Title

Comment on “Topography of the free energy landscape of Claisen–Schmidt condensation: solvent and temperature effects on the rate-controlling step” by N. D. Coutinho, H. G. Machado, V. H. Carvalho-Silva and W. A. da Silva, Phys. Chem. Chem. Phys. , 20...

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Comment on "Topography of the free energy landscape of Claisen–Schmidt condensation: solvent and temperature effects on the rate-controlling step", by Nayara Dantas Coutinho, Hugo Gontijo Machado, Valter Henrique Carvalho-Silva and Wender Alves da Silva, published in PCCP, **2021**, 23, 6738-6745.

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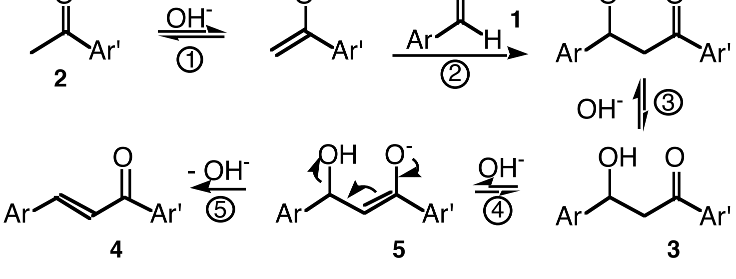
Abstract

The referenced article in PCCP presents calculations of solvent kinetic isotope effects that indicate that the rate-limiting step in base-catalyzed chalcone formation in aqueous solution becomes the second enolization. This disputes our previous conclusion, based on experimental isotope effects in aqueous acetonitrile, that the rate-limiting step is the final loss of hydroxide and formation of the C-C double bond. That conclusion is here affirmed as general for any protic solvent, and it is further concluded that those calculations are flawed.

Aldol Condensation and Mechanism of Chalcone Formation

The aldol condensation is a key organic reaction, capable of forming new C-C bonds.[1] In particular, we address the base-catalyzed reaction of a benzaldehyde ArCH=O (**1**) and an acetophenone Ar'COCH$_3$ (**2**) to form ketol (β-hydroxyketone) **3**, which is then dehydrated to a chalcone (benzylideneacetophenone) **4**, as in Scheme 1.



Scheme 1. Five steps in the formation of chalcone **4**: (1) Enolization of acetophenone **2**, (2) C-C Bond formation by addition to aldehyde **1**, (3) Proton equilibration to form ketol **3**, (4) Second enolization, (5) Hydroxide elimination and C=C bond formation.

Perrin and Chang undertook to elucidate its complete mechanism, with special attention to the rate-limiting step, distinguished as the last one whose rate constant remains in the kinetic equation.[2] We measured the product ratio ([**1**] + [**2**])/[**4**] for the ketol intermediate **3**, independently synthesized and subjected to the reaction conditions.[3] The results mean that **3** partitions primarily by reversion to reactants aldehyde **1** and ketone **2** (as had been observed previously,[4] but misinterpreted as meaning that Step 2 is rate-limiting). We further found that the condensations are faster in D_2O than in H_2O. The results of both comparisons are independent of the substituents in Ar or Ar'.

Because in D_2O the ketol intermediate **3** is rapidly converted to $ArCHODCD_2COAr'$ Step 4, the second enolization, must be retarded by a kinetic isotope effect on the rate of dehydronation (removal of a hydron, which may be either a proton or a deuteron). Because no retardation was observed we concluded that the rate-limiting step in this reaction must be Step 5, the final loss of hydroxide and formation of the C-C double bond.

Computational Study of Chalcone Formation

Recently a computational study of this reaction, "Topography of the Free Energy Landscape on the Claisen-Schmidt Condensation: Solvent and Temperature Effect in the Rate-Controlling Step", was published in This Journal.[5] The conclusion was that in a protic solvent or with a slight increase in temperature Step 4 can become rate-limiting. Figure 1 shows their depiction of the free-energy profiles, including ours based on experimental data showing Step 5 as rate-limiting, and theirs based on calculations in both water and the aprotic solvent acetonitrile. The relative heights for the experimental curve show how sensitive the assignment of rate-limiting step is, because the difference between $\ddagger_4$ and $\ddagger_5$ is only 3 kcal/mol. The difference between $\ddagger_2$ and $\ddagger_5$ is even less, only 1 kcal/mol, which shows how sensitive the energy differences are to the partition ratio of intermediate **3**, which is only ~7:1. It was then concluded that the rate-limiting step in acetonitrile is indeed Step 5, but according to the calculations it is Step 4 in water or other protic solvent (and also at higher temperature).

