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Proton Transfer Reactions of Methylanthracene Radical Cations with Nitrogen-Centered Bases under Non-Steady-State Conditions. A Search for the Possible Effect of Reactant Impurities upon the Kinetic Data

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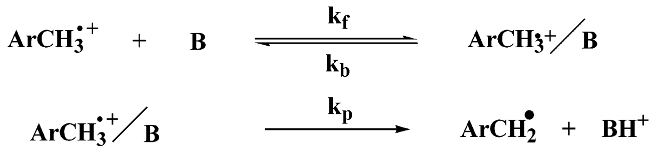

At a recent conference, the issue was raised that our earlier non-steady-state kinetic studies[1−3] may be in error because of the effects of possible impurities in the N-centered bases employed. This prompted our reinvestigation of these systems with that possibility in mind. It was pointed out that in a series of reactions, if a reactive impurity affects the kinetics in one reaction, then it would exert a consistent effect on the kinetics of all of the reactions in the series. Experimental data for three different series of reactions, proton transfer reactions of 2,6-dimethylpyridine, 2,6-diethylpyridine, and 2,6-diphenylpyridine with four different methylanthracene radical cations, were concurrently examined for possible reactant impurity problems. The analysis confirms that the simulated data for the simple second-order mechanism in the presence of a reactive impurity do not fit experimental data for the proton transfer reactions. The hypothesis that deviations from simple second-order kinetics are caused by the presence of reactive impurities is not valid. It was concluded that the presence of reactive impurities was not a significant problem in the studies of proton transfer reactions of methylanthracene radical cations with pyridine bases.

Introduction

Our recent non-steady-state kinetic studies of the proton transfer reactions of methylanthracene radical cations with substituted pyridines[1−3] resulted in the conclusion that the reactions take place by a two-step mechanism involving the formation of a kinetically significant reactant complex. The proton transfer reactions of organic radical cations have been an active area of research over the past 25 years.[4−9] The mechanism of the reaction has up until recently[1−3] been treated as a single-step reaction between the methylarene radical cation and the base to generate the corresponding benzylic radical, which is rapidly converted to products.

The possible effects of impurities in 2,6-dimethylpyridine on our kinetic results for proton transfer reactions of methylanthracene radical cations[1−3] have been brought to our attention at a recent conference. The purpose of this article is to address whether there is any significant effect of impurities in the N-centered bases on our non-steady-state kinetic studies of the reactions of 9,10-dimethylanthracene (DMA) and 9-methyl-10-phenylanthracene (MPA) radical cations with 2,6-disubstituted pyridines.

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Experimental Section

Materials. Commercially available 2,6-lutidine (99+%) was fractionally distilled twice under reduced pressure. Several fractions were collected, and only the mid-fraction was used. 2,6-Diphenylpyridine (97%) was recrystallized three times from 2-propanol. 2,6-Diethylpyridine was prepared using a literature procedure and carefully purified by column chromatography.[10] The substrates DMA, DMA-d_6, MPA, and MPA-d_3 were those used in a previous study.[1]

Instrumentation and Data Handling Procedures. Cyclic voltammetry was performed using a commercially available potentiostat and function generator. After passing through a low pass filter, the data were recorded on a digital oscilloscope with 12-bit resolution. The oscilloscope and function generator were controlled by a personal computer via an IEEE interface.

The current−potential curves were collected at selected trigger intervals to reduce periodic noise,[11] and 10 or more curves were averaged before treating with a frequency domain low pass digital filter and numerical differentiation. The standard deviation in R_I' obtained in this way was observed to equal ±0.004.

Cyclic Voltammetry Measurements. A standard three-electrode one-compartment cell was used for all kinetic measurements. Positive feedback IR compensation was used to minimize the effects of uncompensated solution resistance. Reference electrodes were Ag/AgNO$_3$ (0.01 M) in acetonitrile constructed in the manner described by Moe.[12] The working electrodes, 0.2−0.8 mm Pt, were prepared by sealing wire in glass and polishing to a planar surface as described previously.[13] The working electrodes were cleaned before each series of measurements with a fine polishing powder and wiped with a soft cloth. The cell was immersed in a water bath controlled to ±0.2 °C.

