Intramolecular kinetic isotope effect in hydride transfer from dihydroacridine to a quinolinium ion. Rejection of a proposed two-step mechanism with a kinetically significant intermediate†

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The intramolecular kinetic isotope effect (KIE) for hydride transfer from 10-methyl-9,10-dihydroacridine to 1-benzyl-3-cyanoquinolinium ion has been found to be 5–6 by both ^{1}H NMR and mass spectrometry. This KIE is consistent with other hydride transfers. It is inconsistent with the high intermolecular KIEs derived by fitting to a two-step mechanism with a kinetically significant intermediate complex, and it is inconsistent with the strong temperature dependence of those KIEs. We therefore reject the two-step mechanism for this reaction, and we suggest that other cases proposed to follow this mechanism are in error.

Introduction

In recent years, Vernon D. Parker and his coworkers have published a series of papers that reinterpret some fundamental reactions of organic chemistry. The data from stopped-flow or cyclic-voltammetry experiments deviate from the simple second-order mechanism that has long been accepted [eqn (1)]. The data could be fitted much better to a two-step mechanism with a kinetically significant intermediate complex, A·B [eqn (2)]. A cogent summary of his analysis is based on a plenary lecture presented at the 2004 IUPAC Conference on Physical-Organic Chemistry.[1] Among the reactions that show this mechanistic behavior are nucleophilic substitutions,[2] E2 eliminations,[3] a [4 + 2] cycloaddition,[4] proton-transfers from radical cations,[5] hydrogen-atom abstractions,[6] hydrolysis of *p*-nitrophenyl acetate,[7] and nucleophilic capture of $(p\text{-}CH_3OC_6H_4)_3C^+$ by acetate.[8]

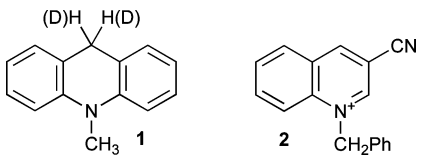
$$A + B \xrightarrow{k_2} \text{product} \quad (1)$$

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} A \bullet B \xrightarrow{k_p} \text{product} \quad (2)$$

This analysis has significant consequences for kinetic isotope effects (KIEs), because the observed KIE is reduced if the first step, which is isotope-independent, is partially rate-limiting. The KIE for the hydrogen transfer itself, in the second step, is then considerably larger than the apparent KIE, measured on the assumption of a simple second-order mechanism. Unusually large KIEs were thus deduced for deprotonation of radical cations by pyridines,[9] and also for proton transfers from nitroalkanes to hydroxide.[10]

These conclusions have been met with some scepticism. Alternative explanations for the deviation from simple second-order kinetics were that reaction occurs *via* both ion pairs and free ions, or that there are acidic impurities, such as CO_2, that consume base, or that photosolvolysis intrudes.[11] These explanations were rejected because neither added salts nor CO_2-containing water affects the kinetics, and because the same results were obtained from solutions stored in the dark.[12] Moreover, other researchers have tended to accept Parker's conclusions.[13]

Of particular interest is the hydride transfer from 10-methyl-9,10-dihydroacridine (**1**) to 1-benzyl-3-cyanoquinolinium ion (**2**). KIEs generally between 4 and 6, depending on temperature, solvent, and overall equilibrium constant, were observed for this and related reactions by Kreevoy and coworkers.[14] Similarly, Table 1 lists rate constants and KIEs calculated according to simple second-order kinetics [eqn (1)], as obtained by Parker and coworkers.[15] Table 2 lists Parker's rate constants and KIEs, derived from fitting to the two-step kinetic scheme of eqn (2). The KIEs in Table 1 are quite ordinary, and in agreement with Kreevoy's, but those in Table 2 are unusually large, especially at lower temperatures. Such large KIEs have been taken as evidence for quantum-mechanical tunneling, which is consistent with the activation parameters associated with the data of Table 2.



For reasons that are presented below, we too were sceptical about the two-step mechanism [eqn (2)] and the derived KIEs. In

Table 1 Second-order rate constants (M^{-1} s^{-1}) and KIEs for hydride transfer from **1**-h_2 and **1**-d_2 to **2**[a]

T/K	k_2^{H2}	k_2^{D2}	k_2^{H2}/k_2^{D2}
291	0.00908	0.0016	5.675
299	0.0165	0.00339	4.87
308	0.0327	0.0066	4.95
316	0.0526	0.0112	4.70
325	0.0766	0.0186	4.12

[a] From Ref. 15.

