality $k_3 \gg k_{-1}f[\text{Im}]_t + k_2(1-f)[\text{Im}]_t$ must be obeyed. Since the inequality must also be applicable to eq 3, it is predicted that the rate of cleavage is second order in buffer concentration, in contrast with the observation of "no sign of upward deviation from linearity in the dependence upon buffer concentration". This alternative, however, is incompatible with the observation that isomerization is considerably slower than cleavage.

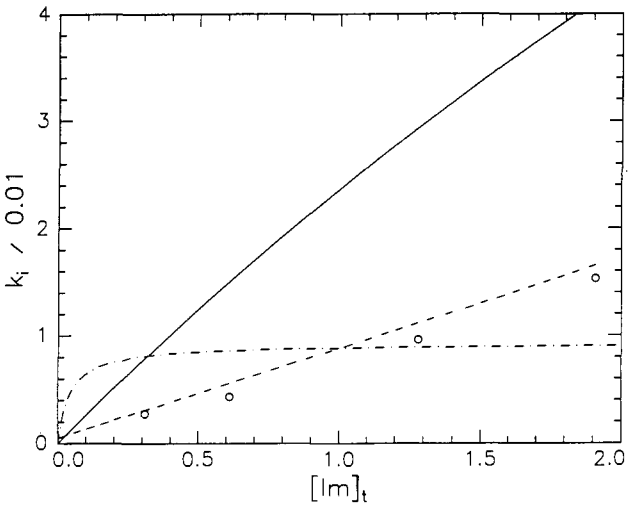


Figure 3. Corrected pseudo-first-order rate constants[13] for isomerization of 3′,5″-UpU vs imidazole concentration. $[ImH^+]/[Im]_t = 0.8$. Circles, experimental points reported in Figure 5B of ref 3. Dashed line, curve calculated by AB with the parameters in Table I of ref 3. Solid line, curve recalculated in the present work with the same parameters. Dotted-dashed line, curve calculated with the nonlinear least-squares parameters given in the text.

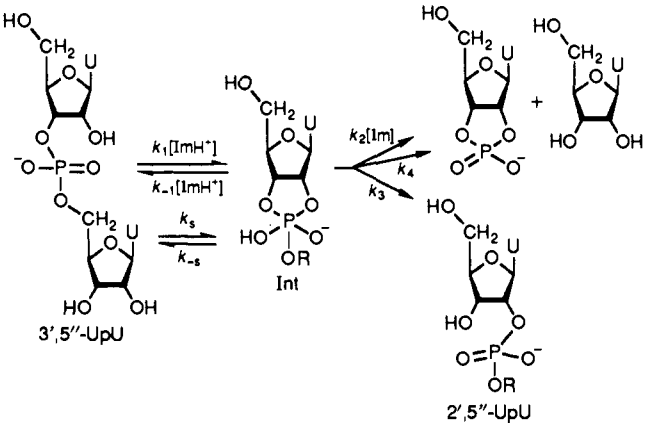
A further illustration of the discrepancies between the proposed mechanism and the experimental results comes from a numerical analysis of the corrected rate constants in the context of the kinetic model (eqs 5 and 6) offered[3,4] to account for the finite rates of

$$\text{rate of cleavage} = \frac{k_1k_2[\text{UpU}][\text{ImH}^+][\text{Im}]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3 + k_w} + k'[\text{Im}] + k''[\text{ImH}^+] \quad (5)$$

$$\text{rate of isomerization} = \frac{k_1k_3[\text{UpU}][\text{ImH}^+]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3 + k_w} \quad (6)$$

cleavage (~60 and ~75% of the maximum rate) at 0 and 100% imidazole protonation. k_w is the rate constant for the return of the intermediate to reactant via a buffer-independent pathway.[11] k' and k'' represent pathways that lead to cleavage but may or may not[6] involve the intermediate. AB optimized the rate constants in eqs 5 and 6 to fit their measurements and reported the numerical values[12] (Table I of AB). Before we present the results of our numerical analysis, we note a serious problem with AB's kinetic model and the rate constants reported in their Table I. AB claims that eqs 5 and 6 with the values of the rate constants given in their table provide an acceptable fit to their data (and thus "lend credence to our interpretation"). This is incorrect. Several of the calculated lines in AB's Figures 1–8 are erroneous. As examples, Figures 1–3 of the present paper display the corrected pseudo-first-order rate constants for the isomerization and cleavage reactions of 3′,5″-UpU (circles), the lines reported by AB (dashed lines), and the curves we recalculated (solid lines) utilizing the *same* model and rate constants.[13,14] Note that the

