The hydrophobic effect as a mechanistic tool

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Abstract: Reactions in water of species with hydrophobic surfaces are slowed by the addition of antihydrophobic cosolvents if the transition states involve shielding of part of those surfaces from solvent, or speeded if the transition states are more hydrophobic than are the reactants. Using this and other tools, some displacements have been shown to occur by single elctron transfer (SET) mechanisms, others by direct nucleophilic attack with various geometries. The results correlate well with the predictions of quantum mechanical calculations.

INTRODUCTION

The hydrophobic effect is the tendency of nonpolar molecules and molecular segments in water solution to avoid contact with the water, either by escaping to a separate phase or by clustering so as to diminish the amount of nonpolar surface that is exposed to water (ref. 1). Water is a poor solvater of nonpolar species and hydrocarbons solvate each other better (ref. 2).

The hydrophobic effect can be decreased by the addition of substances that we have referred to (ref. 3) as "antihydrophobic agents." Both classical denaturing agents such as urea and guanidinium cation and also hybrid polar/nonpolar species such as simple alcohols solvate exposed hydrophobic surfaces and bridge to the water solvent (ref. 4). Antihydrophobic agents thus increase the solubilities of hydrocarbons in water.

We proposed that this effect could be used to reveal transition state geometries for reactions performed in water (ref. 5,6). The concept was simple (ref. 7), and is illustrated in Fig. 1. The solubility of reactants with significant hydrophobic surfaces is increased by the addition of a small amount of ethanol, for example, which lowers the free energy of the reactants. If the transition state for their reaction has the same amount and type of exposed hydrophobic surface, its free energy will also be lowered, and by the same amount. Thus the rate of the reaction will not be changed when small amounts of alcohol are added, if the solvation of hydrophobic surfaces is their sole effect. If however some of the hydrophobic surface is covered in the transition state, the energy of the transition state will be lowered less, slowing the reaction.
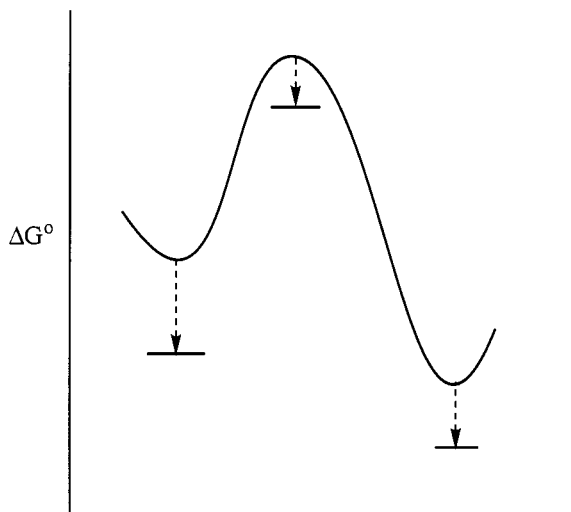

Fig. 1. The effect of added antihydrophobic agents on the free energies of reactants, transition state, and products in water solution. The case shown has a transition state with some decreased exposure of hydrophobic surfaces to the solvent, possibly because of stacking of the surfaces.

To calibrate the method, we showed, by studying solubility changes, that the free energy change induced by an antihydrophobic cosolvent on a solute in water—$\delta\Delta G°$—was proportional to the amount of exposed hydrophobic surface (ref. 7,9). Specifically, doubling from one exposed phenyl group to two exposed phenyl groups in a solute led to twice the increase in $\delta\Delta G°$ on the addition of various alcohols, and where the two phenyls partly occlude each other the $\delta\Delta G°$ was proportional to the expected amount of exposed surface.

