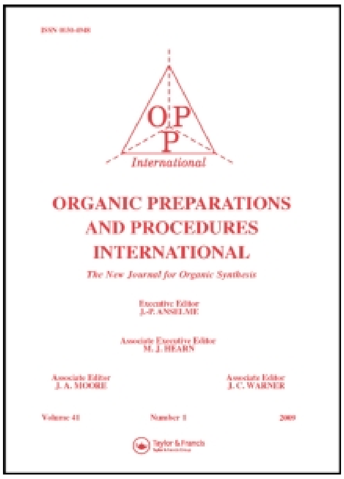

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Perreux, Laurence and Loupy, André(2003) 'EFFECT OF CATIONS, SUBSTRATES AND TEMPERATURE ON THE MICROWAVE-ASSISTED SAPONIFICATION OF BENZOIC AND MESITOIC ESTERS', Organic Preparations and Procedures International, 35: 4, 361 — 368

To link to this Article: DOI: 10.1080/00304940309355841

URL: http://dx.doi.org/10.1080/00304940309355841

ORGANIC PREPARATIONS AND PROCEDURES INT., 35 (4), 361-368 (2003)

EFFECT OF CATIONS, SUBSTRATES AND TEMPERATURE ON THE MICROWAVE-ASSISTED SAPONIFICATION OF BENZOIC AND MESITOIC ESTERS

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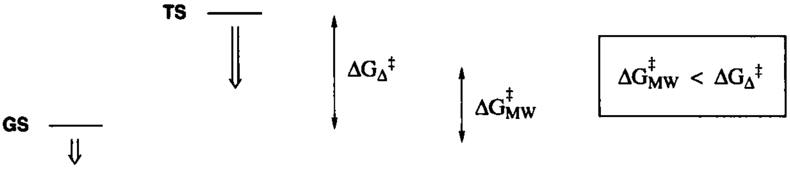
The hydrolysis of esters, one of the most common reactions in organic chemistry, is usually accomplished by heating the ester in either aqueous acid or base.[1] Sterically hindered esters (*e.g.* mesitoic esters) are saponified with difficulty. It has been shown that phase-transfer catalysis (PTC) in toluene allows, albeit with some difficulty, the saponification of methyl mesitoate with potassium hydroxide using dicyclohexyl 18-crown-6[2] or cryptate [2,2,2][3] as catalysts. We previously described an improved solvent-free PTC procedure using Aliquat 336 (5%) in high yields (87-93%) although rather extended reaction times were required.[4] In recent past, the use of microwave irradiation (MW) to simplify and improve classical organic reactions has become very popular[5-9] because it often leads to higher yields, cleaner and shorter reactions. Associated with solvent-free procedures, microwave irradiation (MW) results in an efficient and safe technology.[7,8,10] MW has been used previously for the saponification of esters. Examples of saponification using solvents include the hydrolysis of triglycerides (castor oil)[11] and of cholesteryl esters[12] with potassium hydroxide in ethanol, of methyl and ethyl benzoate in aqueous sodium hydroxide[13] and of waxes in methyl cellosolve.[14] Hydrolyses under solvent-free conditions have been reported for the removal of the pivaloyl,[15] acetyl and benzyl[16] groups from the surface of alumina and silica gel-activated by indium triiodide.[17] In a preliminary study, the solvent-free PTC conditions using KOH and Aliquat 336 were highly efficient (quantitative yields).[18] We now report a study of the influence of cations, substrates and temperature on the microwave-assisted saponification of esters.

In general, reactions using microwaves have been performed using a domestic multimode oven without strict control in temperature and comparison with conventional heating in order to check the possible intervention of specific (non-purely thermal) microwave effects.

Abramovitch concludes his review[5] with the suggestion that if "the microwave energy is absorbed selectively by a reactant, a complex or an intermediate on the way to rate-determining transition state, then large reaction rate increases will result". By extension, with the goal to propose some general interpretation for the microwave specific effects, it can be assumed[19,24] that microwave effects will be favorable if the polarity of the system is increased during the progress of the reaction (MW-materials interactions are enhanced as they are more polar[20]). Therefore, it should be the case for reactions when the transition state (TS) is more polar than the ground state (*Fig. 1*). Langa *et al.*[21,22] proposed a similar approach for the cycloaddition of *N*-methylazomethine ylides with C_{70} fullerene. Theoretical calculations predict an *asynchronous* mechanism, and