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Table 2 Rate constants and KIEs for hydride transfer from **1**-h_2 and **1**-d_2 to **2**, analyzed according to eqn (2)[a]

T/K	k_f/M^{-1} s^{-1}	k_b/s^{-1}	k_p^{H2}/s^{-1}	k_p^{D2}/s^{-1}	k_p^{H2}/k_p^{D2}
291	0.01	0.0031	0.023	0.00058	40
299	0.019	0.0041	0.028	0.0009	31
308	0.047	0.0194	0.03	0.0021	14
316	0.09	0.0172	0.035	0.0035	10
325	0.135	0.033	0.044	0.0053	8.3

[a] From Ref. 15.

order to test this, we have measured the intramolecular KIE for hydride transfer from 10-methyl-9,10-dihydroacridine-9-*d* (**1**-*d*) to 1-benzyl-3-cyanoquinolinium ion (**2**). Regardless of mechanism, this KIE arises solely from the hydride-transfer step. Even if the first step is partially rate-limiting, the second step is product-determining. Therefore, even if eqn (2) is the mechanism, the KIE measured is k_p^H/k_p^D, without the necessity of extracting rate constants from two-step kinetics. Moreover, this KIE can be obtained simply by measuring the deuterium content of the 1-benzyl-3-cyano-1,4-dihydroquinoline product (**3**), according to eqn (3). We now report that this KIE is 5–6, consistent with previous KIEs measured on the assumption of a simple second-order reaction [eqn (1)] and providing no evidence for a two-step mechanism with a kinetically significant intermediate complex [eqn (2)].

$$\frac{k_p^H}{k_p^D} = \frac{[\mathbf{3}\text{-}h_2]}{[\mathbf{3}\text{-}d]} \quad (3)$$

Results

Fig. 1 shows the ^{1}H NMR spectrum of 1-benzyl-3-cyano-1,4-dihydroquinoline (**3**) obtained from hydride transfer from 10-methyl-9,10-dihydroacridine-9-*d* (**1**-*d*) to 1-benzyl-3-cyanoquinolinium ion (**2**). The spectrum shows that the CH_2 and CHD signals are well enough resolved to be integrated separately in order to evaluate the deuterium content. The significant

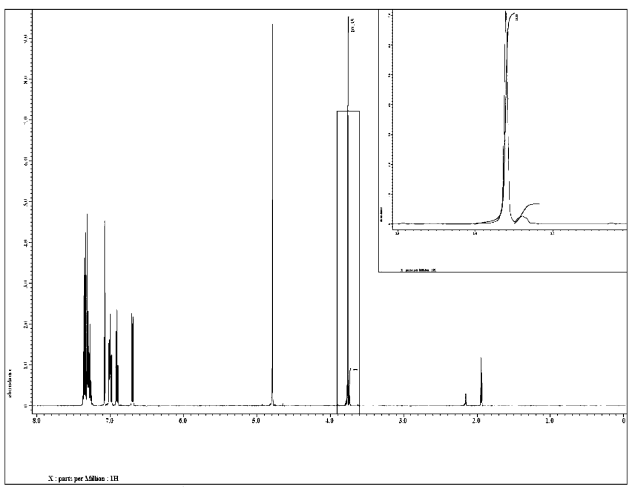


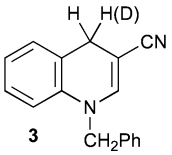
Fig. 1 500-MHz ^{1}H NMR spectrum of **3** in CD_3CN, from reaction of **1**-*d* with **2**. The inset is an expansion, with integration, of the CH_2 and CHD signals near δ 3.7.

