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MICROWAVE ACTIVATION OF THE MUTAROTATION OF α-D-GLUCOSE: AN EXAMPLE OF AN INTRINSIC MICROWAVE EFFECT

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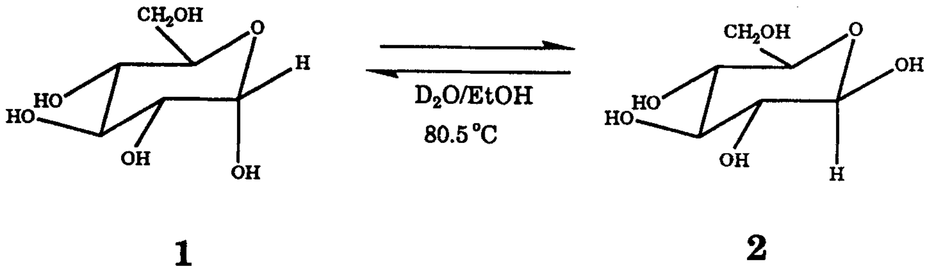
The mutarotation reaction of α-D-glucose in ethanol–water solvent in a modified commercial microwave oven, when compared with control reactions carried out at identical temperatures, shows a non-thermal microwave effect, evidenced both by a more rapid reaction and by a change in relative amounts of α- and β-D-glucose over time.

The efficient generation of high heat by microwaves has been utilized to decrease reaction times dramatically for many organic reactions.[1–5] Striking rate accelerations have been reported for reactions ranging from those involving polar substrates to electrocyclizations with relatively non-polar substrates. Accelerated rates have been attributed to the ability of microwaves to generate elevated temperatures rapidly.

Only a few reports have questioned whether there exist any specific effects on reactivity attributable to changes induced on the molecular level by the absorption of microwave energy. In one example, Sun *et al.*[6] noted an increase in the rate of hydrolysis of phospho anhydride bonds in triphosphates for samples heated with microwaves as compared with samples heated conventionally to about the same temperature; the observed acceleration was tentatively attributed to spectroscopic heating caused by preferential absorption of microwaves by the substrate. However, little if any microwave effect was seen in the esterification of propanoic acid with ethanol.[7] Questions concerning temperature stability and uniformity of heating have cast some doubt on the interpretation of these results.[8] For the Cu(II)-catalyzed addition of tetrachloromethane and ethyl trichloroacetate to styrene, Adamek and Hajek[9] reported non-thermal microwave-induced rate enhancements ranging from 3- to 21-fold as compared with controls heated conventionally to the same temperature; rate enhancements were solvent dependent and were larger in acetonitrile than in dichloroethane.

The mutarotation reaction of α-D-glucose (**1**) to β-D-glucose (**2**), because it proceeds best in microwave-active polar solvents and because it can be performed and monitored easily,[10] is a good model reaction for investigating intrinsic microwave effects. The extent of reaction can be monitored by changes in specific rotation or, alternatively, by ^1H NMR analysis of the cleanly separated anomeric hydrogens; accurate percentage compositions of weighed mixtures were easily determined using this simple analytical method.



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Preliminary investigations were done by comparing the decrease in optical rotation of purified α-D-glucose as a function of time and by comparison with controls carried out at the same temperature. Stock solutions of freshly recrystallized **1** were prepared then partitioned into two 200 ml portions; one was heated conventionally in a thermostated water-bath at 50 °C; the other was heated by microwaves by placing it on a designated 'hot spot' and irradiating at high power. The temperature of the microwave-heated reactions was regulated by inserting the temperature probe supplied by the manufacturer into the solution and setting the temperature control to 120 °F (*ca* 49 °C); the temperature of the solutions was also checked with a rapid-sensing digital temperature probe immediately after irradiation; temperatures of *ca* 50 ± 3 °C were maintained for a few hours using this method. Since the top of the Erlenmeyer flask does not heat appreciably, it acts, in part, as an air-cooled reflux condenser to minimize solvent loss during the reaction. Aliquots were withdrawn and optical rotations were measured immediately. The relative amounts of each epimer were then determined from the experimental specific rotation and the specific rotations of each pure epimer ($[\alpha]_D = 112°$ for α-D-glucose and $[\alpha]_D = 18°$ for β-D-glucose).[11]