The effect of added ethanol on the solubility of cyclopentadiene in water and on the rate of the Diels-Alder dimerization of cyclopentadiene showed that the face-to-face transition state (Fig. 2) for the reaction hid 45% of the total hydrophobic surface from solvent, consistent with calculations of the transition state (ref. 6,8). Furthermore, the effect of antihydrophobic cosolvents on the rate of Diels-Alder addition of N-methylmaleimide to 9-hydroxymethylanthracene (Fig. 2) in water was also consistent with the expected transition state geometry, the maleimide covering ca. half of one face of the anthracene in the transition state (ref. 6,8). Solubility studies in water with various antihydrophobic agents showed that much of the surface hidden in the transition state is again open to solvent in the product, as models indicate.
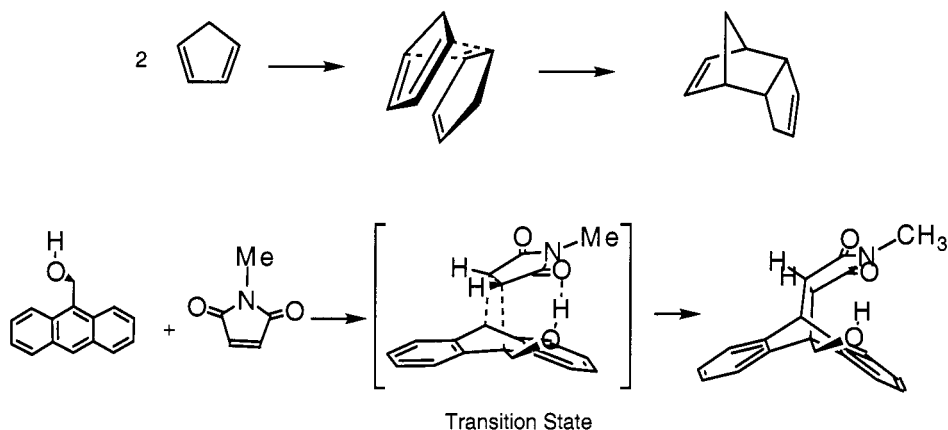

Transition State

Fig. 2. Diels-Alder reactions in which the transition state has essentially complete coverage of one face of each reactant (top) and in which ca. 50% of one face of the anthracene is covered (bottom), but is largely exposed in the product.

The effect of antihydrophobic cosolvents on the relevant $\delta\Delta G°$s for the cyanide catalyzed benzoin condensation in water (ref. 7) indicated that the transition state for the reaction involved an oblique angle of attack by the anion of mandelonitrile onto a benzaldehyde, with partial coverage of phenyl surfaces but less than in the final product benzoin. We also examined (ref. 6,7,9) the effect of antihydrophobic cosolvents on some nucleophilic displacement reactions (Table 1). It was important to show that the rate effects reflected mainly the change in solvation energy of hydrophobic surfaces, not solvent effects on the ionic sections of the transition states, so we examined some displacement reactions in which there was no significant hydrophobic component. The rate of the nucleophilic reaction of hydroxylamine with sodium chloroacetate in water was unaffected by 7 mole% added ethanol, and the rate of reaction of sodium thiomethoxide with sodium chloroacetate also showed a negligible cosolvent effect. Thus, as we hoped, ethanol is recruited to help solvate hydrophobic surfaces in water, but it is excluded from ionic solvation shells, at a modest entropy cost, if it would interfere with the better solvation of ions by water.