Scheme II. Breslow's Mechanism for the Imidazole-Catalyzed Cleavage and Isomerization Reactions of Dinucleotides Modified to Account for the Solvent Contributions



line reported by AB in Figure 1 has a negative intercept, in contrast with the zero intercept predicted by eq 6. Also, our calculated lines exhibit curvature, as predicted on the basis of eqs 5 and 6 and the reported[3] rate constants, whereas the incorrect curves calculated by AB appear to be linear.[14] The results of our numerical analysis also show that the postulate of a common intermediate in the context of the proposed kinetic model is at odds with the measurements. A nonlinear least-squares fit of the corrected rate constants[15] for cleavage to eq 7 yields values of k_1

$$k_{cor} \text{ for cleavage} = \frac{k_1k_2[\text{ImH}^+][\text{Im}]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3 + k_w} + k_c'[\text{Im}] + k_c''[\text{ImH}^+] \quad (7)$$

$$k_{cor} \text{ for isomerization} = \frac{k_1k_3[\text{ImH}^+]}{k_{-1}[\text{ImH}^+] + k_2[\text{Im}] + k_3 + k_w} \quad (8)$$

$= 0.298 \pm 0.064$, $(k_{-1}/k_2) = 0.387 \pm 0.222$, $(k_3 + k_w)/k_2 = 0.022 \pm 0.170$, $k_c' = 0.243 \pm 0.009$, $k_c'' = 0.185 \pm 0.009$.[16] Our parameters provide a better fit[17] of the data for cleavage than those in Table I of AB. The unweighted sum of the squares of the deviations is 4.63×10^{-3} for the calculations with our parameters compared with 1.49×10^{-2} for the calculations with the parameters in Table I of AB. Moreover, with the small value of $(k_3 + k_w)/k_2$ (0.022, zero within the rather large standard deviation, compared to 3.20 reported[18] by AB), our calculated curves of pseudo-first-order rate constants for cleavage vs total imidazole concen-

(11) The question of microscopic reversibility deserves some elaboration. If eqs 5 and 6 (eqs 1 and 2 of AB) are rigorous kinetic rate laws derived from a mechanism and each rate constant represents an elementary step (or the product of a rapid equilibrium and an elementary step), then microscopic reversibility is violated. If the denominator has a k_w term that corresponds to reaction of the intermediate with water, then there must be a term in the numerator that corresponds to generation of the intermediate by reaction of the substrate with water.[5] On the other hand, if the equations are taken to represent empirical equations ("kinetic model") with the solvent contribution removed, then there is no need to be concerned about microscopic reversibility. But of course, under these circumstances the assignment of the k_w term to an elementary reaction for which there is no microscopic reverse is inappropriate.

(12) Throughout their paper, AB give incorrect units for their reported rate constants. The captions of Figures 1–9 state that they are plots of pseudo-first-order rate constants vs concentration or state of protonation but the units for the ordinate are μM/min. In Table I of ref 3, AB report first- and second-order rate constants but give units of μM/min for all the constants.

(13) We take the figures in AB to be plots of pseudo-first-order rate constants, as stated in the captions and in parts of the text. However, in other parts of the text the plots are referred to as representing rates of reaction. Regardless as to whether they are rates or rate constants, the *numerical values* in Figures 1–3 of the present paper are conmensurate with the *numerical values* in the figures of AB.

(14) The solid lines in Figures 1–3 are plots of pseudo-first-order rate constants that we calculated utilizing the constants in Table I (ref 3) of AB and eqs 5 and 6, except that [UpU] was omitted from the equations. On this basis, there is agreement (~10%) between our calculations for cleavage and those of AB, but for isomerization our calculations differ from those of AB by several fold. Also, our calculated lines are curved, whereas all lines drawn by AB in their Figures 1B, 2B, 5–8B appear to be linear, when in fact their model and reported rate constants predict curvature. We have no explanation for the discrepancies.

(15) If the reported values in the figures are rates rather than rate constants, then the fitted values of the constants k_1, k_c', and k_c'' include the concentration of substrate.

(16) For mechanisms involving steady state intermediates, only ratios of rate constants for elementary reactions of the intermediate can be obtained from conventional kinetic measurements.

(17) We first fitted the data for cleavage *only* whereas BA attempted to carry out a *simultaneous* fit of cleavage and isomerization.

(18) The large value of $(k_3 + k_w)/k_2$ reported by AB is needed if the linear dependence of isomerization upon buffer is to be accounted for, but this introduces upward curvature in the cleavage plots.

