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Thermolysis of Unsaturated Dicarboxylic Acids in Sulfuric Acid and Oleum. A Comparison with the CIMS Fragmentation Patterns

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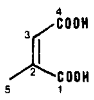
Citraconic (1), mesaconic (2), and itaconic (3) acids have been protonated in sulfuric acid containing variable amounts of water or sulfur trioxide. A series of cationic species have been detected by ^{1}H and ^{13}C NMR, showing the different basicity of the two carbonyl groups and the influence of the acidity, stereochemistry, and substitution pattern on the degree of stability of the C–C double bond toward cis–trans isomerization and/or dehydration to the corresponding protonated anhydrides $4H^+$ or $8H^+$. Thermolysis gives rise to reversible C-protonation that results in the interconversion between the protonated acids, via the common intermediate $9H^+$, to afford the protonated lactone $11H^+$. Further heating in solutions containing free sulfur trioxide results in mono- or disulfonation to $13H^+$ and $14H^+$. These transformations are correlated with the previously reported fragmentation patterns for the title diacids in CIMS.

The study of protonated organic molecules has been undertaken in the past from two independent standpoints: approaches using NMR techniques for cations in condensed phase (superacid media and low temperatures)[1] or MS for studies of the analogous species in the gas phase (chemical ionization with different reactant gases).[2] The results obtained by using these alternative methodologies have been compared in very few instances,[2b,3] in spite of the fruitful correlations found between EI–mass spectral fragmentation and the reactivity of neutral molecules.[4]

We have recently reported on the thermochemistry and photochemistry[3,5] of protonated unsaturated carboxylic acids and found some analogies with their CIMS spectra. Now, we extend these studies to citraconic (1), mesaconic (2), and itaconic (3) acids, whose CIMS spectra have been previously described.[6]



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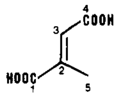

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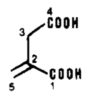

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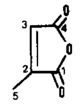

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In a first stage, we attempted to correlate the results obtained by Sakai[7] in his studies on the isomerization and thermal rearrangement of 1, 2, and 3 in aqueous acidic solutions with the known CIMS data. However, the experimental procedure used[7] does not allow such a comparison, since the products were isolated after azeotropic distillation and subsequent acid-catalyzed esterification with methanol, a treatment that does not preclude cis–trans isomerization, dehydration to the anhydrides, nucleophilic ring opening of the latter compounds, or other undesired byprocesses. Furthermore, an unambiguous spectroscopic characterization of the intermediate O- and/or C-protonated species appeared essential to understand the course of the thermal processes and to assess the structures of the ions in the proposed CIMS fragmentation pattern.[6,8]

For the above reasons, we decided to perform the systematic protonation of the unsaturated diacids 1, 2, and 3 at different sulfuric acid concentrations and temperatures.

Protonation of Citraconic (1), Mesaconic (2), and Itaconic (3) Acids. Citraconic acid (1) was dissolved in sulfuric acid of different concentrations and the ^{1}H and ^{13}C NMR spectra recorded at 40 °C (temperature probe). The spectral parameters are given in Table I. The protonation in 96% sulfuric acid gave a single set of five signals in the carbon spectrum that could be attributable at first to the O-protonated acid $1H^+$ or to the O-protonated anhydride $4H^+$. Carbon protonation was easily ruled out in view of the presence of one sp^3- and two sp^2-hybridized carbons with the expected multiplicity in the coupled spectrum. It is to be noted that both maleic acid (5) and maleic anhydride (6) under similar conditions[5] gave a 9:1 mixture of the protonated acid $5H^+$ and the protonated anhydride $6H^+$. A comparison of the $\delta(^{13}C)$ values for the carbonyl carbons obtained upon protonation of 1 (170.0 and 169.5 ppm) and those of $5H^+$ (175.8 ppm) and $6H^+$ (168.8 ppm) suggests for the former the structure $4H^+$. Then, the following experiments were performed to ascertain this assignment: (a) citraconic acid (1) was dissolved in 50% aqueous sulfuric acid and the carbon spectrum recorded giving rise to two separate sets of signals; the major component in the mixture was $4H^+$ and the minor one was $1H^+$ (ca. 7:1 molar ratio by ^{1}H NMR integration), that was now present due to the increased amount of water in the reaction medium; (b) a similar experiment using 40% aqueous sulfuric acid showed the formation of a 4:5 mixture of the same products, but now the major component was $1H^+$; (c) upon protonation of 1 with oleum the protonated anhyride $4H^+$ was observed as the only product. Of course, the protonated species must be considered to be in equilibrium with their neutral counterparts. In this context, the total δ value ($\sum\delta$) was found to increase with the acidity of the medium, as measured by the acidity function H_0[1a] as a result of the progressive degree of protonation being complete in neat oleum.