Table 3 Deuterium content of **3** from reaction of **1**-***d*** with **2**

T/K	$t_{elapsed}$/min	[**1**-***d***]$_{init}$/M	[**2**]$_{init}$/M	[**3**-h_2]/[**3**-***d***][a]	[**3**-h_2]/[**3**-***d***][b]
273	180	0.061	0.053	6.4	6.1
273	240	0.062	0.048	6.1	5.9
273	300	0.056	0.051	5.8	6.0[c]
299	31	0.056	0.05	5.35	5.3
299	32	0.059	0.049	5.2	5.4
299	53	0.059	0.043	5.02	5.0
299	1440	0.038	0.042	1.12	—

[a] By NMR analysis. [b] By MS analysis. [c] From [M + NH_4^+] and [M + NH_4^++1].

intensity of the CHD signal is immediate evidence that deuterium *is* transferred, and that the intramolecular KIE is not large. Moreover, the 10.35 : 1 integration ratio corresponds to a [**3**-h_2] : [**3**-***d***] ratio of 5.2 : 1.



3

The deuterium content of 1-benzyl-3-cyano-1,4-dihydroquinoline (**3**) obtained from reaction of 10-methyl-9,10-dihydroacridine-9-*d* (**1**-*d*) with 1-benzyl-3-cyanoquinolinium ion (**2**) under various conditions is compiled in Table 3. There is good agreement between the values obtained by NMR and those by mass spectrometry, indicating that NMR integration is not overly sensitive to the range of chemical shifts assigned to the CHD signal.

The average ratio [**3**-h_2]/[**3**-***d***] across the first six runs in Table 1 is 5.6 ± 0.5. There are small variations with time and temperature, which are discussed below. The immediate conclusion though is that this ratio, which measures k_p^H/k_p^D, agrees reasonably well with the KIEs in Table 1 but is much smaller than the KIEs in Table 2.

The ratio of 1.12 after 1440 minutes of reaction represents complete scrambling of deuterium. After so many half-lives both H and D have been transferred among **1**, **2**, **3**, and 10-methylacridinium ion.

According to the data in Table 3, the average ratio at 299 K is 5.2 ± 0.2. The average ratio at 273 K is 6.05 ± 0.2. The increase at lower temperature is expected for KIEs, as seen in Tables 1 and 2, but the variation is small and barely beyond the experimental error.

Discussion

Doubts about the two-step mechanism

Our scepticism about the two-step mechanism [eqn (2)] and the derived KIEs was prompted by a perceived inconsistency regarding the energetics of the intermediate complex. A representative example is the reaction of **1** with **2**. According to Parker's data in Table 2, k_f at 299 K is 0.019 M^{-1}s^{-1} and k_b is 0.0041 s^{-1}, corresponding to an equilibrium constant, k_f/k_b, for formation of the complex of 4.6 M^{-1}. This is certainly weak binding, with a free energy of complex formation of only –0.9 kcal mol^{-1}. Nevertheless, the rate constant k_b for dissociation of the complex is small,

corresponding to a $\Delta G^{\ddagger}$ of 21 kcal mol^{-1}. This is an unbelievably high activation energy for the dissociation of a complex with such weak binding. If there is hardly any energy holding the complex together, why is so much activation energy required to take it apart? Fig. 2 is an energy diagram representing these rate constants, including both the intermediate complex and a weak encounter complex or charge-transfer complex, but omitting such a complex involving the products.

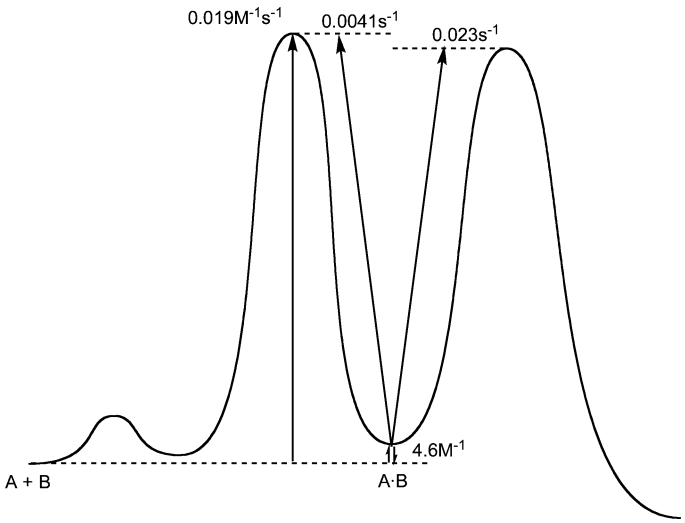


Fig. 2 Energy diagram, with energies to scale, corresponding to the mechanism of eqn (2) with the rate constants at 299 K from Table 2 and including a weak encounter complex or charge-transfer complex.