When the nucleophile and electrophile carried phenyl groups, the cosolvent effects were remarkable. In the displacement by N-methylaniline on *p*-carboxybenzyl chloride in water, added 3.5 or 7 mole% ethanol led to a significant slowing of the reaction (ref. 7). By contrast, when the nucleophile was phenoxide ion there was no cosolvent effect. We interpreted these date to indicate that the aniline nucleophile attacks with nitrogen electrons that are part of the pi system, which leads to a geometry with partial overlap of hydrophobic phenyl surfaces of the nucleophile and electrophile (Fig. 3), but the phenoxide reaction does not involve such overlap. Instead, attack by phenoxide ion involves not the oxygen electrons that are part of the pi system but instead those that are more or less in the plane of the phenyl ring (Fig. 3). The resulting geometry has no phenyl overlap in the transition state (ref. 7,9). This interpretation was confirmed when we saw (ref. 9) that nucleophilic substitution on *p*-carboxybenzyl chloride by 2,6-dimethylphenoxide ion indeed showed slowing by added alcohol, just as the aniline case had. The two methyl groups block attack by in-plane electrons, sending the reaction to the oxygen pi electron attack that causes phenyl overlap in the transition state (Fig. 4). It is important to note that both the neutral N-methylaniline nucleophile and the anionic 2,6-dimethylphenoxide nucleophile showed <u>slowing</u> with added alcohol, so in this case at least the slowing is not a simple reflection of the charge types involved.
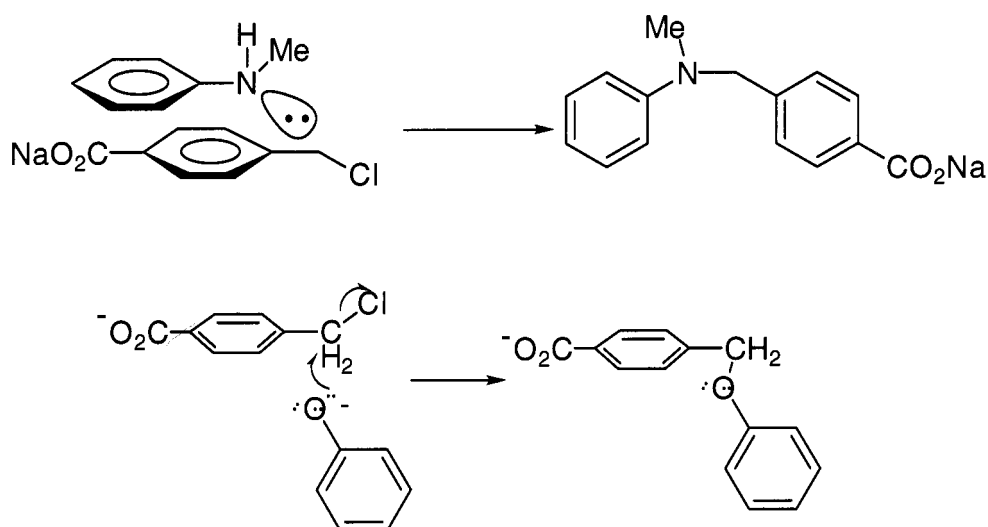
Fig, 3. Displacement by the aniline nucleophile uses nitrogen electrons that are conjugated with the pi system, so there is hydrophobic overlap, but phenoxide displaces using non-conjugated electrons, in a transition state without hydrophobic overlap.
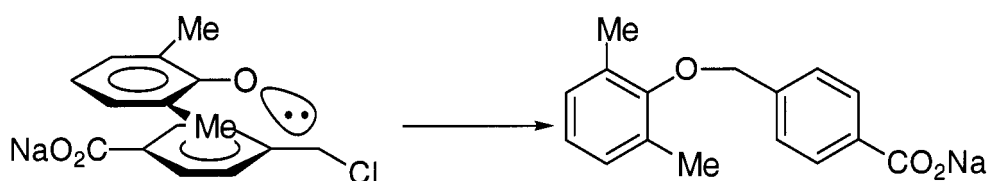

Fig. 4. The two methyl groups prevent attack by in-plane electrons of the oxygen, as in the bottom of Fig. 3, so the pi electrons are used. This leads to slowing by added ethanol.
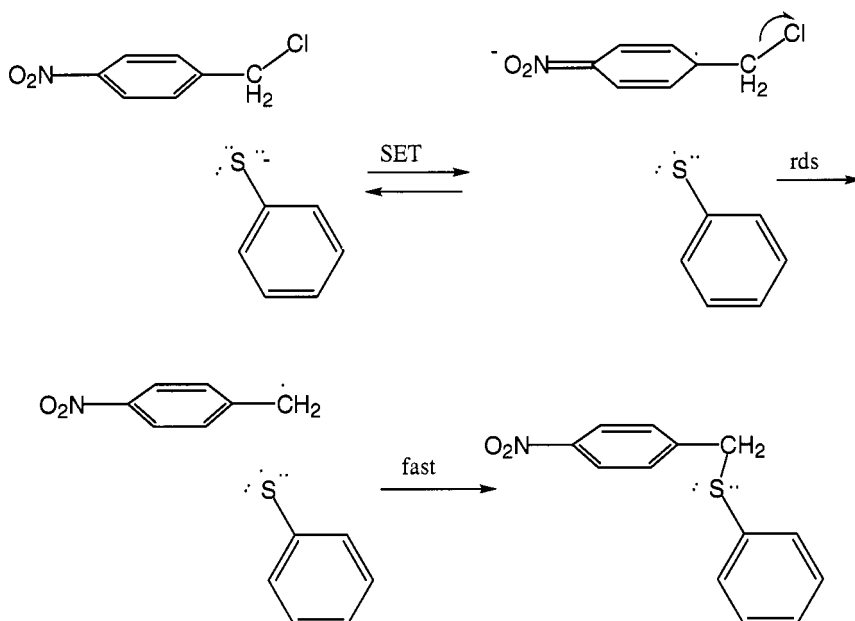

Fig. 5. The SET mechanism in displacement by thiophenoxide ion. There is no hydrophobic overlap in the transition state, and the thiophenoxy radical is less hydrophobic than is the anion.