A further concern is the ambident nature of compounds 1 and 4 due to the slightly different basicity of the two

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[1] (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; John Wiley & Sons: New York, 1985. (b) Vogel, P. *Carbocation Chemistry*; Elsevier: Amsterdam, 1985.

[2] (a) Harrison, A. G. *Chemical Ionization Mass Spectrometry*; CRC Press: Boca Raton, FL, 1983. (b) Kingston, E. E.; Shannon, J. S.; Lacey, M. *J. Org. Mass Spectrom.* **1983**, *18*, 183. (c) Bowers, M. T., Ed. *Gas Phase Ion Chemistry*; Academic Press: London, 1979–1984; Vol. 1–3.

[3] Amat, A. M.; Asensio, G.; Castelló, M. J.; Miranda, M. A.; Simón-Fuentes, A. *J. Org. Chem.* **1987**, *52*, 4790.

[4] Dougherty, R. C. *Top. Curr. Chem.* **1974**, *45*, 93.

[5] Amat, A. M.; Asensio, G.; Castelló, M. J.; Miranda, M. A.; Simón-Fuentes, A. *Tetrahedron* **1987**, *43*, 905.

[6] Harrison, A. G.; Kallury, R. K. M. R. *Org. Mass Spectrom.* **1980**, *15*, 277.

[7] Sakai, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 219.

[8] Dallinga, J. W.; Nibbering, N. M. M.; van der Greef, J.; Ten Noeverde Brauw, M. C. *Org. Mass Spectrom.* **1984**, *19*, 10.

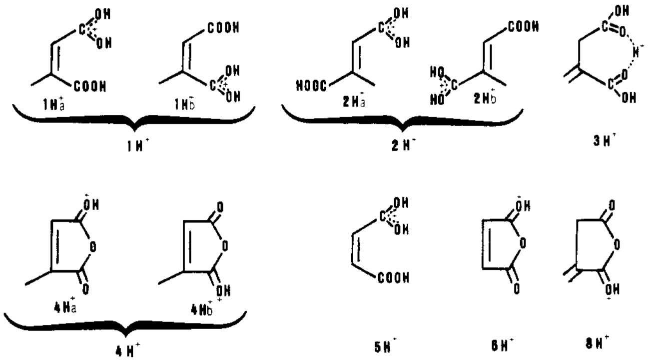
0022-3263/88/1953-5480$01.50/0

Table I. ^{1}H and ^{13}C NMR Spectral Data for the Cationic Species and Precursors[a]

entry	compd	neutral precursor	medium	acidity (H_0)[b]	$\delta_{^1H}$ for indicated H[c] 2	3	4	5	$\delta_{^{13}C}$ for indicated C[d] 1	2	3	4	5	$\sum\delta$
1	1		DMSO-d_6			5.80		2.05	170.5	147.1	121.1	167.3	20.9	626.9
2	1H$^+$	1	40% H_2SO_4	−2.3		6.20		2.20	174.2	147.8	122.9	170.2	21.0	636.1
3	1H$^+$	1	50% H_2SO_4	−3.4		6.20		2.20	174.4	148.2	123.9	170.0	21.2	637.7
4	2		DMSO-d_6			6.70		2.20	169.3	143.9	127.9	168.1	14.9	624.1
5	2H$^+$	2	96% H_2SO_4	−12.0		7.00		2.40	172.5	154.3	124.1	178.8	16.2	645.9
6	3		DMSO-d_6			3.25		5.70 6.10	169.0	136.6	38.8	173.7	129.0	647.1
7	3H$^+$	3	96% H_2SO_4	−12.0		3.85		6.40 6.80	177.0	127.0	37.0	186.4	143.0	670.4
8	4		$CDCl_3$			6.70		2.25	167.4	150.2	130.2	165.3	11.3	624.4
9	4H$^+$	1	40% H_2SO_4	−2.3		6.80		2.10	169.0	151.4	131.0	167.3	11.6	630.3
10	4H$^+$	1	50% H_2SO_4	−3.4		6.80		2.10	168.9	151.5	131.0	167.5	11.6	630.5
11	4H$^+$	1	96% H_2SO_4	−12.0		6.80		2.10	169.5	152.9	131.2	170.0	11.5	635.1
12	4H$^+$	1	H_2SO_4/22% SO_3	−13.6		6.90		2.20	169.1	153.8	131.1	171.1	11.7	636.8
13, 14	4H$^+$	1 or 2	H_2SO_4/35% SO_3	−14.1		6.90		2.20	168.3	154.7	131.1	173.2	11.9	639.2
15	4H$^+$	1	H_2SO_4/46% SO_3	−14.4		6.90		2.20	167.3	156.0	131.1	175.4	12.4	642.2
16, 17	4H$^+$	1 or 2	H_2SO_4/70% SO_3	−14.9		6.95		2.25	166.0	157.3	131.1	177.7	12.8	644.9
18	8H$^+$	3	H_2SO_4/35% SO_3	−14.1		3.90		6.30 6.75	174.5	127.4	33.7	172.8	136.8	645.2
19–21	11H$^+$	1, 2, or 3	96% H_2SO_4	−12.0	3.30	3.90	5.00		191.5[e]	33.7	39.8	78.3	178.6[e]	521.9
22–24	13H$^+$	1, 2, or 3	H_2SO_4/35% SO_3	−14.1		7.30		4.50	166.6[e]	140.2	137.3	166.4[e]	47.6	658.1
25–27	14H$^+$	1, 2, or 3	H_2SO_4/35% SO_3	−14.1				5.00	162.0[e]	141.6[f]	140.3[f]	159.3[e]	47.2	650.4