The proposed intermediate of eqn (2) is recognized as distinct from the encounter complex that must be formed in any bimolecular reaction.[16] It is also distinct from the charge-transfer complex that is often formed between electron-rich and electron-poor reactants.[17] Both of these complexes share the feature of weak binding, but they are formed at nearly a diffusion-controlled rate and they dissociate very quickly, with little activation barrier. These aspects of the encounter complex or charge-transfer complex are also illustrated in Fig. 2

Parker's rationalization for a weakly bound intermediate complex with high activation barrier to dissociation is not convincing. He proposed that the intermediate complex differs from a charge-transfer complex "by a shortening of the distances between the reaction centers and by the extrusion of solvent, giving rise to a significant reaction barrier".[1] Similarly, he proposed ion–dipole complexes in proton transfers from nitroalkanes to hydroxide, nucleophilic substitutions, and E2 eliminations. In no case did he address the dilemma of weak binding and slow dissociation, except to assert that the activation barrier to dissociation is high. For the nucleophilic capture of $(p\text{-}CH_3OC_6H_4)_3C^+$ by acetate he expanded his rationalization by suggesting that the intermediate complex is analogous to an intimate ion pair in solvolysis.[8] However, Winstein's ion-pair intermediates are all very short-lived. Indeed, Parker's energy diagrams show the intermediate complex at high energy and with a fairly low activation barrier to reaction. This is inconsistent with the energetics of Fig. 2, which was constructed in accord with the rate constants in Table 2. The unlikelihood of such a complex is what led us to reinvestigate the KIE in the hydride transfer from **1** to **2**.

Comparison of intermolecular and intramolecular KIEs

A standard test of multistep reactions is the comparison of intermolecular and intramolecular KIEs.[18] Equality of the two KIEs is good evidence that the rate-limiting step is also the product-determining step. In contrast, inequality of the KIEs is good evidence that these steps are distinct, thus indicating the involvement of an intermediate following the rate-limiting step. Examples of the first case are the ene reaction of methylenecyclohexane with dimethyl dioxosuccinate and the reaction of $ArNMe_2$ with diphenylpicrylhydrazyl.[19] These are one-step hydrogen-atom transfers. Unequal KIEs are seen in the dimerization of allene, the Swern oxidation of benzyl alcohols with Me_2SCl^+, the reaction of $^1O_2$ with tetramethylethylene, and the oxidation of $ArNMe_2$ by an iron porphyrin + PhIO, all of which proceed *via* an intermediate that then partitions subject to an intramolecular KIE.[20] One cautionary exception that is similar to the study reported here is the observation of an intermolecular KIE different from the intramolecular KIE in the hydride transfer from a dihydropyridine to $PhCOCF_3$, but this is not due to an intermediate but rather to the reversible formation of an adduct.[21]

To use this test, it is necessary to measure both intermolecular and intramolecular KIEs. Parker measured only the intermolecular KIE, as in Table 1.[15] His evidence for a kinetically significant intermediate was the inadequacy of the fit of the data to simple second-order kinetics. Thus the KIEs in Table 2 were not measured directly, but only by adjusting the observed KIEs for the kinetic complexity of eqn (2). We now have measured the intramolecular KIE, to test whether it is the same as the KIEs in Table 2.

Evidence against the two-step mechanism

Our key result is that the intramolecular KIE, from the deuterium content of the 1-benzyl-3-cyano-1,4-dihydroquinoline product (**3**) is 5.6 ± 0.5. This value is inconsistent with the rate constants and KIEs in Table 2, obtained by fitting to the two-step mechanism [eqn (2)]. We therefore reject this mechanism, and the energy diagram of Fig. 2