Nucleophilic attacks on *p*-carboxybenzyl chloride by thiophenoxide ion or 2,6-dimethylthiophenoxide ion were not slowed by added alcohol. Indeed, their reactions with *p*-nitrobenzyl chloride were <u>accelerated</u> by added alcohol, as were the reactions of phenoxide and 2,6-dimethylphenoxide ions. We interpreted this as an indication that the reactions with *p*-nitrobenzyl chloride involved the single electron transfer (SET) mechanism (Fig. 5), in which the nucleophilic anions were converted to neutral radicals at the transition state (ref. 9). Previous evidence (ref. 10,11) indicated that the reaction of *p*-nitrobenzyl chloride with thiophenoxide ion did indeed use an SET mechanism (ref. 12-16). If the electrophilic species has a negative charge shared between the nitro group and the departing chloride ion, neither significantly hydrophobic to start with, the overall result of SET is an increase in hydrophobicity in the transition state with no shielding of the hydrophobic surfaces, as delocalized phenoxide and thiophenoxide ions become the more hydrophobic radicals. As will be described later, our calculations support this proposal. Specifically, a model for the ethanol solvation effect shows that it solvates phenoxide and thiophenoxide ions more poorly than it solvates the neutral radicals, and there is even rough agreement between the calculations and the experimental results.

In the new work reported here, we have explored further the rate effects of antihydrophobic ethanol on substitution reactions in water. The results are consistent with SET mechanisms in several interesting cases, direct displacements in others.

RESULTS AND DISCUSSION

Quantum Mechanical Calculations.

We have used an open shell Hartree-Fock 6-31G** method with continuum solvent Self Consistent Reaction Field (SCRF) called Jaguar (ref. 17) to examine, by calculation, whether thiophenoxy and phenoxy radicals are more hydrophobic than are the corresponding anions. The results are consistent with our proposal. Calculation of the effects of antihydrophobic cosolvents on the energies of various species in water solution involved a simple model. When there is 7 mole% ethanol in the solution, it will be only partially coordinated to the hydrophobic surfaces of the solutes, and we do not attempt to estimate the extent of that partial coordination. Instead we bring an ethane molecule into van der Waals contact with the solute in water, in the computer, and calculate the energy change that results after it relaxes to a local minimum.

The calculated energies were to some extent a function of the positioning of the ethane, but on a benzene molecule the interaction energy with ethane was essentially the same no matter where the ethane was placed; even facial and edge placements were equivalent. The decrease in energy when the ethane was brought to the solutes was 1.40 kcal/mol for benzene, 1.45 kcal/mole for benzaldehyde, and 1.44 kcal/mol for N-methylaniline; the values of their experimental solubility increases by 7 mole% ethanol at 25 °C, translated into $\delta\Delta G°$s, were respectively 0.35 kcal/mol, 0.37 kcal/mole, and 0.35 kcal/mol. Thus the ratio of the experimental $\delta\Delta G°$s to those calculated was 0.25 for all three cases. This ratio reflects both the effectiveness of ethanol in stabilizing the benzene rings and the fraction of the time that there is any interaction with ethanol at all in this dilute ethanol solution.

The situation was quite different with phenoxide and thiophenoxide species. The $\delta\Delta G°$ for interaction of the radicals was calculated to be -1.31 kcal/mol for phenoxy and -1.21 kcal/mol for thiophenoxy, but for the anions putting the ethane on the face of the benzene ring led to only a -0.46 kcal/mol change in energy for phenoxide, and -0.16 kcal/mol for thiophenoxide. This must reflect the negative charge delocalized into the ring, making it less hydrophobic. Apparently the decreased electronegativity of the sulfur atom more than makes up for its poorer pi bonding ability (bond distances and 3p-2p overlap).