[a] For ^{1}H NMR literature data of **1**, **2**, **3**, and **4**, see ref 9a. For ^{13}C NMR literature data, see ref 9b for **1**, **2**, and **4** and ref 9c for **3**. [b] See ref 1a. [c] ppm ± 0.05 downfield from TMS. [d] ppm ± 0.1 downfield from TMS. [e] Assignment interchangeable. [f] Assignment interchangeable.

carbonyl oxygen atoms that should give rise to the formation of two O-protonated species in each case: $1Ha^+$ and $1Hb^+$ or $4Ha^+$ and $4Hb^+$, respectively. A first inspection of the proton-decoupled ^{13}C NMR spectra did not allow for assignment of the carbonyl carbons since in the case of $4H^+$ a possible point of crossing in the δ values was observed near an H_0 value of −11 (Figure 1). Fortunately, the coupled carbon spectra (gated decoupled experiment) exhibited a clear coupling between C_1 and the methyl protons, thus allowing an unequivocal assignment. Then, a different behavior toward protonation was observed for the two carbonyl groups. Under highly acidic conditions (H_0 = −14.9) the C_4 carbonyl group of the anhydride **4** is the almost exclusive site of protonation found as indicated by the increase of the δ value relative to that in the neutral molecule[9] ($\Delta\delta$ = 12.4 ppm) while the C_1 chemical shift value remains essentially unchanged. This behavior is to be expected due to the stabilization by the methyl group of the positive charge partially localized by conjugation on C_2. As a consequence this carbon also becomes considerably deshielded. It is interesting to note that in more dilute acid the selectivity of the protonation is less pronounced as reflected by the $\Delta\delta$ value, although the C_4 carbonyl oxygen is still the preferred site.



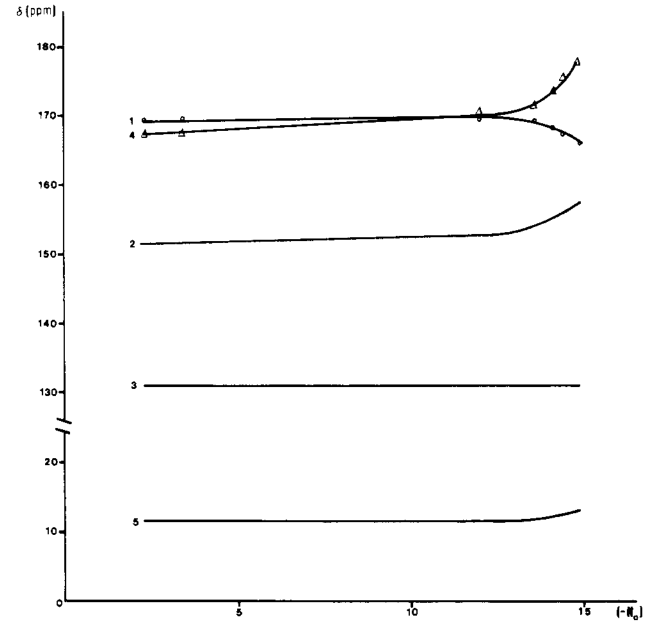


Figure 1.

In the case of citraconic acid (**1**) the spectral data for the fully protonated species $1H^+$ were not available, due to the quantitative dehydration under high acidic conditions. However, in aqueous sulfuric acid the protonation appears to be even less selective according to the observed similar increase of the δ values of C_1 and C_4 relative to those of the neutral precursor[19] (see Table I). Furthermore the C_1 carbonyl oxygen is now somewhat more protonated than C_4, a fact that is also supported by the deshielding of C_3.