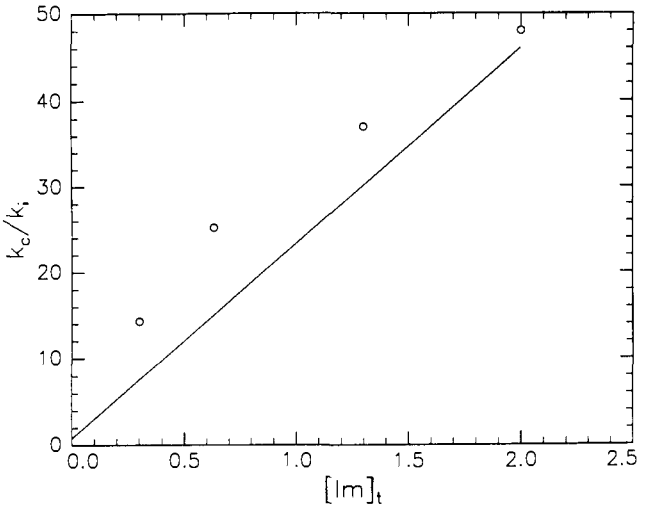


Figure 4. Ratio of cleavage to isomerization uncorrected rate constants for 2′,5″-UpU vs total imidazole concentration. State of protonation 0. Circles, experimental values from ref 1. Solid line, calculated with the parameters given in the text.

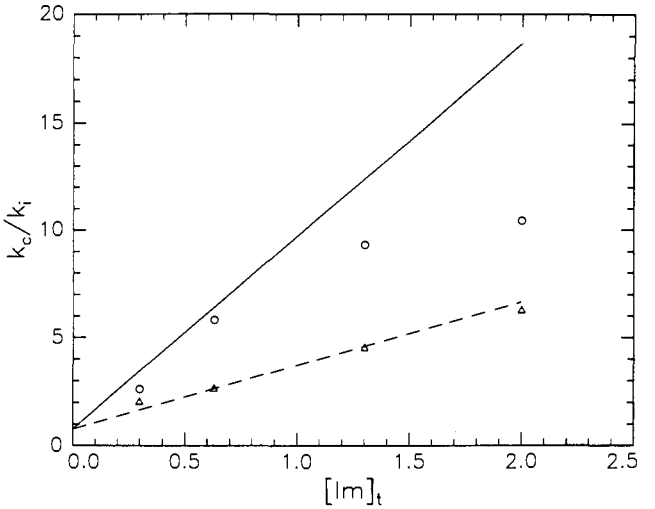


Figure 5. Ratio of cleavage to isomerization uncorrected rate constants for 2′,5″-UpU vs total imidazole concentration. State of protonation: for circles and solid line 0.6; for triangles and dashed line, 0.87. Circles and triangles, experimental values from ref 1. Solid and dashed lines, calculated with the parameters given in the text.

tration are linear. If the cleavage and isomerization reactions proceed via a common intermediate, then we must be able to fit the kinetics of the two reactions with the same values of the common parameters k_1, k_{-1}/k_2, and $(k_3 + k_w)/k_2$. A nonlinear least-squares treatment of isomerization according to eq 8 and keeping the common parameters fixed at the values given above yielded $k_3/k_2 = (1.97 \pm 0.21) \times 10^{-2}$ M. Although the value is physically reasonable (isomerization is considerably slower than cleavage), the fits, as shown in Figure 2, are unacceptable: the saturation kinetics is at variance with the observed first-order dependence. In fact, the independence of k_{cor} for isomerization with respect to imidazole above $[Im]_t = 0.1$ M confirms quantitatively the qualitative argument presented earlier, namely, if cleavage is first order in imidazole, isomerization must become zeroth order if it is to proceed via the common intermediate of Scheme I. Evidently, the kinetic model cannot account for the observed functional dependences of the corrected rate constants for both cleavage and isomerization, and thus, contrary to the claim,[3] the model provides no support for the proposed interpretation.

Treatment of the Measured Rate Constants

We now turn to a possible mechanistic interpretation of the measured (e.g., uncorrected) rate constants. One of the claims in BH is that the (corrected) negative rate constants "reflect a decrease in the rate of uncatalyzed (by buffer) isomerization when imidazole is added". Under these circumstances, it is apparent that, if buffer-dependent and buffer-independent pathways proceed via the same intermediate, the corrected rate constants utilized by AB and BH provide an inaccurate measure of the buffer-dependent pathways. Therefore, it is important to carry out a mechanistic analysis of the *uncorrected* rate constants. The pertinent mechanism, Scheme II, is basically Breslow's mechanism augmented by the three solvent elementary steps needed to account for the buffer-independent contributions.[19] For convenience in presentation and because Breslow's key claim[3,4] is that the kinetic measurements *prove* that there is a common intermediate for cleavage and isomerization, we focus on the ratio of measured rate constants for cleavage (k_c) to isomerization (k_i).[20] On the basis of Scheme II, k_c/k_i is given by eq 9. The uncorrected rate