Kinetic Measurements. Rate constants were obtained by comparing derivative cyclic voltammetry (DCV)[14] data to that obtained by digital simulation. The observable in DCV is the ratio of the height of the derivative peak on the return scan to that observed on the forward scan (R_I'), and the electrochemical variable is the voltage sweep rate (v). The reactions were studied using solutions (CH$_2$Cl$_2$/0.2 M Bu$_4$NPF$_6$) containing substrate (1.00 mM) and base (2−50 mM) at 291 K. The experimental R_I'/v data were adjusted to 0.05 R_I' intervals in the range 0.85−0.50 by linear log−log interpolation. We have previously observed that log R_I'/log v^{-1} curves are nearly linear in that interval.[15] To avoid interpolation error, several R_I' values were recorded very close to either side of the desired value and averaged before interpolation. For example, to determine $v_{0.5}$, the voltage sweep rate where R_I' is equal to 0.50, v values were selected to give R_I' equal to about 0.51−0.52 and about 0.48−0.49. Ten or more determinations were made in these ranges, and the average values were then used in the interpolation. The minimum number of experimental cyclic voltammograms processed to give a single R_I' value was 20, and most R_I' values were derived from more than 50 experimental voltammograms. The resulting v values, for example $v_{0.85}$ or $v_{0.5}$, were directly proportional to apparent rate constants at the extent of the reaction corresponding to R_I', that is, R_I' equal to 0.85 or 0.50 in the examples given.[16]

SCHEME 1

$$\mathbf{A} + \mathbf{B} \xrightarrow{k} \mathbf{C}$$

$$\mathbf{A} + \mathbf{B'} \xrightarrow{k_{imp}} \mathbf{C'}$$

TABLE 1. Apparent Second-Order Rate Constants for Radical Cation Proton Transfer Reactions[a]

reactants	$k_{app}{}^{H}$ (M^{-1} s^{-1})	$k_{app}{}^{D}$ (M^{-1} s^{-1})
DMA$^{\bullet+}$/DPP	601	44.3
DMA$^{\bullet+}$/LUT	4820	650
DMA$^{\bullet+}$/DEP	3030	387
MPA$^{\bullet+}$/DPP	485	44.0
MPA$^{\bullet+}$/LUT	4690	651
MPA$^{\bullet+}$/DEP	2570	286

[a] Second-order rate constants calculated from R_I' = 0.50 data.

Simulation of DCV Data for Competitive Second-Order Reactions of the Radical Cations with N-Centered Bases. Simulations were carried out using the Feldberg finite difference method,[17] which has been shown to give highly accurate data for these reactions.[1] The simulations used 0.1 mV voltage steps. The reactions simulated are shown in Scheme 1.

In Scheme 1, A is a radical cation generated at the electrode, B is a N-centered base present in the solution, and B′ is a structural isomer of B present as a reactive impurity. The rate constants in the simulations are k (the experimental apparent second-order rate constant), and k_{imp} is varied to give the desired ratio, k_{imp}/k. It is convenient to consider the reactions as three distinct series comprising each base reacting with four radical cations The experimental rate constants are listed in Table 1 for the reactions of the radical cations with LUT, DEP, and DPP in dichoromethane/Bu$_4$NPF$_6$ (0.2 M) at 291 K. Those labeled $k_{app}{}^{D}$ are for the reactions of DMA-d_6 and MPA-d_3.

Efficient Representation of the Simulation Data. When working with large quantities of simulation data, it is convenient to define a parameter that represents the most essential information in the data set. The sets of simulated DCV data consist of R_I' values of 0.85 down to 0.50 at 0.05 intervals as one column and the voltage sweep rates necessary to observe them as the other. The latter are labeled as $v_{0.85}$ to $v_{0.50}$, respectively. Since the simulated profiles are smooth curves, the data set can be represented as the ratio $v_{0.85}/v_{0.50}$ without significant loss of information.