Figure 1 compares the ratio of the amounts of **1** and **2** over time as a function of solvent composition ranging from 100% water to 90% ethanol–water. The control reactions, which were heated conventionally to 50 °C, all reached stable equilibria; these are not shown for clarity. Interestingly, for the microwave-heated reaction in 50% ethanol–water the **1**:**2** ratio, as measured by specific rotation and assuming no other reactions to have occurred (see below), appears to reach equilibrium and then to rise with continued irradiation; this phenomenon was seen in at least five other runs done with different concentrations and volumes. By comparison, the other solvent compositions showed almost no changes between microwave- and conventionally heated pairs. Solvent losses, which were monitored carefully for each reaction, were minimal and certainly not appreciable enough to account for the results obtained with the 50% ethanol–water run. Better temperature controls are needed in order to compare rates and to discern more modest changes in product ratios as a function of solvent compositions; these studies are in progress.

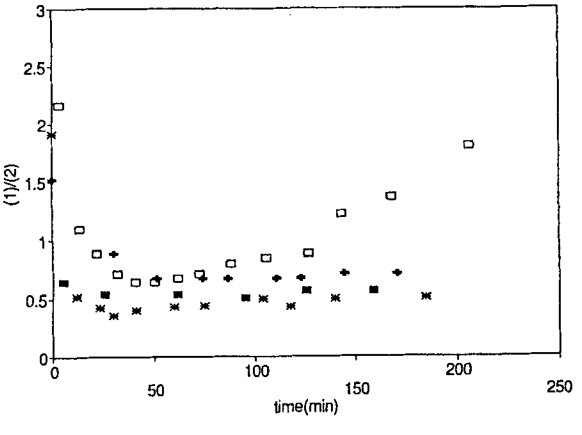

Figure 1. Ratio of [**1**] to [**2**] (α-D-glucose to β-D-glucose) vs time (minutes) for microwave-heated reactions in (□) 50% ethanol–50% water, (■) 70% ethanol–30% water, (+) 90% ethanol–10% water and (∗) 100% water. Relative amounts of **1** and **2** were determined by measurements of specific rotation

Because temperatures in microwave-heated Erlenmeyer flasks are not easily controlled, there remains the possibility that the interesting microwave-induced effect seen in 50% ethanol–water might perhaps be due to changes in temperature and/or concentration. A prefered method for regulating temperature is to run both the control and microwave-heated reactions at reflux temperatures. Simple modifications of our commercial microwave oven have enabled us to run reactions at reflux temperatures, thereby allowing much better temperature control and, consequently, more meaningful comparisons of rates and product distributions with 'classical' reactions heated conventionally.[12] However, the size of the microwave cavity restricts reflux set-ups to those whose volumes would be too small to be measured by optical rotation; instead, for these reactions NMR analyses were used.

Mutarotation reactions at reflux temperatures were performed on 0·13 M stock solutions of recrystallized **1** in 50% (v/v) ethanol–D_2O, which was partitioned into two portions, one heated conventionally to a constant reflux temperature of 80·5 °C and the other placed in a designated 'hot spot' and heated to reflux in a modified microwave oven at a power setting of 10 (full power), with ice-cold cooling water circulating through the condenser. The microwave reaction rapidly achieved a steady reflux rate, which remained constant and vigorous despite the on–off cycling sequence of irradiation built into all commercial microwave ovens. Neither reaction showed any appreciable solvent loss. A small wooden applicator stick was used to moderate the rate of reflux in the microwave-heated reactions. Both reactions were started simultaneously; aliquots were withdrawn from each at staggered intervals and placed in 5 mm NMR tubes, which were then capped and quenched immediately by immersion in liquid nitrogen. The reflux set-up was then placed back in the same position and orientation after each aliquot was removed. Each sample was individually thawed and analyzed by proton NMR spectroscopy. Control studies showed that no significant reaction occurs in the freezing–thawing cycles, so we are obtaining a reasonably instantaneous 'snapshot' of the reaction.

