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Classical Organic Reactions in Pure Superheated Water

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At high temperatures and pressures, pure liquid water becomes a surprisingly effective medium for the reactions of organic compounds. It may function simultaneously as a convenient solvent, catalyst, and reagent for reactions which are typically acid- or base-catalyzed. Rapid and highly selective conversions are observed for the majority of the compounds in this study.

The low cost of water and its environmental friendliness are incentives for the growing interest in water as an effective medium for organic reactions that can take advantage of favorable changes in the chemical and physical properties of water at high temperatures and pressures.[1,2] A gradual decrease in the dielectric constant of water with increasing temperatures[3] is paralleled by increasing water solubility of organic compounds. At 300 °C, the polarity and density of water approach those of acetone at room temperature.[4] Further, the enhanced self-ionization of water at high temperatures, for example, $-\log K_W = 11.30$ at 200 °C,[5] suggests that, as a consequence of the higher hydronium and hydroxide ion concentrations, acid- and base-catalyzed reactions that cannot occur readily at ordinary temperatures could be promoted. This paper reports the investigations of bond cleavage reactions in superheated water (aquathermolysis) of some organic compounds whose acid- or base-catalyzed reaction mechanisms are well established under conventional conditions, as a test of the role of the enhanced ionization of water at high temperatures.

For these mechanistic studies in superheated water, compounds were chosen that would undergo selective and simple reactions uncomplicated by the formation of products that would change the pH or ionic strength of the medium. Our approach required that all substrates be water soluble in the temperature range from 200 to 300 °C at pressures generated solely by expansion of the liquid medium (autogenic; approximately 250 to 1100 psi). This focus complements extensive work by Siskin, Katritzky, and co-workers,[6] which generated a wealth of information concerning the reactivity of many organic compounds in hot water regardless of their solubilities, reaction pathways, or complexity of products. Those studies emphasized the effects of the hot aqueous medium compared to the relatively unreactive hydrocarbon solvents that served as a control solvent system for generating possible thermal radical pathways. Product identification and distribution were used to ascertain the effects of changing aqueous reaction conditions through the addition of acids, bases, clays, and salts.[7]

As reported below, the search for compounds appropriate for physical studies revealed that the dehydration of benzyl alcohols and cyclohexanols, ring cleavage of furans, hydrolysis of acetals and ketals, as well as pinacol rearrangements occurred at unexpectedly rapid rates, at rates too high for convenient kinetic studies.

Results and Discussion

Elimination Reactions. α-Ethyl-4-methoxy- and *d,l*-4-chloro-α-propylbenzyl alcohol (0.50 M) underwent nearly quantitative elimination reactions in pure liquid water at 277 °C within 75 min. Only a trace, less than 1%, of an unidentified side product was formed in each case. Neither cleavage of the para-substituents nor polymerization of the products was detected by ^{1}H or ^{13}C NMR of chloroform extracts of the two-phased product mixtures. Because of the very rapid conversion of both alcohols, para-substituent effects could not be established. Conversion of a related benzyl alcohol derivative, α-phenethanol, to a slate of compounds *via* intermediacy of the α-phenethyl cation was reported by Katritzky et al., following reactions at 250 °C for 1 and 5 days.[8]

Cyclohexanol and methylcyclohexanol derivatives underwent exclusively dehydration in pure deuterium oxide at 250–300 °C. A 60-min treatment of cyclohexanol in pure water at 300 °C led to a 33% conversion solely to cyclohexene; during 18 h at 278 °C an 85% yield of the cycloalkene was obtained. The acid-catalyzed conversion was enhanced when sulfuric or hydrochloric[9] acid (0.02 wt %, 5 mM at room temperature) was added. Nearly complete dehydration (99%) was achieved at a concentration of 2 M cyclohexanol in the presence of sulfuric acid[10] (0.05 wt %, 5 mM at room temperature) after 30 min at 250 °C. The dehydrations of 1- and 2-propanol in supercritical water have been reported by Antal and

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(8) Katritzky, A. R.; Luxem, F. J.; Siskin, M. *Energy Fuels* **1990**, *4*, 518–524.