Results and Discussion

Comparison of Experimental DCV Data with That Expected for the Simple Second-Order Mechanism. The experimental DCV data for the reactions of the radical cations with the N-centered bases are summarized in Table 2. The numbers in parentheses are those expected for the simple second-order mechanism

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TABLE 2. Comparison of the Slopes of DCV Response Curves for the Reversible Consecutive Second-Order Mechanism to Those for the Simple Second-Order Mechanism

	12.5 mM 2,6-DEP $\nu_{0.85}/\nu_{0.50}$[a]	50.0 mM 2,6-DPP $\nu_{0.85}/\nu_{0.50}$[a]	2.00 mM 2,6-LUT $\nu_{0.85}/\nu_{0.50}$[a]
DMA	7.18 (7.5)[b]	6.91 (7.3)[b]	9.07 (9.7)[b]
DMA-d_6	11.1 (7.5)	8.55 (7.3)	11.2 (9.7)
MPA	10.2 (7.5)	6.67 (7.3)	9.44 (9.7)
MPA-d_3	11.1 (7.5)	9.02 (7.3)	13.0 (9.7)

[a] $\nu_{0.85}$ is the voltage sweep rate necessary for $R_I' = 0.85$, and $\nu_{0.50}$ is that necessary for $R_I' = 0.50$. [b] The numbers in parentheses are the values for the simple second-order mechanism under the experimental conditions.

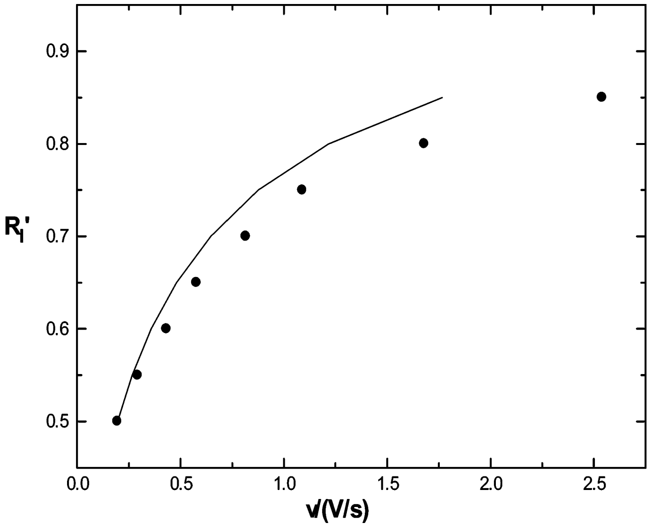
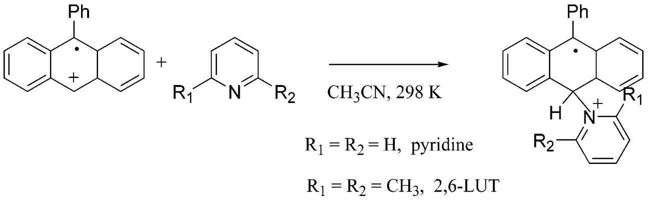


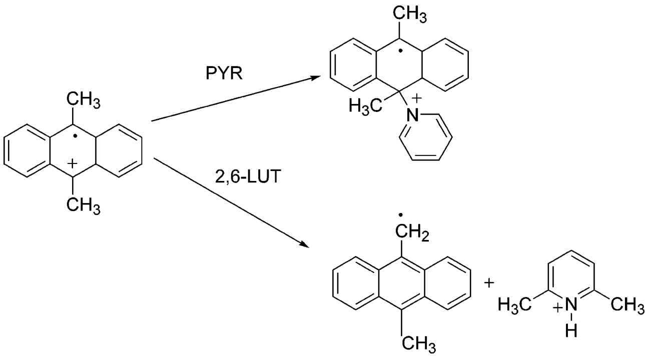
FIGURE 1. Comparison of experimental DCV data (●) for the reaction between MPA-d_3 and 2,6-LUT with the data simulated (—) for the simple second-order mechanism.

under the conditions of the experiments. A representative example of the complete data set for one of the entries in Table 2, that for the reaction between MPA-d_3 and 2,6-LUT, is shown in Figure 1. The experimental data are represented by solid circles, and the solid line shows the simulated data for the simple mechanism.