Figure 2 compares the ratio of the amounts of **1** and

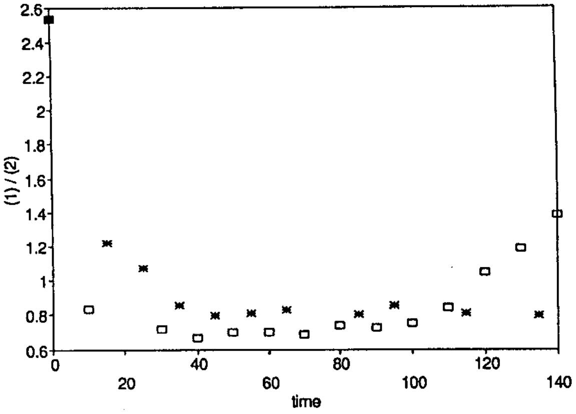

Figure 2. Ratio of [1] to [2] (α-D-glucose to β-D-glucose) vs time (minutes) for (∗) conventionally heated and (□) microwave-heated reactions. Relative amounts of **1** and **2** were determined by ^{1}H NMR spectroscopy

2 as a function of time for both the microwave- and conventionally heated reactions. A least-squares analysis of ln(% **1**) vs time from the first 40 min was used to estimate a three-fold rate enhancement for the microwave-heated reaction. After *ca* 40 min, the conventionally heated reaction attains a stable equilibrium distribution of 45% **1** to 55% **2**; this equilibrium distribution of α- to β-D-glucose does not change significantly with time. The microwave-heated run reaches nearly the same distribution, 43% **1** to 57% **2**, more rapidly than the conventionally heated reaction at the identical temperature. The relative amount of **1** in the microwave-heated reaction then begins to increase steadily with time, indicating a change in distribution induced by microwaves. At least two repeated runs of this reaction gave similar results.

Careful comparisons of the ^{1}H NMR spectra of the microwave-heated and a control reaction showed no discernible differences: this suggests strongly that the wooden applicator stick is not altering the ratio of **1** to **2**, nor are any other products formed during long-term irradiation. Other control reactions heated conventionally and by microwaves in ethanol–D_2O and in D_2O showed no evidence for the formation of an ethylglycoside, a possible by-product resulting from the reaction of glucose with ethanol.

Although care was taken to replace the reflux set-up in the same position and orientation after each aliquot was removed, there still remains the question of whether inadvertent repositioning of the apparatus might be causing some inconsistencies which could account for the observed results. To address this problem, the variation of power absorbed as a function of distance from the designated 'hot spot' was estimated by measuring the rise in temperature when 1000 ml of water was heated for 60 or 120 s. The power absorbed is calculated according to an accepted method:[13]

$$P\ (\mathrm{W}) = \frac{\Delta T C_p m \times 4\cdot 184\ \mathrm{J\ cal^{-1}}}{\Delta t}$$

where ΔT = change in temperature (°C), C_p = average heat capacity for water = $1\cdot 0$ cal g^{-1} K^{-1}, m = mass (g) and Δt = time(s).

The power absorbed at the 'hot spot', 567 ± 4 W, decreases by less than 5% to 544 ± 14 W at a position 4 cm from the 'hot spot' (each value represents the average of at least three measurements). These results suggest that if our reflux apparatus, the diameter of which is 4 cm, is repositioned close to the 'hot spot' each time, then the power absorbed should be constant enough so as not to be the cause of the unexpected results seen in 50% ethanol–D_2O.

While it remains possible that the observed rate enhancement, albeit small, could be due to localized heating of the solvent(s), it is more difficult to explain the observed changes in relative amounts of **1** and **2** with time. While it is also possible that small changes in solvent composition due to selective solvent loss in the microwave-heated reaction might explain the changes in the ratio of **1** to **2** with time, this effect was not observed with other solvent compositions. An ongoing study on the effect of microwaves on the relative selectivity in competitive Diels–Alder reactions of cyclopentadiene for dimethyl maleate and dimethyl fumarate as a function of solvent also strongly suggests a relationship between microwave effect and solvent composition.[14]

Since it is well established that polar functionalities lead to efficient microwave absorption,[13] it might be expected *a priori* that hydroxy-rich glucose, in addition to ethanol and water, both polar protic solvents, would be efficient absorbers of microwaves. Undoubtedly, a complex of glucose solvated by both ethanol and water would also be expected to be an efficient absorber. Spectroscopic heating of glucose or selective spectroscopic heating of one of the solvents could disrupt the solvent cage, resulting in changes in reaction rates and equilibrium compositions. If it is assumed that the temperatures for both the microwave and classical runs are nearly identical and constant and that there is no significant solvent loss from either reaction, then a non-thermal microwave effect is probably the cause of both the discernible rate enhancement and the changes in composition with time. In a similar vein, changes in equilibrium distributions with continued microwave irradiation have been reported in the preparation and equilibration of some metal salts.[15]

It is not known whether microwaves are acting on the solvent alone or on the substrate alone, or whether microwaves might be altering the delicate balance found in substrate–solvent complexes, a possibility that cannot be ruled out. In any case, regardless of the underlying cause, the ability of microwaves to promote and alter a reaction at the molecular level at a constant average temperature has been demonstrated.