Attempts to salvage the two-step mechanism

Might reversibility of the reaction, equilibrating products with reactants, lead to a lower apparent KIE than in Table 2? The reaction is indeed reversible, with an equilibrium constant of only 6.7 or 11.7 favoring products.[14,15] Reversibility would then equilibrate H and D among all species and increase the D content of **3**. Indeed, when the reaction was allowed to proceed for 24 h, the ratio of [**3**-h_2] to [**3**-***d***] was found to be 1.12, corresponding to an apparent KIE near 1. It is necessary to measure the KIE for the hydrogen transfer, rather than an apparent KIE that is reduced by isotopic scrambling. Therefore the reaction must be carried out only to low conversion. The reaction times in Table 3 were chosen as a compromise, to permit sufficient product for isolation and isotopic analysis while minimizing equilibration. Those times correspond to approximately one or two half-lives. Simulation of the kinetics, with the rate and equilibrium constants of Kreevoy and Kotchevar,[14] shows that even at two half-lives the observed KIE is reduced by only 6% by isotopic scrambling. The lower KIEs observed after longer reaction times is a reflection of this scrambling. Correcting the values in Table 3 for the incursion of

isotopic scrambling then leads to a KIE for hydrogen transfer of 6.3 ± 0.2 at 273 K and 5.5 ± 0.2 at 296 K. The temperature dependence is real but small, and the KIE of 5.9 ± 0.5 averaged over both temperatures is less dependable than the 5.5 ± 0.2 at 296 K.

A further correction that must be applied is due to the 2.2% undeuterated 10-methyl-9,10-dihydroacridine in the sample of **1-*d***. This leads to a greater proportion of [**3**-h_2], so that k_p^H/k_p^D is overestimated. To account for this, k_p^H/k_p^D from eqn (3) must be reduced by 4.2%.

In comparing this intramolecular KIE that we measure with Parker's intermolecular KIE, it is further necessary to consider secondary KIEs due to the hydrogen that is not transferred. The observed intermolecular KIE in Table 1 or 2 is k_2^{H2}/k_2^{D2}, the product of a primary and a secondary KIE. The observed intramolecular KIE of eqn (3), k_p^H/k_p^D, is the ratio of the primary and the secondary KIEs. The secondary KIE for hydride transfer from NADH is 1.15.[22] Therefore values in Tables 1 and 2 should be decreased by 15% to obtain the primary KIE, and values in Table 3 should be increased by 15%.

These three corrections are not all in the same direction. Cumulatively they contribute an average increase of ~16% that should be applied to the values in Table 3. Therefore we conclude that the average KIE for hydride transfer from **1** to **2** is 6.6 ± 0.5. A more reliable measure is the KIE at 296 K of 6.1 ± 0.2. However, the corrections probably generate more uncertainty than the statistical errors. Nevertheless, this intramolecular KIE is in reasonable agreement with the intermolecular KIEs measured by Kreevoy and coworkers,[14] and with the values in Table 1 for the simple second-order mechanism [eqn (1)]. This KIE is very much lower than the values in Table 2, from fitting to a two-step mechanism with a kinetically significant intermediate complex [eqn (2)]. Moreover, the KIE at 273 K is 7.0 ± 0.2, which is very different from the extremely high KIE > 40 expected by extrapolating the values in Table 2. No correction will bring the intramolecular and intermolecular KIEs into agreement.

Significance of discrepancy between intermolecular and intramolecular KIEs

Finally, we must address the question of whether the low intramolecular KIE that we measure can be reconciled with the high intermolecular KIEs that Parker derived.[15] One possibility is that a barrier to rotational diffusion within the postulated intermediate complex decreases the intramolecular KIE. If that intermediate complex has a high activation barrier for dissociation to separated components, perhaps it also has a high activation barrier for one component of the complex to rotate relative to the other. This might be due to an attractive interaction between the π faces of **1** and **2**. Above we have disputed a high activation energy for the dissociation of a complex with such weak binding, and the same objection applies to the activation energy for internal rotation. Despite those objections, we can consider the case of slow rotation, where the selectivity for H or D transfer would be partially determined by which face of **1**-*d* is in proximity to **2**. However, according to a simulation of these kinetics, with the rate constants for 299K in Table 2 and with a 21 kcal mol^{-1} barrier to internal rotation, equal to the barrier for dissociation, the intramolecular KIE would be reduced only to 10. This is certainly not observed. Therefore a high barrier to rotational diffusion within an intermediate complex cannot account for the discrepancy between the low intramolecular KIE that we measure and the high KIEs of Table 2.