(9) Caution: Halide ions, particularly Cl$^-$, may cause stress fractures in stainless steel reactors.

(10) H_2SO_4 has been reported to act as a monoacid in hot water with only negligible dissociation of the bisulfate ion. See ref 11b and Shock, E. L.; Helgeson, H. C. *Geochim. Cosmochim. Acta* **1988**, *52*, 2009–2036.

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Narayan.[11] Only low concentrations (1–25 mM) of added acid were required to dehydrate these alcohols at 374 °C, the supercritical temperature of water.

Conversions of methyl-substituted cyclohexanols proved to be the least selective of the reactions investigated. *cis*- and *trans*-2-methylcyclohexanol underwent elimination to 1-methylcyclohexene in low yield, but with 100% selectivity during a 60-min, 300 °C treatment with pure water. An 18-h reaction of the *trans* isomer at 270 °C yielded, however, a mixture of methylcyclohexenes that were clearly the products of dehydration/hydration equilibria, at a total conversion of approximately 70%. The predominant product was identified by NMR and GC to be 1-methylcyclohexene (>70% relative to other isomers). Similar results were obtained for *cis*-2-methylcyclohexanol; however, even greater 1-methylcyclohexene formation was observed relative to double-bond migration products. *Cis* and *trans* isomers were examined to probe whether the elimination reactions occurred *via* an E1 or E2 mechanism. Higher reactivity of the *cis* isomer would point toward the bimolecular E2 pathway, because only in this isomer could the leaving group (H_2O) assume the required antiperiplanar conformation. Equal conversion rates would be expected for E1 reactions. Results obtained thus far are not sufficient to clarify these mechanistic aspects or the primary role of water in this reaction. The most complex product mixture was obtained for the reaction of 1-methylcyclohexanol. Again, isomerized methylcyclohexenes and, also, the corresponding intermediate methylcyclohexanols provided evidence for alcohol–alkene equilibria. Small amounts of dimethyl- and ethylcyclopentenes were detected by GC/mass spectroscopy as well. It is not clear at this time if radical or ionic pathways predominated. Dehydration of neopentyl alcohol or pentaerythritol, concomitant with the required carbon-bond migration, did not take place in 60 min at 250–300 °C. None of the alcohols studied underwent dehydration to ethers to any observable degree.

Pinacol Rearrangements. Quantitative rearrangements of pinacol, 1,1′-dihydroxy-1,1′-dicyclopentyl, and 1,1′-dihydroxy-1,1′-dicyclohexyl[12] to the corresponding ketones, with negligible alkene formation, occurred in deuterium oxide in 60 min at 275 °C. The efficiency of aquathermolysis is very much in evidence here, considering that quantitative formation of pinacolone from pinacol *via* a classical method requires boiling in 25% H_2SO_4 for 3 h.[13] Further, pure superheated water apparently affords an environment which sustains cationic intermediates long enough to allow rearrangements.

Cleavage/Hydrolysis Reactions. Rapid and clean acid-catalyzed ring cleavage of 2,5-dimethylfuran in pure deuterium oxide at 250 °C yielded 2,5-hexanedione quantitatively within 30 min. The reaction was not reversible, that is, 2,5-hexanedione did not undergo ring closure at this temperature in 60 min. These reaction conditions are in contrast to those reported in a (mechanistic) study of this reaction in which a 0.1 M DCl solution at 70 °C was required to cleave the ring.[14] Dibenzofuran[15] and 2-hydroxydibenzofuran[16] proved to be stable to aquathermolysis and may represent the other extreme on the reactivity scale.