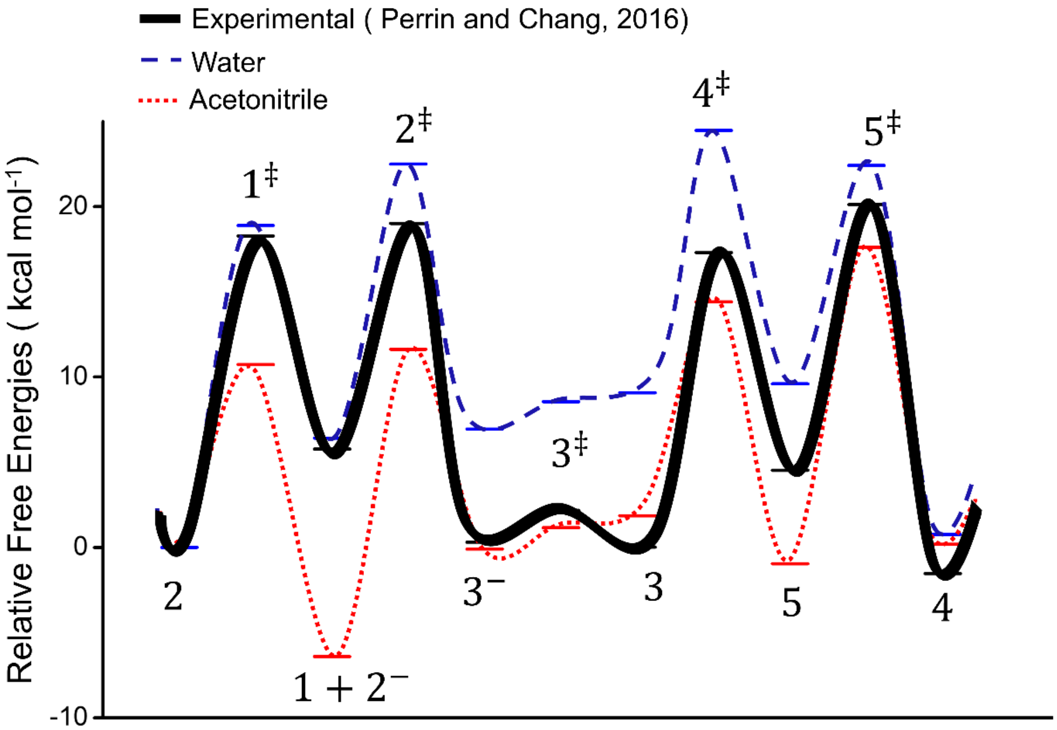


Figure 1. Free energy diagrams for base-catalyzed chalcone formation (Scheme 1), estimated from experimental data and calculated in water and acetonitrile, from Ref. 5.

Inconsistencies in Calculations

Table 1 lists rate constants *k* (including tunneling) and inverse kinetic isotope effects iKIE = k_{D2O}/k_{H2O} for each of the forward and reverse steps of Scheme 1 in water, copied from Tables S1 and 2 of Ref. 5. The data do not correspond, for reasons that are not made clear.

Table 1. Calculated rate constants and inverse KIEs for steps in Scheme 1, from Ref. 5.

Step	k_{H2O}	k_{D2O}	iKIE, 298K	iKIE, 273K
1	382.766	27.355	.	
-1	138433	449.267		
2	8722	10702	1.02	0.88
-2	1420	1046	0.29	0.002
3	3.063e10	3.452e10		
-3	5.773e12	6.257e12		
4	351.513	45.955	4.63	2.47
-4	2249	15.706		
5	1877	2893	1004	983

Some of the values in Table 1 are far out of normal range. The kinetic isotope effects (KIEs) k_{H2O}/k_{D2O} of 14 and 308 derived from the rate constants for Steps 1 and -1 respectively are beyond the usual maximum of 8 for a proton transfer.[6] The iKIEs of 1004 and 983 for Step 5 are far beyond the usual maximum of 4. The KIE of 143 derived from the rate constants for Step -4 is unreasonable for the ketonization of an enolate. Likewise the iKIEs of 10.12 and 26.38 reported in Table 2 of Ref. 5 for the overall reaction at 298 K and 273 K respectively are too large, as is the variation over a temperature range of only 25º. It is further unlikely that the iKIE for step -2, which does not involve proton transfer, can be 0.29 at 298 K but then decrease to 0.002 at 273 K. Such extreme values are evidence that the calculations are in error.