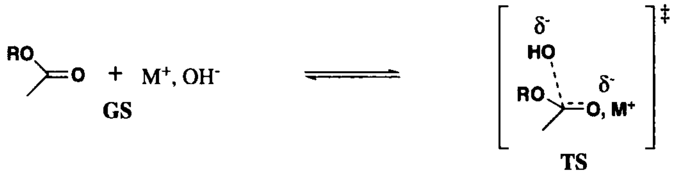


Relative Stabilization of Transition State and Ground State by Dipole-dipole Interactions with Electromagnetic Field if TS is more polar than GS

Fig.1

thus this phenomenon could be rationalized by the consideration that, under kinetic control, "microwave irradiation will favor the more polar path corresponding to the hardest transition state". The microwave effects may be dependent not only upon the polarity increase from GS to TS but also on the position of TS along the reaction coordinates.[23] If the TS occurs early (*i.e.* reactant-like TS for facile reactions), MW effects will be limited, whereas if TS intervenes later (product-like TS for difficult reactions), specific effects will become more important.

The addition of hydroxide ion to the carbonyl function is the rate-determining step (*Scheme 1*) and specific microwave effects could be affected by ion pairing between M^+ and OH^-. The looseness or tightness of ion pairs with different cations (Na^+ or K^+) can be affected by the



Mechanism for Ester Saponification

Scheme 1

presence of a phase-transfer agent and thus may have significant influence on the polarity of the GS. Consequently, the looseness or tightness of ion pairs may induce differences in polarity modification from GS to TS which is constituted of polar loose ions pairs due to the extension of the negative charge (*Scheme 1*). Similarly, the nature of the ester substituents can induce some effects on the position of TS along the reaction coordinates and the magnitude of activation energy. With less reactive species (long chain aliphatic R groups, hindered aromatic group), an increase in the specific MW effects might be expected. Finally, in order to establish some possible specific microwave effects, it is more advisable to operate at sufficiently low temperatures because it has been demonstrated that those specific MW effects could be impeded by a too elevated temperature level.[25-28]

Reactions were performed using MW with mechanical stirring using a monomode reactor[7] (Synthewave® 402 from Prolabo) involving focused waves; the temperature was measured by infrared detection[29] and kept at a constant value by modulation of the emitted power. The temperature can be selected and maintained by operating in the presence of a non-polar solvent (*i. e.* transparent to microwave), which limits the temperature to its boiling point. In order to check the possible intervention of specific (non-purely thermal) microwave effects, comparisons were made with conventional heating (Δ) in a thermostated oil bath strictly under the same conditions (vessels, temperature, pressure, time) with identical profiles of increases in temperature under both types of activation.

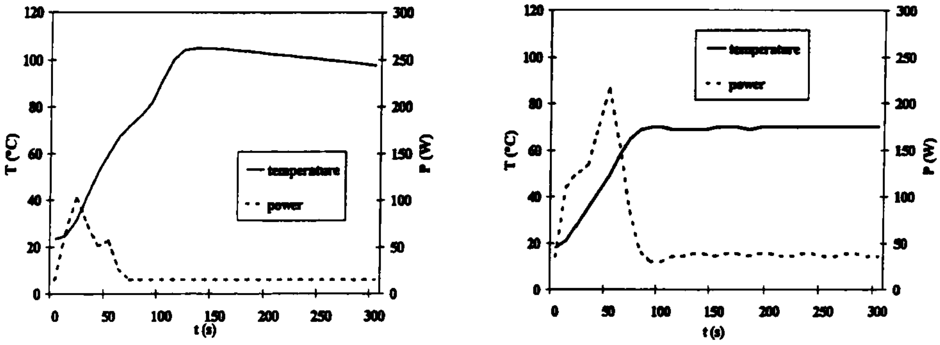
Benzoic Esters

Under solvent-free conditions, the temperature rose to 110°C without any possibility of

$$\underset{\mathbf{1}}{PhCO_2R} + M^+OH^- \xrightarrow[\text{then HCl (2N)}]{\text{(PTC)}} \underset{\mathbf{2}}{PhCO_2H} \qquad (1)$$

a) $R = CH_3$ b) $R = n\text{-}C_8H_{17}$ PTC = Aliquat 336 (10% mol eq.) $M^+ = Na^+, K^+$

control when potassium hydroxide was used. In this case, it was possible to maintain the temperature at 70°C by operating in the presence of hexane [*Fig. 2*].