Acetals and ketals were highly reactive to aquathermolysis, undergoing in nearly all cases 100% hydrolysis within 30 min at 205–250 °C without any side or secondary reactions. Greater than 90% deprotection of cyclopentanone ethylene ketal and 1,4-cyclohexanedione bis(ethylene ketal) was achieved at 250 °C. Equal reactivities to pure water were determined for benzaldehyde and tolualdehyde diethyl acetals at 186 and 250 °C resulting, during 30-min reactions, in 91–94% and 100% conversion, respectively. Hydrolysis of benzaldehyde diethyl acetal went to completion overnight at room temperature but decreased to 33% in the presence of basic barium oxide at 80 °C over 45 min. At 254 °C, quantitative hydrolysis of this acetal in aqueous KOH at acetal:base molar ratios as low as 1:0.25 (72.5 mM in KOH) was followed by a Cannizarro disproportionation, as indicated by the formation of benzyl alcohol, benzoic acid, and, *via* subsequent decarboxylation of the acid, small amounts of benzene. Formation of Cannizarro products of benzaldehyde in the presence of a much weaker base, pyridine, was reported previously by Katritzky et al.[17] Tsao and Houser suggested the possibility of a Cannizarro reaction of this aldehyde catalyzed by ammonia in supercritical water, but, based on product distributions, they appear to favor the involvement of radical pathways.[18]

Diacetone-D-glucose (0.31 M) and 1,6-anhydro-β-D-glucose (0.30 M) were converted quantitatively at 205 °C to predominantly D-glucose and traces of another glucose isomer. Under the same conditions in the presence of 1 equiv of KOH (0.29 M), 1,6-anhydro-β-D-glucose was unreactive and only the exocyclic, 5,6-acetone moiety of diacetone-D-glucose was cleaved.

None of the products formed in the reactions described above is expected to significantly alter its particular reaction environment. This is not the case, however, in the hydrolysis of esters, wherein, because of the formation of soluble carboxylic acids, the potential for autocatalysis arises. Siskin et al., reported quantitative hydrolysis of methyl 1-naphthoate after 2-h and 5.5-day treatments at 343 and 250 °C, respectively.[15] Decarboxylation of naphthanoic acid, the major product at the lower temperature, led predominantly to the formation of naphthalene during a 2-h conversion at 343 °C; the reaction is catalyzed by the generated carbonic acid. Our examinations of methyl benzoate and the 4-chloro, 4-methyl, and 4-methoxy derivatives of this ester revealed up to 50% hydrolysis within 30 min at 250 °C. No evidence of decarboxylation was observed. Partial cleavage of the *p*-methoxy group is assumed to be caused by the increased acidity of the medium as a result of carboxylic acid formation since it was not observed during the reaction of α-ethyl-4-methoxybenzyl alcohol, that is, in a reaction occurring in

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Table 1. Hydrogen/Deuterium Exchange in Ketones

compound	% D (position)	reaction conditions °C	min
pinacolone[a]	100 (α CH_3)	277	60
acetone	97 (α, α' CH_3)	200	60
cyclopentanone[b]	100 (α, α' CH_2)	225	30
1,4-cyclohexanedione	100 (α, α' CH_2)	225	30
acetophenone	>88 (α CH_3)	250	60
deoxybenzoin[c]	99 (α CH_2)	250	30

[a] Exchange observed in the rearrangement product of pinacol. [b] Exchange observed in the hydrolysis product of the corresponding ethylene ketal. [c] $PhCH_2COPh$.

Table 2. Hydrogen/Deuterium Exchange in C–H Acids

compound	% D (position)	reaction conditions °C	min
toluene	0	300	75
triphenylmethane	0	300	60
biphenylyldiphenylmethane[a]	0	250	60
fluorene	0	200	60
	30 (C9)	250	60
	100 (C9)	300	60
9-phenylfluorene	0	200	60
	100 (C9)	300	75
9-isopropylfluorene	*b*	300	75
9-bromofluorene	*b*	300	75
1-methylfluorene	0	200	60

[a] $(C_6H_5C_6H_4)CH(C_6H_5)_2$. [b] Decomposed.

neutral water under otherwise more extreme conditions (277 °C, 75 min). In a reaction typical of β-keto esters, ethylacetoacetate underwent complete conversion to acetone, ethanol, and CO_2 (not analyzed) in 30 min at 250 °C. Under the same conditions, *tert*-butyl acetate decomposed to a bright red, highly insoluble mixture of unidentified products resulting from polymerization of isobutylene;[19] methyl trimethylacetate was unreactive.