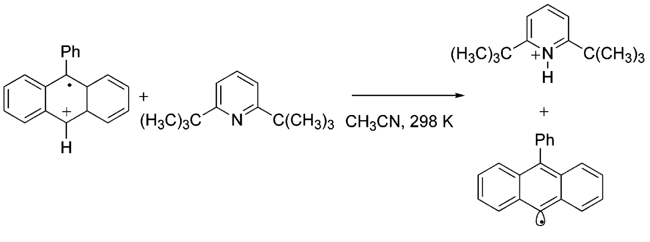
SCHEME 2



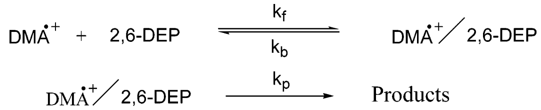
SCHEME 3



SCHEME 4



SCHEME 5



The Problem. The issue of whether substituted pyridines contain structural isomers with very different reactivity is typical of what has been termed the “insidious impurity problem”.[18] This is a pertinent issue since we have observed a range of reactivities of pyridine derivatives in our studies of the reactions between arene radical cations and nitrogen-centered bases, a facile general reaction in aprotic solvents such as acetonitrile and dichloromethane. These reactions are highly susceptible to steric hindrance to nucleophilic reaction of the lone pair on nitrogen with the electron deficient Π-system of the arene radical cation.[5−12] For example, the apparent rate constant for the nucleophilic addition reaction of pyridine to 9-phenylanthracene radical cation is 4 orders of magnitude greater than that for the reaction involving 2,6-LUT (Scheme 2).[5] This result is highly pertinent to this study, since it shows that the 2,6-LUT that we used in that study did not contain significant concentrations of isomeric dimethylpyridines in which the nitrogen lone pairs are considerably less sterically hindered. Another pertinent point of a high degree of relevance to the present work is that, in a comparison with the reactions of DMA radical cation with pyridine and with 2,6-LUT, only the latter base was observed to directly abstract a proton from DMA$^{•+}$, while pyridine was found to undergo nucleophilic addition followed by a slower elimination reaction (Scheme 3).[7]

The steric effect caused by 2,6-*tert*-butyl groups is even more severe. The reaction between 9-phenylanthracene with 2,6-di-*tert*-butyl pyridine does not lead to an adduct, but rather is the first documented case of aryl proton transfer (Scheme 4) from an arene radical cation.[5,6] This again is pertinent, since less highly substituted pyridines present as impurities would have been expected to undergo nucleophilic addition in essentially barrier-free reactions.

Finally, results of non-steady-state kinetic studies already published[1,3] show that DMA$^{•+}$ reacts with the highly hindered 2,6-diethylpyridine (2,6-DEP) and 2,6-diphenylpyridine (2,6-DPP) according to the same reversible consecutive second-order mechanism (Scheme 5). The results of reactions of the radical cation with these bases appear to differ in only one significant respect from that of reactions of DMA$^{•+}$ with 2,6-LUT, that is, the rate

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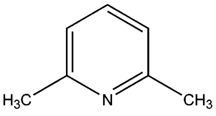
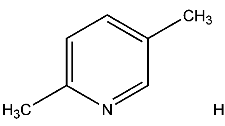
[18] Doll, K.; Finke, R. G. *Inorg. Chem.* **2004**, *43*, 2611.

constants are diminished because of the greater steric effect of the 2,6-diethyl groups. All other parameters such as the apparent and real deuterium kinetic isotope effects are remarkably similar for the reactions of all of the N-centered bases.