Interaction of the ethane with the edges of these rings led to a smaller predicted energy decrease, but still in the same direction. Considering only the face solvation calculation, it is predicted that the ethanol should give a 55% rate acceleration of an SET process in which the thiophenoxide ion is transformed to the radical, and no other major effects are seen in the other reactant. This agrees well with the 56% rate increase in the 4-carboxycyclohexylmethyl iodide reaction, the 39% rate increase in the displacement by thiophenoxide ion on *p*-nitrobenzyl chloride, and the 56% rate increase in the displacement on *m*-nitrobenzyl chloride. For the phenoxide ion, an SET mechanism is expected to show a rate increase with ethanol, from the calculations, of 42% compared with the observed rate increase in the reaction of phenoxide ion with *p*-nitrobenzyl chloride of 79%. The agreement is less good if edge solvation is included as well, but considering what is being calculated the conclusions are clear: it is calculated that the SET mechanism with thiophenoxide ion and phenoxide ion should be accelerated in water solution by added ethanol, and by rate factors that are not too different from those actually observed.

We have also done some calculations relevant to the apparent preference of phenoxide ion to use its electrons that are not conjugated with the pi system when acting as a nucleophile. Rough gas phase calculations support this sensible idea, but the treatment is not yet complete.

Experimental Studies.

Since our previous displacement reactions that exhibited SET and hydrophobic shielding effects all involved benzylic chlorides, we have extended the range of electrophiles used. The saturated analog of *p*-carboxybenzyl was examined, E-4-carboxycyclohexylmethyl. The preparation of the corresponding iodide involved conversion of the commercially available aminomethyl compound via thermolysis of the pyridinium iodide, prepared by amine reaction with 2,4,6-triphenylpyrilium iodide (ref. 18,19). Displacement on this iodide by N-methylaniline showed a negligible 12% rate increase in water with the addition of 7 mole% ethanol (Table 1). We interpret this as a classical displacement reaction with no overlap of hydrophobic surfaces. Such overlap, or an SET mechanism that converted the neutral aniline to a delocalized anilinium cation radical, should have led to rate decreases. Models suggest that the bulky cyclohexyl group cannot pack onto the nucleophilic aniline phenyl ring in this transition state, as the benzylic halide had.

By contrast, displacement on this iodide by thiophenoxide ion and by 2,6-dimethylthiophenoxide ions both showed ca. 75% rate increases with added 7 mole% ethanol, consistent with an SET mechanism that converts the thiophenoxide ions to thiophenoxy radicals. Furthermore, the rates with these two nucleophiles were essentially the same, indicating that the steric hindrance of the dimethylated case is not felt in the transition state, as it would have been for a direct displacement (*vide infra*).

An SET mechanism is precedented for displacements on some alkyl iodides (ref. 20-26), but is not expected for alkyl mesylates, whose reduction potential is more negative. Thus we also examined E-4-carboxycyclohexylmethyl mesylate as a reactant. This showed only a negligible 4% rate increase with added ethanol in the thiophenoxide displacement, and an 8% increase with the dimethylthiophenoxide, indicating a classical S_N2 mechanism without hydrophobic overlap. As expected for this mechanism, the rate with the unhindered thiophenoxide **2** is 40% faster than with the hindered dimethylated nucleophile **3**. Also, the rate of displacement of the iodide by thiophenoxide ion is 4 (water) or 7 (with ethanol) times faster than the rate of displacement of the mesylate, while in direct displacements on methyl derivatives (*vide infra*) by N-methylaniline or by phenoxide ion (Table 1) the mesylate is faster. Furthermore, adding 4.2 M LiCl to the water solvent in the reaction of 2,6-dimethylthiophenoxide **3** with iodide **4** caused no rate effect, but doubled the reaction rate with mesylate **5**. This further supports a change in mechanism upon going from the iodide to the mesylate substrate. Thus our results from the addition of antihydrophobic ethanol to these reactions are consistent with expectations and other evidence. They support the idea that such antihydrophobic effects can be used to distinguish among various geometries for direct displacement reactions, and help distinguish between direct displacements and SET mechanisms, with nucleophilic thiophenoxide and phenoxide ions.

Possible Complications.