Hydrogen Exchange Reactions. When the ring cleavage reaction of 2,5-dimethylfuran was conducted in deuterium oxide,[20] extensive deuteration of the methyl and methylene groups of the product, 2,5-hexanedione, was observed; the same result was detected by ^1H and ^{13}C NMR when this dione was the initial reagent. Thus, it became evident that this medium was suitable to effect $^1H/^2H$ exchange. These exchange reactions afforded a means to study organic transformations in a constant reaction environment undergoing minimal changes; for example, no products are formed that have significantly different properties or reactivities from those of the initial reagents. Also, no changes occur in reaction mechanisms, volume, vapor pressure, or the dielectric or dissociation constants of deuterium oxide because of the formation of ionic products and potential catalysts or cosolvents.

Deuterium oxide treatment of methyl (300 °C, 93 h), isopropyl, and neopentyl alcohol (200 °C, 30 min and 300 °C, 60 min, respectively) did not induce any exchange of C–H hydrogens; the same negative results were obtained in experiments with ethylene glycol (300 °C, 60 min) and pentaerythritol (250 °C, 60 min). Hydrogen exchange was achieved rapidly and nearly quantitatively in the α and α' (where applicable) positions of ketone carbonyl groups. Table 1 lists the extents and sites of deuteration observed in selected ketones. Kinetic studies of hydrogen exchange in pinacolone are currently being conducted. In all cases, the operating enol–keto tautomerism led exclusively to hydrogen exchange; no aldol products were observed.

Our examination of hydrogen exchange in C–H acids revealed fluorene to be a stronger acid in deuterium oxide than triphenylmethane under equal reaction conditions (Table 2). This order in acidity corresponds to that established by Bordwell in DMSO; it also agrees with results obtained in methanolic sodium methoxide by Streitwieser and co-workers, which reported pK_{HB} values of 22.6 and 23.04 for fluorene[21,22] and 31.48 for triphenylmethane.[23] The upper limit of H/D exchange in water at 200–300 °C and reaction times of less than 2 h for compounds not containing heteroatoms (see discussion of acetone reaction, below) appears to lie below pK_{HB} of 40. The basicity of D_2O at 300 °C proved insufficient to abstract methyl hydrogens of toluene, which has a reported pK_{HB} of 40.9.[24]

Interestingly, in deuterium oxide, the acidity of acetone (Table 1) may actually exceed that of fluorene, whereas pK_{HB}'s in DMSO of approximately 20 for the hydrocarbon and 26 for acetone[21] indicate lower acidity of acetone in this organic medium. Additional stability gained by hydrogen bonding and solvation—attainable for acetone in water but not DMSO and for fluorene in neither medium—may actually contribute to this apparent reversal of acidities. The increased acid/base character of hot water and the decrease in its dielectric constant could therefore allow expansion of acidity determinations of acids with H-acceptor/donor capacity in aqueous solutions to higher pK_{HB} ranges than those accessible under traditional conditions.

Summary

Acid- or base-catalyzed organic reactions in pure water at high temperatures and pressures appear to follow the same pathways elucidated under traditional conditions with added acid or base. Detailed kinetic studies are in progress to confirm this assumption. No new chemistry involving either ionic or radical mechanisms was indicated. These findings may allow extrapolations of reactions in superheated water to a broader array of organic materials with greater certainty. The fact that a wide range of C–H acids undergo hydrogen exchange in hot water can provide rough estimates of the acidities of very weak acids in such solutions. Most importantly, very facile and selective transformations are accessible by reactions in pure, hot water without the need to neutralize product mixtures or the use (and subsequent disposal) of potentially toxic and environmentally destructive materials such as cosolvents or added catalysts.