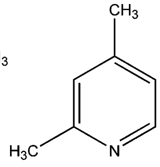
Evaluation of the Possible Effects of Reactive Impurities on the Kinetics of the Reaction between Methylanthracene Radical Cations and 2,6-LUT. The structures of 2,6-LUT and its structural isomers are shown below. All of the isomers are expected to be more reactive than 2,6-LUT, in which methyl groups occupy both of the ring positions adjacent to the heterocyclic nitrogen. The most reactive isomers are expected to be 3,5- and 3,4-LUT, in which both ring positions adjacent to the heteroatom are unsubstituted. LUT and all other isomers have a single methyl group adjacent to nitrogen. Thus, the 3,4- and 3,5-LUT are prime candidates to act as reactive impurities when present in 2,6-LUT.



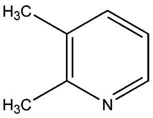
2,6-LUT



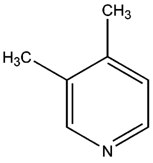
2,5-LUT



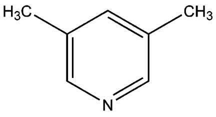
2,4-LUT



2,3-LUT



3,4-LUT



3,5-LUT

The expected effect of methyl substitution in the 3- and 4-positions, where there are no steric effects toward reaction involving the lone pairs on nitrogen, is to enhance the reactivity by electron-donating effects. This has clearly been shown to be the case in studies of the nucleophilic addition of methylpyridines to 9-phenylanthracene radical cation and related electrophiles. In analogy, it appears reasonable to expect 3,4- and 3,5-LUT to be as much as 10^4 times as reactive toward $DMA^{\bullet+}$ and $MPA^{\bullet+}$ as is 2,6-LUT.

Attempts To Fit DCV Kinetic Data for a Series of Methylanthracene Radical Cation Reactions with Possible Impurity Levels in the Various N-Centered Bases. The three bases—2,6-LUT, 2,6-DEP, and 2,6-DPP—employed in the study of the proton transfer reactions were subjected to reaction with the four radical cations, $DMA^{\bullet+}$, DMA-$d_6^{\bullet+}$, $MPA^{\bullet+}$, and MPA-$d_3^{\bullet+}$. The purity of each N-centered base was invariant in the study of all four proton transfer reactions. Thus, if kinetic results from one of the proton transfer reactions of a given base can be attributed to the presence of a reactive impurity, the reactive impurity would exert a consistent effect upon the kinetic results for the other three proton transfer reactions. This provides a unique opportunity to test for the possible effects of reactive impurities on the kinetics of an extensive series of reactions.

A fortran fitting program was written to test the compatibility of the hypothesis that deviations of the DCV response from simple mechanism behavior of the series of radical cations with 2,6-LUT, 2,6-DEP, and 2,6-DPP are due to the presence of reactive impurities in the N-centered bases. The input to the program includes experimental reactant concentrations, voltage sweep rates to ensure that the simulations of R_I' encompass the range from 0.85 down to 0.50, experimental sweep rates for each R_I' value in the range, and experimental apparent second-order rate constants for all four reactions in each of the three reaction series.

SCHEME 6

$$\mathbf{A + B} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \textbf{Reactant Complex}$$

$$\textbf{Reactant Complex} \xrightarrow{k_p} \textbf{Products}$$

Attempts were made to find the best fits between experimental and simulated DCV kinetic data for three different experimental data sets: those corresponding to the reactions of 2,6-LUT, 2,6-DEP, and 2,6-DPP. Simulations were carried out for the competitive impurity mechanism (Scheme 1) with reactive impurity levels ranging from 0.1 to 1.0% (at 0.10 intervals) and with k_{imp}/k ranging from 1.0 to 1024 (varied by factors of 2). For each of the three bases, this resulted in a total of 11 different sets (one for each k_{imp}/k value) of simulated DCV data corresponding to DCV profiles for the reactions with the radical cations of each of the four substrates (DMA, DMA-d_6, MPA, and MPA-d_3). Each of the 11 data sets was constructed from simulations for 10 different reactive impurity levels.

The fitting program operated on the three data sets separately. For each of the 10 impurity levels, concurrent comparison of the DCV profiles for the reactions of the four radical cations was carried out. The goal of the procedure was to attempt to find the k_{imp}/k value that resulted in the best concurrent fit of data for all four radical cations at each of the 10 impurity levels. Without exception, attempts to concurrently fit the experimental data for the radical cation–base combinations failed. We concluded that this was a futile exercise and that no fit exists between experimental data and data simulated for the competive impurity mechanism (Scheme 1).