Without solvent In the presence of *n*-hexane (5 mL)

Profiles of temperature rise for the saponification of **1a** (5 mmol) with KOH (2 eq.)

Fig. 2

Table 1. Saponification of **1a** and **1b** (5 mmol) under Microwave Activation (MW) or Conventional Heating (Δ)

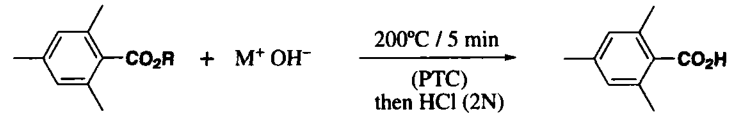
Entry	Substrate	M^+	OH^- (eq.)	Temp (°C)	Time (min)	Yield of **2** (%)[a]			
						No PTC		With PTC (10%)	
						MW	Δ	MW	Δ
1	**1a**	K	2	200	5	94	90	98	98
2	**1a**	K	2	70[b]	5	89	87	90	90
3	**1a**	K	2	70[c]	5	6	12	----	----
4	**1a**	K	1	70[b]	5	18	5	56	24
5	**1a**	K	1	70[b]	60	**77**	**42**	**67**	**65**
6	**1a**	Na	2	200	5	**92**	**77**	**90**	**73**
7	**1b**	K	2	200	5	94	93	98	89
8	**1b**	K	2	70[b]	5	16	----	27	----
9	**1b**	K	1	70[b]	30	74	62	58	48
10	**1b**	Na	2	200	5	95	93	93	86
11	**1b**	Na	1	110	5	30	12	42	40
12	**1b**	Na	1	110	30	**66**	**41**	**61**	**37**

a) Isolated yields. b) 2.5mL of *n*-hexane added. c) 5mL of *n*-hexane added.

At 200°C, with two equivalents of KOH, even in the absence of a PTC agent (*entries 1 and 7*), yields are very high within 5 minutes, whatever the mode of activation. On the other hand, by decreasing the temperature and the amount of base (from 2 to 1 eq), the presence of Aliquat 336 appears to be beneficial (*entries 4, 8 and 11*). The effect of the amount of *n*-hexane was noticeable as a too large volume induced a major decrease in yields (*entries 2 and 3*). Specific microwave effects were operating essentially under two types of conditions either by replacing KOH by NaOH (*entries 1 and 5* for **1a**) [MW: Δ = 94:90 (KOH) and 92:77 (NaOH) within 2 min. at 200°C] or by decreasing the temperature to 70°C (*entry 4*; MW: Δ = 77:42) whereas no effect was observed using 2 eq KOH at 200°C (*entry 1*; MW: Δ = 94:90).

Mesitoic Esters

It is evident that in the cases of **3a** and **3b**, the use of KOH in the absence of PTC led to noticeable specific microwave effects with the most difficulty case (**3b**>**3a**): MW: Δ = 82:80



3 **4** (2)

a) R = CH_3 b) R = n-C_8H_{17} PTC = Aliquat 336 (10% mol eq.) $M^+ = Na^+, K^+$

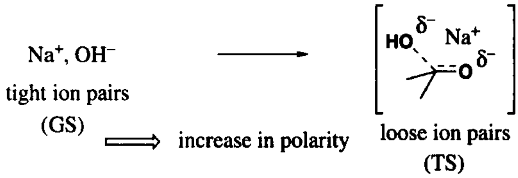
(**3a**) and 92:50 (**3b**); in addition, specific microwave effects disappeared in the presence of Aliquat 336 within 5 minutes at 200°C with KOH (**3b** / entry 4) MW: Δ = 92:50 (no PTC) and 95:92 (with PTC) while specific microwave effects increased when NaOH was used instead of KOH (*entries 1 and 3* for **3a**; *entries 4 and 5* for **3b**).

Table 2. Saponification of **3a** and **3b** under Solvent-free Conditions using Microwave Activation (MW) or Conventional Heating (Δ) at 200°C (5 min.)