EXPERIMENTAL

All microwave reactions were run in a General Electric microwave oven, Model JE 1034T, operating at a frequency of 2450 MHz and a maximum power of 1·2 kW. ^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument; chemical shifts are reported in ppm against an internal standard of DSS, DSS = (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt). Optical rotations were recorded at 25 °C with sodium D light using an Optical Activity Ltd polarimeter. Melting points were obtained using a Thomas–Hoover melting point apparatus and are uncorrected. Temperatures were measured using a Type K thermocouple attached to a Barnant 90 digital thermometer. Data were analyzed by the Cricket Graph 1.0 program, distributed by Cricket Software for use on an Apple Macintosh personal computer, or by QuattoPro 4.0, distributed by Borland, for use on an IBM MS-DOS personal computer.

Materials. Commercial anhydrous ethanol and D_2O were used without further purification. α-D-Glucose was purified by recrystallization from acetic acid following a published procedure (m.p. = 146–150 °C; lit.[11] m.p. = 146 °C).

Optical activity method. Stock solutions were prepared by placing a weighed amount (*ca* 9 g) of freshly recrystallized α-D-glucose into a 500 ml volumetric flask and diluting to the mark with solvent; for mixed solvent solvents, the measured volume of water was added first to dissolve the glucose and then the flask filled to the mark with absolute ethanol and mixed well. The solution was partitioned into two 200 ml portions in two 500 ml Erlenmeyer flasks. The conventionally heated reaction was carried out in a preheated thermostated bath. To minimize spills and ease handling, the microwave-heated reaction flasks were set in a round plastic evaporating dish (diameter 16·5 cm, height 10 cm) and surrounded by a small amount of vermiculite; the dish was placed on a 'hot spot' and heated at power 10 with the temperature probe supplied by the manufacturer set at 120 °F (*ca* 49 °C). Using a T.D. pipette, 20 ml aliquots were withdrawn rapidly and used to fill a 2 dm polarimetric cell. Optical rotations were recorded at 25 °C.

Reflux procedure. A 0·605 g (3·36 mmol) amount of freshly recrystallized α-D-glucose was placed in a 25 ml volumetric flask and dissolved by sonication at room temperature in the measured amount of 50% ethanol–D_2O to make a 0·13 M stock solution of α-D-glucose. An 8 ml volume of the stock solution was placed in a 10 ml round-bottomed flask attached to a condenser and heated in an oil-bath to a constant reflux temperature of 80·5 °C. Another 8 ml portion was placed in a 10 ml round-bottomed flask fitted with a small bump flask and a small condenser, placed in a designated 'hot spot' ('hot spots' were determined by lining the floor of the oven with small marshmallows and heating at full power until the onset of charring) in a modified GE microwave oven[12a] and heated at a power setting of 10 (full power) with ice-cold cooling water circulating through the condenser; a small applicator stick was used in the microwave reactor in place of a boiling stone and a small piece of cotton loosely plugged the top of the condenser. Both reactions were started simultaneously; 0·4 ml aliquots were withdrawn by syringe from each at staggered intervals and placed in 5 mm NMR tubes, which were then capped and quenched immediately by immersion in liquid nitrogen. Each sample was individually thawed and analyzed immediately by proton NMR spectroscopy.

^{1}H NMR analyses. The region between 4·3 and 5·4 ppm was expanded and the relative amount of each epimer determined by analysis of the integration of each anomeric hydrogen: α-D-glucose, δ 5·217, d, $J = 3·60$ Hz, 1H); β-D-glucose, δ 4·630, d, $J = 7·93$ Hz, 1H. For those spectra in which the large water peak at δ 4·75 interfered with the integration, relative areas were estimated by triangulation. Comparison of results by triangulation and integration showed no differences.

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