On the other hand, the experimental data are readily accommodated by the reversible consecutive second-order mechanism (Scheme 6) as we have proposed in our recent work.[1–3]

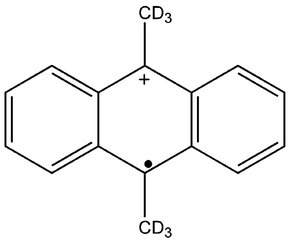
Simulation of Data for the General Pseudo-First-Order Case for the Competitive Impurity Mechanism (Scheme 1). To further test the near invariance of the DCV mechanism probe with changes in k_{imp}/k and % impurity, a series of simulations were carried out for the general pseudo-first-order case over the entire range of the two variables. The data summarized in Table S1 show that $\nu_{0.85}/\nu_{0.50}$ is indeed very nearly constant within experimental error. The only exception to this is that at the highest value of k_{imp}/k the ratio is as much as 10% greater than the usual value of $\nu_{0.85}/\nu_{0.50}$ equal to 6.86.

It is of interest to consider the reason the mechanism probe ($\nu_{0.85}/\nu_{0.50}$) is not sensitive to k_{imp}/k and to % impurity. The reason lies in the fact that $\nu_{0.85}/\nu_{0.50}$ is equivalent to a ratio of instantaneous rate constants and is independent of what has taken place during the initial stages of the reaction. Since the reactive impurity is effectively consumed during the first 15% of the reaction (roughly the case for $\nu_{0.85}$), the DCV mechanism probe does not sense the effect of the reactive impurity.

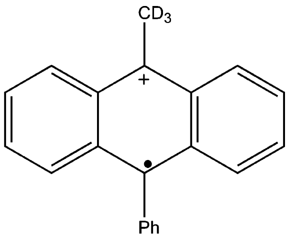
Comments on the Reactions of 2,6-DEP and 2,6-DPP with Methylanthracene Radical Cations. The larger ethyl and phenyl groups at the 2,6-positions of pyridine exert larger steric effects than methyl groups upon reactions involving the lone pair on nitrogen, and the rates of the proton transfer reactions of these bases with $DMA^{\bullet+}$ and $MPA^{\bullet+}$ are significantly diminished. A beneficial effect in terms of purification of the nitrogen-centered bases is found in the fact that 2,6-DPP is a solid and can be purified by repeated recrystallizations. 2,6-DPP is synthesized from high-purity pyridine in a reaction that is regiospecific for phenylation at the ring position adjacent to nitrogen. 2-Phenylpyridine, which is an intermediate in the synthesis, is readily separated from 2,6-DPP by the recrystallization procedure. In the case of 2,6-DEP, it was prepared by Wolff–Kishner reduction of 2,6-diacetylpyridine, which was recrystallized several times before use. Since 2,6-diacetylpyridine is synthesized by a cyclization reaction, the final product (2,6-DEP) does not contain isomeric impurities. Thus, isomeric impurities are highly unlikely in either 2,6-DEP or 2,6-DPP.

Thus, of the three hindered bases, it is only conceivable that 2,6-LUT might possibly contain isomeric impurities. The fact that the relative kinetic behavior of all three bases toward the four methylanthracene radical cations is nearly the same suggests that it is highly improbable that these reactions are subject to the “insidious impurity” problem.

A Comparison of the Temperature-Dependent Apparent Kinetic Isotope Effects for the Reactions between the Radical Cations and the Hindered Nitrogen-Centered Bases. Apparent kinetic isotope effects for all of the reactions in this series are extent of reaction dependent and increase significantly from low conversion up to about the first half-lives of the reactions. For clarity, the structures of DMA-$d_6^{\bullet+}$ and MPA-$d_3^{\bullet+}$ are shown below.