The (normal) KIE of 7.65 derived from the rate constants for Step 4 is very reasonable for a C-H dehydronation, but the calculated iKIEs of 4.63 and 2.47 in Table 1 are then inverse, not normal. Indeed, the experimental observation of iKIEs between 1.12 and 1.43 was the evidence for excluding Step 4 as rate-limiting. Thus the KIE for a proton transfer ought to be normal, and the inverse values are strong evidence that the calculations are in error.

The computed isotope effects can be compared with experimental isotope effects in similar systems. The overall isotope effect on the equilibrium constant [**3**]/[**1**][**2**] can be estimated from the change in zero-point energy of the sp^3 C-H or C-D bond that is converted to an O-H or O-D. If those frequencies for H are taken as 3000 and 3600 cm^{-1}, respectively, the ratio of equilibrium constants K_D/K_H is ~4. This is in good agreement with the calculated value of 3.5 derived from the data in Table 1. From that value and the primary and solvent kinetic isotope effects of 8.5 and 1.55 respectively on the dehydronation of *N*-(β-*p*-nitrophenylethyl)quinuclidinium ion,[7] the iKIE for Step 4 as rate-limiting can be estimated as 0.7, quite different from the 4.63 in Table 4, but consistent with a *normal* KIE, as expected for a deprotonation. That was not observed, which was the basis for rejecting Step 4 as rate-limiting. Finally, the iKIE if Step 5 is rate-limiting can be estimated from the previous equilibrium constant, along with the isotope effect on the equilibrium constant [**5**]/[**3**], modeled by the ratio, 8.2/9.1, of the KIEs on keto-enol interconversion in 2-acetylcyclohexanone,[8] and assuming no isotope effect on the final hydroxide elimination. The resulting iKIE is then 3.8. This is admittedly larger than the observed iKIE of 1.12-1.43, but it clearly documents how mistaken the calculated value of 1004 is. Likewise there is no evidence from other computations for such large iKIEs.[9]

Relevance of Computations

I question the relevance of many of the calculations in Ref. 5. The calculations in acetonitrile, which happen to reproduce our experimental results, are reliable. However, our results were not obtained in acetonitrile but in aqueous acetonitrile. The acetonitrile was present solely to maintain solubility of reactants and product. Nevertheless, the solvent remains a protic one, which forms hydrogen-bonds to hydroxide and to enolate anions. The continuum SMD solvation model used in Ref. 5 cannot reliably model reactions in such a solvent, where hydrogen-bonding must be significant.

It is also questionable whether the rate-limiting step can change from Step 5 at 273 K to Step 4 at 298 K, which is where we carried out the measurements that led to the conclusion that Step 5 is rate-limiting.

This is not to deny the value of computations for addressing this issue, but the sensitivity of the conclusions to small energy differences means that the methodology must be capable of great accuracy. Such calculations are to be encouraged.

Conclusions

Admittedly, we cannot conclude that the rate-limiting step in chalcone formation is always Step 5, under all reaction conditions. Nevertheless, according to the solvent kinetic isotope effect, this is unquestionably the rate-limiting step in aqueous acetonitrile. This agrees with calculations of rate constants and isotope effects in acetonitrile, but those calculations also indicate that the rate-limiting step in water switches to Step 4. Yet those calculations are weakened by inconsistencies, and they do not properly model aqueous acetonitrile, which is still a protic solvent. It is erroneous to conclude that this protic solvent changes the rate-limiting step from Step 5, as evidenced by the solvent isotope effect in aqueous acetonitrile, to Step 4. We therefore affirm that the rate-limiting step in any protic solvent remains Step 5, as evidenced by an inverse solvent kinetic isotope effect.

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