The substantial discrepancy between our observed intramolecular KIE of 5.2 at 296 K, or a corrected KIE of 6.1, and KIEs as high as 40 from analysis of stopped-flow data thus lead us to reject the two-step mechanism of eqn (2). Measurement of the intramolecular KIE is an independent method that avoids the necessity for analysis of the deviations from simple second-order kinetics in stopped-flow data. We therefore conclude that there must be an error in that analysis, even though we admit that we are unable to find it, and we are grateful to Vernon Parker for his patience and cooperation in providing details and raw data. Nevertheless, the key result is that the intramolecular KIE is inconsistent with the KIEs derived from the two-step mechanism of eqn (2), which corresponds to the energy diagram of Fig. 2

Whether there are errors in the other studies[1–10] is uncertain. We have no independent measurements to test those rate constants, but all of those studies entailed a high activation energy for the dissociation of a weakly bound complex, with an energy diagram like Fig. 2. We therefore suggest that the error that must be present in the analysis of stopped-flow kinetic data for the reaction of **1** with **2** may also be present in those other cases, which might warrant reinvestigation.

Experimental

Instrumentation

^{1}H NMR spectra were obtained on a 400-MHz Varian Mercury or 500-MHz JEOL ECA spectrometer. Mass-spectral analyses were obtained with electrospray ionization on a Thermo-Finnigan LCQDECA instrument. Samples were injected as solutions in methanol, and the total HPLC intensity at each of m/z 245, 246, 247, and 248 was integrated.[23]

Synthesis

10-Methylacridinium iodide was prepared by a standard method and converted to 10-methyl-9,10-dihydroacridine-9-*d* with $NaBD_4$. Its ^{1}H NMR spectrum shows 97.7% deuteration. 1-Benzyl-3-cyanoquinolinium bromide was prepared by a standard method and converted to the perchlorate salt. Details of all procedures are provided in the Supporting Information†.

Measurement of kinetic isotope effect

The hydride transfer reaction between 10-methyl-9,10-dihydroacridine-9-*d* (**1**-*d*) and 1-benzyl-3-cyanoquinolinium (**2**) perchlorate was carried out in acetonitrile under a narrow variety of conditions. A temperature between 291 K and 299 K was chosen to test the largest KIEs in Table 2, as well as a lower temperature, at which the KIE would be extrapolated to even larger values. A 1.2–1.3-fold excess of dihydroacridine over quinolinium ion was generally used. The reaction was quenched after approximately one or two half-lives. The product 1-benzyl-3-cyano-1,4-dihydroquinoline (**3**) was purified by extraction, flash column chromatography, and recrystallization.

Isotopic analysis

Isotopic analyses of product (**3**) were performed by both ^{1}H-NMR in CD_3CN or $CDCl_3$ and mass spectrometry. An isotope shift leads to distinct C4 signals for CH_2 and CHD. The former appears as a singlet at δ 3.732, and the latter as a broadened 1 : 1 : 1 triplet at δ 3.711, owing to spin–spin coupling to the D. The CHD intensity can be compared to that of CH_2 by integration. The deuterium content of **3** was also obtained from the summed intensities of $[M + H^+] = 247$ and $[M + H^+ - 2] = 245$ peaks, compared to $[M + H^+ + 1] = 248$ and $[M + H^+ - 1] = 246$. In one case the $[M + NH_4^+]$ and $[M + NH_4^+ + 1]$ intensities were found to be more reliable. In order to correct for the natural abundance of ^{13}C the mass spectrum of the **3-*d*** sample was compared with that of **3-h_2** alone. From replicates the mass-spectroscopic [**3-h_2**]/[**3-*d***] ratio has a precision of ±0.15, but there are slight disagreements with the NMR analyses.

Conclusions

We have unambiguously measured an intramolecular KIE of 5–6 for hydride transfer from 10-methyl-9,10-dihydroacridine (**1**) to 1-benzyl-3-cyanoquinolinium ion (**2**). This KIE is consistent with other hydride transfers. It is inconsistent with the high intermolecular KIEs derived by fitting to the mechanism of eqn (2). We therefore reject the two-step mechanism for the reaction between **1** and **2**, *via* a kinetically significant intermediate. Besides, that intermediate is implausible, because it is bound only weakly but has a high activation energy for dissociation, and an energy diagram like Fig. 2. These results cast doubt on other cases of the two-step mechanism of eqn (2), involving intermediates with these same implausibilities, and those results might warrant reinvestigation.

Acknowledgements

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