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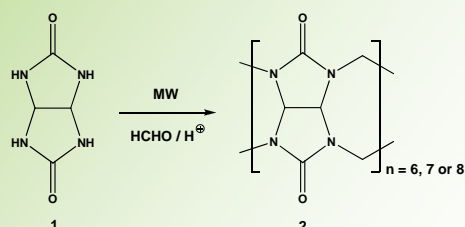
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Abstract: The synthesis of cucurbit[n]urils (CB[n]; $n = 6, 7$ or 8) using microwave irradiation has been examined and the effect of acid type, concentration, reaction time and temperature on the distribution of products has been determined.

Introduction: The cucurbit[n]uril (CB[n]; $n = 5, 6, 7, 8$ or 10) family of macrocycles represents a unique class of compounds that display a variety of host-guest interactions.^{2,3} Cucurbit[n]urils (**2**) are typically prepared through the condensation of glycoluril (**1**) and formaldehyde (or paraformaldehyde) in hot concentrated acid.^{4,5} By varying the type of acid used, the acid concentration or the concentration of glycoluril, the distribution of CB[n] products can be tuned.



Scheme 1. Microwave synthesis of cucurbit[n]urils

In this study the synthesis of cucurbit[n]urils using microwave irradiation⁶ has been examined and the effect of acid type, concentration, reaction time and temperature on the distribution of products determined.

Materials and Methods: All reagents were purchased from commercial sources and used without further purification. The microwave synthesis (**Scheme 1**) was carried out using a Biotage Initiator-8 microwave system (400W, operating at 2.45 GHz, **Figure 1**) using the method detailed below. ¹H-NMR and MALDI-TOF analysis of the samples was carried out in the Department of Pure and Applied Chemistry on a Bruker Avance 400 MHz NMR spectrophotometer and a Axima CFR MALDI-TOF mass spectrometer (m/z range 1-3000 Da; +ve ion reflectron mode) respectively.



Figure 1. Biotage Initiator-8

General procedure for the synthesis of cucurbit[n]urils: Glycoluril (1.08 mmol) and paraformaldehyde (2.26 mmol) were weighed into a microwave vial (0.5 – 2.0 mL) and the respective acid (0.8 mL) added. The vial was capped and the mixture ultrasonicated (1 – 2 min) to affect solution (in some cases a gel formed). The vial was transferred to the microwave synthesiser and after pre-stirring for 30 s, irradiated for the appropriate time and temperature using a power setting of “High”. The samples were diluted with water (2 mL), concentrated *in vacuo* and redissolved in H₂O/DCI for ¹H-NMR and in 500 μ M aqueous NaCl (1:1) for MALDI-TOF MS analysis (for representative example of MALDI-TOF analysis see **Figure 2**).

Results and Discussion:

- The optimum heating time and temperature conditions were determined to be 10 min (for HCl) and 3 min (for H₂SO₄) at 160 °C. This represents a significant improvement over the hotplate method (typically 15 – 36 h at 70 – 110 °C).

- The product distribution (determined by ¹H-NMR) in HCl is observed to be CB[5] (23%), CB[6] (58%), CB[7] (13%) and CB[8] (6%) whilst H₂SO₄ gives predominantly CB[6] (>90%).

- The product distribution in HCl is not affected by variations in temperature; however in H₂SO₄ at temperatures <150 °C a mixture of CB[5-8] are formed, whilst at >160 °C CB[6] is the major product.

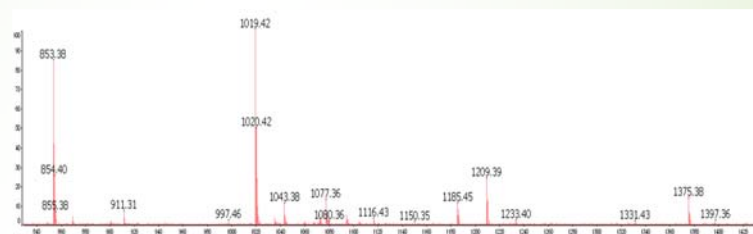


Figure 2. MALDI-TOF spectrum of the CB[n] products synthesised from microwave irradiation for 10 min of a concentrated HCl solution of glycoluril and paraformaldehyde showing typical Na⁺ adducts of CB[5] (m/z 853), CB[6] (m/z 1019 and 1209), CB[7] (m/z 1185) and CB[8] (m/z 1375).

- The use of HCl-H₂SO₄ mixtures (1:9 – 9:1) or diluted acid (25 and 50% aq. solutions) gave mixtures of CB[n] with CB[6] as the major component.

- Other acids (HNO₃, H₃PO₄, AcOH, HCOOH or TFA) do not form any of the desired products, though AcOH and TFA gave an uncharacterisable, insoluble white precipitate that increased with increasing heating time.

- HNO₃ proved unfeasible as a violent reaction and off-gassing occurs when the acid is added to the reagents.

- Scale-up (2x) forms very large CB[6] crystals (0.5 – 1 cm) with a hexagonal morphology (**Figure 3**).

- Scale-up (4x) forms smaller crystals (<0.5 cm) and are a mixture of two crystal morphologies: a hexagonal and a square morphology. These most likely represent different phases due to differences in the hydration states. Single crystal X-ray studies of these two morphologies are currently being determined.



Figure 3. CB[6] crystals

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