DMA-$d_6^{\bullet+}$



MPA-$d_3^{\bullet+}$

Data for all three hindered bases are summarized in Table 3. A point of special interest is that the extent of reaction dependencies of the KIE_{app} is at least as prominent for the reactions involving 2,6-DEP and 2,6-DPP as they are for those of 2,6-LUT. Since the likelihood of reactive impurities are much greater for 2,6-LUT than for the other two bases, this again provides strong evidence against the hypothesis that deviations from simple second-order kinetics are caused by the presence of reactive impurities.

All of the reaction systems exhibit large real kinetic isotope effects (KIE_{real}) that increase with decreasing temperature.[2,3] All of the C–H proton transfer reactions[2,3] take place with significant proton tunneling as indicated by Bell’s experimental criteria; $E_a^D - E_a^H > 1.414$ and $A_D/A_H > 1$.[19–21] Although the number of well-documented cases of proton tunneling in organic chemistry is limited, it is a well-accepted phenomenon. We believe that our data for the proton transfer reactions between methylanthracene radical cations and hindered nitrogen-centered bases represent one of the most comprehensive data sets on proton tunneling in organic chemistry and is of general interest. It should be noted that hydrogen tunneling in enzymatic systems is of intense current interest, and the reader is referred to recent articles[18,23] for references in this area.

TABLE 3. Comparison of the Range of Apparent Kinetic Isotope Effects Observed for the Reactions of $DMA^{\bullet+}$/DMA-$d_3^{\bullet+}$ with Different Nitrogen-Centered Bases[a]

	KIE_{app} in the presence of:		
T/K	2,6-LUT	2,6-DEP	2,6-DPP
291	6.0–7.3	5.9–8.0	9.5–13.7
273	6.6–9.2	6.1–12.2	12.0–19.1
252	9.1–13. 9	8.0–14.0	17.9–27.7

[a] The lowest value in each range was found at $\nu_{0.90}$ and the value at $\nu_{0.50}$. Intermediate values increase smoothly.

Conclusions

The slope of the DCV mechanism probe ($\nu_{0.85}/\nu_{0.50}$) varies over a wide range for the reversible consecutive second-order mechanism (Scheme 6) depending upon the various rate constants in the reaction, while its value is essentially invariant for the competitive impurity mechanism in Scheme 1. Thus, the DCV mechanism probe is highly effective in differentiating between the two mechanistic possibilities.

It is pointed out that the DCV mechanism probe is equivalent to a ratio of instantaneous rate constants, and this fact renders $\nu_{0.85}/\nu_{0.50}$ almost totally insensitive to k_{imp}/k and to % impurity. Thus, DCV mechanism analysis is free from complications brought about by the possible presence of a reactive impurity.

We point out the fact that if a reactive impurity affects the kinetics of one reaction in a series using the same reagent (B in Scheme 1), a consistent effect will also be observed in every other reaction in the same series. We have applied this observation to the reactions of 2,6-LUT, 2,6-DEP, and 2,6-DPP with a series of four radical cations ($DMA^{\bullet+}$, DMA-$d_6^{\bullet+}$, $MPA^{\bullet+}$, and MPA-$d_3^{\bullet+}$) to provide conclusive evidence that the deviations from simple mechanism behavior are not due to the presence of

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(19) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980.

(20) Siebrand, W.; Wildman, T. A.; Zgierski, M. Z. *J. Am. Chem. Soc.* **1984**, *106*, 4083.

(21) There have been many more recent advances in the dynamics of proton transfer and proton tunneling, and the introductory and subsequent articles in an issue of the *Ber. Bunsen-Ges. Phys. Chem.* devoted to “Hydrogen Transfer: Theory and Experiment” provide ready access to this literature.[22]

(22) Limbach, H.-H.; Manz, J. *Ber. Bunsen-Ges. Phys. Chem.* **1998**, *102*, 289.

(23) Doll, K. M.; Bender, B. R.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10877.

reactive impurities. All of the kinetic data for all of these systems remain consistent with the reversible consecutive second-order mechanism illustrated in Scheme 6.

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Supporting Information Available: Simulation data for the effect of impurities on the DCV mechanism probe. This material is available free of charge via the Internet at http://pubs.acs.org.

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