Entry	Ester	M^+	OH^- (eq.)	Yield of **4** (%)[a]			
				No PTC		With PTC (10%)	
				MW	Δ	MW	Δ
1	**3a**	K	2	92	80	94	88
2	**3a**	K	1	63	15	62	57
3	**3a**	Na	2	90	56	92	57
4	**3a**	K	2	82	50	95	92
5	**3b**	Na	2	84	25	97	39

[a] Isolated yields

The differences in behavior can be rationalized in terms of the structure of the reactants and the enhancement in the polarity of the systems during the progress of the reaction. It would appear that the magnitude of specific microwave effects is dependent on the nature of the reactive ion pairs as a function of the cation. With NaOH, the microwave effect is more important compared to the reaction carried out with KOH. This fact is consistent with tighter ion pairs in the previous case (cation hardness: $Na^+ > K^+$), thus leading to less polar species. The polarity enhancement toward TS which consists of loose polar ion pairs (due to negative charge delocalization) is then more important with NaOH than with KOH (looser ions pairs) (*Scheme 2*).



Modification of Ion-pairing during Ester Saponification from Ground to Transition State

Scheme 2

The same phenomenon could also explain the absence of microwave effect in the presence of a phase-transfer agent (*entry 4*) as in this case, the reactive species in the GS is yet constituted of very loose ion pairs: R_4N^+ and OH^-. Similarly, in connection with the involvement of a long alkyl chain R and even more, with hindered systems (*e. g.* mesityl >> phenyl), specific microwave effects are evident. With an increased steric hindrance (larger activation energy), the transition state may occur later along reaction coordinates and, consequently, become more likely to develop more important interactions with the electromagnetic field. The importance of these effects is highly dependent upon the reactivity of the systems and become more critical when the temperature and the amount of alkaline hydroxide is decreased; the situation is improved with the less nucleophilic NaOH when compared to KOH.

The saponification of hindered esters has been achieved in solvent-free conditions within short times and appreciable yields under microwave activation. In order to observe specific microwave effect in the case of the easier reaction (benzoic esters), it is necessary to decrease the reaction temperature and the amount of alkali hydroxides. The differences in behavior can be understood when the enhancements of the polarity of systems during the reaction progress and the structures of the reactants are considered. It appears that the magnitude of specific microwave effects is dependent on the nature of the reactive ion pairs as a function of cation and on the position of the transition state along the reaction coordinates.

These conclusions were supported by a wide frequency band dielectric spectroscopy study[30,31] which allows macroscopic temperature measurements during microwave heating. Comparisons of the evolution of the relaxation frequency versus temperature during classical heating and microwave exposure provide some insights on the phenomena involved. It was also shown that the energy of activation associated with ionic conductivity is lower under microwave compared to conventional heating.

EXPERIMENTAL SECTION

The microwave reactor was a monomode system (Synthewave® 402) with focused waves operating at 2.45 GHz. The temperature was controlled throughout the reaction and estimated by an infrared detector which indicated the surface temperature (the IR reading was calibrated by tuning the emissivity factor using a thermo-couple introduced into the reaction mixture). Temperature was maintained constant at a chosen value by modulation of emitted MW power. Mechanical stirring during the irradiation provided good homogeneity (power and temperature) and data treatment which was followed by a computer. All reactions were performed in cylindrical tubes Pyrex open vessels.

General Procedure for the Saponification of Esters.- Saponification of esters was performed under microwave irradiation or conventional heating. In a Pyrex cylindrical open reactor adapted to the Synthewave reactor, 5 mmoles of ester were mixed with 10 mmoles of base, 0.5 mmoles of Aliquat 336 (and 5 mL of hexane when appropriate see Tables). The mixture was then submitted to microwave exposure under mechanical stirring. At the end of irradiation, the reaction mixture was cooled to room temperature and extracted with methylene chloride. The aqueous layer was acidified with a solution of 2N HCl (3 mL) and extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give a white solid requiring no further purification.

In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (weight of reactants, time and temperature) in a thermostated sand bath. The temperature was estimated with a digital thermometer or an optical fibre introduced into the reaction mixture. The rate of the temperature rise under microwave irradiation was adjusted to the conventional one by computerized modulation of emitted microwave power.

Acknowledgments.- We sincerely thank Electricité de France (E.D.F.), Research and Development Division -77818 Moret sur Loing Cedex - (France) and especially Dr. Michel Moneuse and Dr. Karine Burle for their financial and scientific support. We thank Dr. Stéphane Chevalier and Prof. Arlette Fourrier-Lamer (Laboratoire du Génie Electrique de Paris) for helpful collaboration with frequency band dielectric spectroscopy. The authors are indebted to Prof. J.-P. Anselme for his efficient and welcome help and the number of hours he has invested in handling and editing this manuscript.

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(Received September 18, 2002; in final form February 25, 2003)