In the cases where an antihydrophobic cosolvent in very small mole% slows the reaction, the conclusion that some hydrophobic surface is being shielded in the transition state seems still valid. However, we must consider all possible explanations for rate <u>increases</u> when the cosolvent is added. A trivial one would be a rate increase if one of the reactants were brought increasingly into solution by the cosolvent. In the work we have described here this is not a problem, since all compounds were shown to be completely soluble both with and without the cosolvent, but we have seen that the very large rate acceleration reported in ref. 7 with 2,6-dimethylphenoxide ion was in part caused by solubility problems. With complete solutions the cosolvent still increases the rate, but by less than was reported.

A second worry is that the decrease in hydrophobicity proposed and calculated for phenoxide and thiophenoxide ions when they are converted to the corresponding radicals in the SET mechanism could also be seen when their delocalized negative charges are neutralized not by electron transfer but by coordination during a simple nucleophilic displacement. We observe (Table 1) rate increases with added 7 mole% ethanol for the displacement reactions of phenoxide ion with both methyl iodide and methyl mesylate, by 100% in the first case and 60% in the second. Furthermore, with nucleophilic thiophenoxide ion we see rate increases with added ethanol of 48% with methyl iodide and 43% with methyl mesylate. We believe that this probably reflects significant neutralization of the charge on the nucleophile at the transition state. We did not see any such large rate increase in the displacement by phenoxide ion, thiophenoxide ion, or their 2,6 dimethyl derivatives on *p*-carboxybenzyl chloride, but benzylic halides are quite different from methyl derivatives. We posit that in the benzylic cases the nucleophilic anions have not yet lost much of their charge in the transition states.

The increased reactivity of methyl mesylate relative to methyl iodide in displacements with N-methylaniline and particularly with phenoxide ion is reversed with thiophenoxide ion. The changes may indicate some electron transfer character in the thiophenoxide/iodide case. This is also supported by the finding that displacement on methyl mesylate by thiophenoxide ion is 90% faster than that by the 2,6-dimethylthiophenoxide in water, and 60% faster with added ethanol, while with methyl iodide the unhindered thiophenoxide displacement is only 40% faster in water than the hindered case, and the two have

the same rate with added ethanol. The absence of a steric hindrance effect in the water/ethanol solution also suggests an SET mechanism in thiophenoxide displacement on methyl iodide.

There may also be solvation effects on strongly basic nucleophiles that change with the added ethanol and could affect the results, although this is not yet established. In spite of these concerns the conclusions that some SET mechanisms are involved in reactions of p-nitrobenzyl chloride and 4-carboxycyclohexylmethyl iodide seem clear, from the aggregate of evidence. That such mechanisms with nucleophilic phenoxide and thiophenoxide ions lead to transition states that are more hydrophobic than the reactants is as expected. Such increased hydrophobicity, leading to rate increases induced by the addition of antihydrophobic cosolvents to the water solution, is thus useful evidence for the SET mechanism, but not sufficient. The observed rate increases must be supported by other evidence to establish the SET mechanism.

Table 1. Rate Constants and Ratios for some Displacement Reactions.[a]

Electrophile	Nucleophile	k(Water)	k(EtOH/water)	ratio[b]
4-Carboxycyclohexylmethyl	N-methylaniline	0.00146	0.00163	1.12
Iodide[c]	PhS-	0.306	0.534	1.75
"	2,6-dimethylPhS-	0.300	0.527	1.76
4-Carboxycyclohexylmethyl	PhS-	0.069	0.072	1.04
Mesylate[c]	2,6-dimethylPhS-	0.049	0.053	1.08
4-Carboxybenzyl Chloride[d]	Methoxyamine	0.006	0.0047	0.78
Methyl Iodide[d]	PhO-	0.00099	0.00210	2.11
"	PhS-	7.96	12.1	1.48
	2,6-dimethylPhS-[e]	5.6	12	2.1
	N-Methylaniline	0.038	0.046	1.21
Methyl Mesylate[d]	PhO-	0.022	0.037	1.67
	PhS-	6.45	9.29	1.44
	2,6-dimethylPhS-	3.35	5.86	1.75
	N-Methylaniline	0.107	0.114	1.07

a. Average of triplicate rate constants (calibrated initial rate plots) in $M^{-1}min^{-1}$ (<4% error), monitored by HPLC assay for the reaction product. b. The rate constant with 7 mole% EtOH divided by the rate constant in water alone. c. At 30 °C. d. At 25 °C. e. Duplicate runs, <7% error.

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