$$(k_c/k_i) = (k_4/k_3) + (k_2/k_3)(1 - f)[Im]_t \qquad (9)$$

constants for the reactions of 2′,5″-UpU were fitted to eq 9 by least squares and yielded $(k_4/k_3) = 0.77 \pm 1.85$ and $(k_2/k_3) = 22.6 \pm 2.5$ M. The experimental values and the lines calculated on the basis of eq 9 and the least-squares parameters are depicted in Figures 4–6. It will be seen that, except for the data at $f = 0.87$, there is very poor agreement between the predictions from the mechanism and the experimental observations.[21] In particular, it will be seen that linear and inverse linear dependences of k_c/k_i upon $[Im]_t$ and upon f, respectively, are predicted from Scheme II, whereas the data exhibit pronounced curvature. Moreover, the deviations between experimental points and least-squares fits are not random. Evidently, just as the corrected rate constants do not conform to Breslow's preferred mechanism, the uncorrected rate constants do not conform to the same mechanism modified

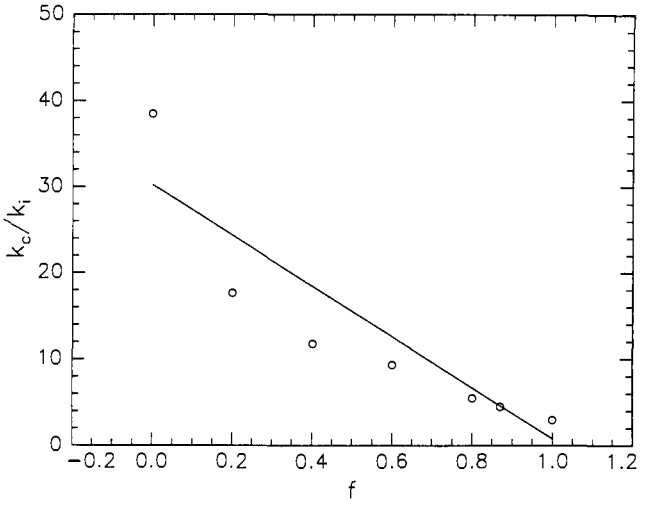


Figure 6. Ratio of cleavage to isomerization uncorrected rate constants for 2′,5″-UpU vs state of protonation. $[Im]_t = 1.3$ M. Circles, experimental values from ref 1. Solid line, calculated with the parameters given in the text.

(19) Scheme II may be an oversimplification because only pH-independent solvent pathways are included.

(20) Since we are dealing with *ratios*, it does not matter, as long as the substrate concentration is constant, whether the plots in AB refer to rates or rate constants.

(21) We attempted to fit the uncorrected rate constants for cleavage to the rate equation derived from Scheme II but met with failure. Values of k_{-1}/k_4 for 3′,5″-UpU and of k_s and k_{-1}/k_4 for 2′,5″-UpU were negative. The negative value of k_s for 2′,5″-UpU is particularly distressing because k_s was included in order to account for the buffer-independent reactions. Good fits for cleavage (albeit with standard deviations of the constants larger than the values of the constants) were obtained if the k_c' and k_c'' terms (cf. eq 7) were included in the rate equation derived from Scheme II. But then, the optimized parameters predict a decrease in rate of isomerization with increasing buffer concentration for all values of the state of protonation, in contrast with the observation in AB that only for 0 state of protonation does the rate decrease.

to account for the buffer-independent reactions.

Conclusion

In view of the serious discrepancies noted above, it is apparent that Breslow's proposed mechanism and postulated reactions of the common intermediate as in Schemes I or II are not supported by the measured[3,4] functional dependences of the rates of cleavage and isomerization. Modifications to the mechanism, such as the addition of buffer-dependent terms to the reaction of the intermediate that leads to isomerization or reversing the role of the two components of the buffer, but keeping the requirement of a common intermediate, also yield rate laws incompatible with the reported functional dependences. Since the key claims in BH and AB are based on the purported agreement between rate measurements and proposed mechanism, it is evident that several of Breslow's mechanistic inferences can no longer be taken as proven. One of the claims in AB is that two mechanisms that bear a mirror image relationship are indistinguishable on the basis of the kinetic measurements of cleavage only, but that the ambiguity was resolved by considering the kinetics of isomerization. With the revelation that the proposed mechanism is incompatible with the reported rates, the kinetic ambiguity remains unresolved. The case for questioning BH is even more compelling because here the whole study revolves around the flawed[22] demonstration of a common intermediate.