Experimental Section

General Information. All reactions were carried out in $^3/_4$-in. 316SS Swagelok fittings (supplier, R. S. Crum), total volume

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[20] The ion product of D_2O is approximately 1 order of magnitude larger than that of H_2O at equal temperature, e.g., at 250 °C $-\log K(H_2O) = 11$, $-\log K(D_2O) = 12$. See Perrin, D. D. *Ionization Constants of Inorganic Acids and Bases in Aqueous Solutions*, 2nd ed.; IUPAC Data Series 29; Pergamon: New York, 1982.

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[24] Streitwieser, A., Jr.; Granger, M. R.; Mares, F.; Wolf, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 4257–4261.

4.9 mL, and heated in a Techne fluidized sand bath. No significant effects on the reactions by the metal surfaces have been observed in liquid water.[25] Analysis by inductively coupled plasma emission spectroscopy (ICPES) of deuterium oxide after a 10-day exposure at 300 °C and of the reactor contents following reactions failed to indicate any significant amounts of metallic components. The reactors were charged with deionized water or deuterium oxide (Cambridge Isotope Laboratories, 99.9%) that had been purged with nitrogen for at least 30 min and were flushed with nitrogen prior to sealing.

High-purity reagents purchased from Aldrich were assessed by NMR and used as received. The water solubilities of all reagents were ascertained up to 100 °C and at ambient pressure by visual observation of the homogeneity of the aqueous solutions. Concentrations were equal to or exceeded those employed in the experimental runs. Thus, reaction mixtures, typically 0.3–0.5 M in organics at room temperature, were assured to be homogeneous at reaction temperatures. The total volume of water and organics was calculated to almost completely fill the reactor with liquid at reaction temperature.[26]

The reactor temperatures, monitored by an externally mounted thermocouple in direct contact with the reactor wall, equilibrated (±2 °C) within approximately 5 min in the sand bath. Reactions were quenched in a cold water bath immediately following removal from the sand bath. Conversions and product identities were determined primarily by NMR spectroscopy at ambient temperature using a Bruker AM 360.

Reaction of 2,5-Dimethylfuran. The following is a representative example of the procedures used. Deviations from this procedure, such as particular reaction temperatures, times, and concentration, are noted in the text. 2,5-Dimethylfuran (0.17 mL, 1.60 mmol) and deuterium oxide (3.00 mL) were measured by syringe into the reactor. The reactor was sealed under N_2 and immersed in the sand bath at 250 °C. Temperature equilibration of the reactor was monitored at 1-min intervals until temperature fluctuations stabilized at 251–253 °C. The reaction was terminated after 30 min by a cold water quench. Following transfer of the clear, slightly yellow, homogeneous product solution to a centrifuge tube, the reactor was rinsed with ca. 0.75 mL of chloroform-*d*. The wash was used, in two aliquots, to extract the aqueous product solution. The separated phases were analyzed by ^{1}H and ^{13}C NMR. ^{1}H NMR ($CDCl_3$; referenced to solvent at 7.2 ppm): δ 2.13 (methyl); (D_2O; referenced to solvent at 4.6 ppm): δ 2.00 (multiplet, methyl), 2.57 (broad, methylene). ^{13}C NMR ($CDCl_3$, referenced to solvent at 77.0 ppm): δ 29.40 (multiplet, methyl), δ 36.22 (multiplet, methylene), δ 182.20 (carbonyl).

Preparation of Benzaldehyde and Tolualdehyde Diethyl Acetals. These acetals were prepared according to the method of Fife.[27] Benzaldehyde (0.20 mol, 20.33 mL) was placed in a 250-mL round-bottomed flask equipped with a magnetic stir bar and drying tube. Following addition of absolute ethanol (0.20 mol, 12 mL) and triethyl orthoformate (0.21 mol, 35 mL), a few drops of concentrated HCl were introduced. The reaction was continuously stirred at room temperature and was termined after 23 h by addition of anhydrous potassium carbonate. The yellow solution was decanted, and volatiles were removed by rotoevaporation (70 °C, 50 mm). Tolualdehyde diethyl acetal was prepared using identical molar amounts of reagents.

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