In the foregoing analyses of the kinetic measurements and of the implications of the proposed mechanism and kinetic model, the reported rate constants were taken at face value. However, it must be noted that the studies were carried out at variable ionic strength[23] and pH[24] and therefore the reported rate measurements are of limited value in arriving at detailed mechanistic conclusions.[25] Under these circumstances, although the proposed mechanism and the claim of a common intermediate are not sustained by the kinetic data, some of the postulated reactions in Schemes I or II may be operative.

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(22) In principle, detailed kinetic and stoichiometric studies are helpful in demonstrating the occurrence of intermediates along reaction pathways. In this context, we note that Breslow's claim[4] of an "unusual kinetic tool" is a minor variation on the well-known common ion retardation and chemical competition methodologies: Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: New York, 1953.

(23) Since the pK_a of ImH^+ varies with ionic strength (the values are 7.01, 7.18, 7.31, and 7.90 at 25 °C and ionic strength 0.1, 0.5, 1.0, and 3.0: Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum: New York, 1989; Vol. 5), even solutions with the same $[ImH^+]/[Im]$ ratio will differ slightly in pH.

(24) Nearly half the measurements were carried out with only one of the two buffer components added and therefore at variable pH. For example, the calculated values of pH for 0.10 and 1.0 M solutions of imidazole are 10.0 and 10.7, respectively.

(25) Specifically, we note that the bulk of the experiments which exhibit a decrease in rate of isomerization with increasing buffer concentration (and thus negative corrected rate constants) were carried out at 0 state of protonation (only imidazole, no imidazolium added). Under these circumstances, an increase in imidazole is accompanied by an increase in pH.[24] Since there is evidence that the rate of the buffer-independent isomerization decreases with increasing pH (the intercepts at 0 buffer concentration in Figures 5 and 6 of AB increase with a decrease in pH), the reported decrease in rate with increasing imidazole concentration may simply be a manifestation of the decrease in the rate of the buffer-independent contribution and may bear no relationship to the mechanism of the buffer-catalyzed pathways.

Computational Study of Jahn–Teller Type Distortions in Radical Cations of Methyl-Substituted Cyclopropanes

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Abstract: We have studied Jahn–Teller (JT) type distortions in a series of methyl-substituted cyclopropane cations with ab initio molecular orbital techniques. Two sets of cyclopropane cation structures are considered for the parent (**1a**) and the 1-methyl-substituted (**1b**), 1,1-dimethyl-substituted (**1c**), 2,3-dimethyl-substituted (**1d** (trans), **1e** (cis)), and 2,2,3,3-tetramethyl-substituted (**1f**) species. These structures reflect the first-order JT distortions occurring in the parent cation (**1a**) from a doubly degenerate $^2E'$ (D_{3h} symmetry) ground state to nondegenerate states of $^2A_1$ and $^2B_2$ symmetry (C_{2v} point group). States of the "$^2A_1$ type" possess one long and two short ring C–C bonds, are always structural minima on their respective potential energy surfaces, and represent the minimum energy structures for **1a**, **1d**, **1e**, and **1f**. The "$^2B_2$-type" states are structurally characterized by two long and one short ring C–C bonds and are always transition states, although they are the preferred first-order JT type distorted structures for both 1-methylated cations (**1b,c**). Unsymmetrical (scalene) triangular structures actually represent the absolute minima for **1b** and **1c**. These structures may be viewed as distorted from the "$^2B_2$-type" geometries via a second-order JT type mechanism or, alternatively, as "$^2A_1$-type" with the substituents at the "wrong" carbon atom. The predicted fine-tuning of cation state preference and substantial differences in spin density distributions should be verifiable by spectroscopic means (ESR). The qualitative charge density distributions might be probed by chemical means (nucleophilic capture); an unequivocal interpretation is questionable, however.

Radical cations of cyclopropane (**1a**) and derivatives have attracted considerable attention for over one decade. Molecular orbital calculations suggest that the vertical ionization of cyclopropane occurs from a degenerate pair of in-plane e′ orbitals (**2**, **3**); first-order Jahn–Teller (JT) distortion of the resulting doubly degenerate $^2E'$ state leads to two nondegenerate electronic states, $^2A_1$ and $^2B_2$ (C_{2v} symmetry).[1-7] The $^2A_1$ component (orbital **2** singly occupied) relaxes to an equilibrium structure with one lengthened C–C bond, which is accepted as the lowest energy

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