Mesaconic acid (**2**) was dissolved in concentrated sulfuric acid to afford the protonated acid $2H^+$. The total $\Delta\sum\delta$ (21.8 ppm) reveals a nearly complete protonation of **2** under these conditions and the simultaneous deshielding observed for C_2 and C_4 indicates that $2Ha^+$ is the predominating species in the equilibrium. In mixtures of concentrated sulfuric acid and oleum as well as in neat oleum the quantitative transformation of $2Ha^+$ into pro-

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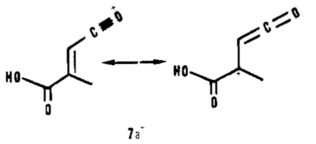
[9] (a) Pourchet, C. J.; Campbell, J. R. *The Aldrich Library of NMR Spectra*; Aldrich Chemical Company, 1974; Vol. 1,2. (b) Braun, S. *Org. Magn. Reson.* **1978**, *11*, 197. (c) Bremser, W.; Franke, B.; Wagner, H. *Chemical Shift Ranges in Carbon-13 NMR Spectroscopy*; Verlag Chemie: Weinheim, 1982.

Table II. Thermal Transformations of Compounds 1, 2, and 3 in Acidic Media

				products (yield, %)[a]						
compd	medium	temp, °C	time, h	$2H^+$	$3H^+$	$4H^+$	$11H^+$	$13H^+$	$14H^+$	$CH_3C\overset{+}{O}_2H_2$
1	96% H_2SO_4	140	8			92	trace[b]			
			14			72	21			7
			100			20	trace[b]			77
1	35% SO_3	140	2			100				
			33			9		67	24	
			123					58	42	
1	70% SO_3	140	2			76			24	
			10			29			71	
			33						100	
2	96% H_2SO_4	100	2	97		trace[b]				
			8	82		16				
			16	68		25	trace[b]			trace[b]
		140	35	15		47	27			11
			70			36	10			54
2	35% SO_3	100	3	5		95				
			6			100				
		140	21			36		51	13	
			36			5		59	36	
			47					64	36	
2	70% SO_3		1			74			26	
			7			37			63	
3	96% H_2SO_4	100	2	trace[b]	77	trace[b]	15			
			13	5	30	trace[b]	63			
			27	7	12	7	74			
		140	2	9	9	11	71			
			6	18	6	26	50			
			24	25	trace[b]	40	22			10

[a] Measured by ^{1}H NMR. [b] <5%.

tonated citraconic anhydride $4Ha^+$ was observed to take place. The intermediate for this very fast trans–cis isomerization and subsequent dehydration must be the acylium ion $7a^+$, whose C_2–C_3 single-bonded ketene-like structures would be even more stable than in the case of fumaric acid,[5] due to the presence of the methyl group on C_2.



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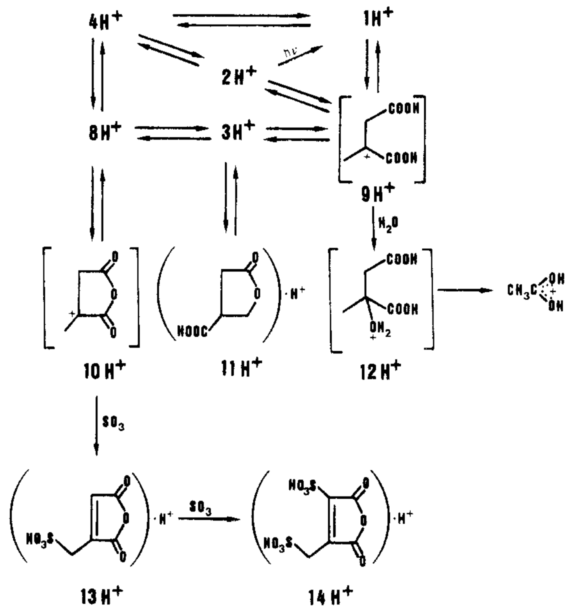
Itaconic acid (**3**) was protonated by treatment with concentrated sulfuric acid to afford $3H^+$. The total chemical shift increase in the carbon spectrum ($\Delta\sum\delta$ = 23.3 ppm) indicates the nearly complete protonation. On the other hand, the fact that both carbonyl groups become deshielded to a comparable degree, in spite of their different chemical nature, suggests that the proton could be shared by them in a cyclic arrangement.

The solution of $3H^+$ was stable at the NMR probe temperature and remained unaltered after storage for long periods of time at 0 °C, showing the lack of reversible C-protonation that would result in isomerization to $2H^+$ and/or $4H^+$. When the protonation was performed with a 1:1 mixture of concentrated sulfuric acid and oleum, although no significant changes were observed in the ^{1}H NMR, a very different carbon spectrum was obtained, indicating the transformation of **3** into the protonated anhydride $8H^+$. The preferential protonation site found was the C_1 carbonyl oxygen obviously due to the stabilization by resonance with the double bond. This assignment was easily done on the basis of the parallel deshielding of the C_1 and C_5 carbons.

Scheme I



Thermal and Photochemical Transformations of Ions $1H^+$, $2H^+$, $3H^+$, $4H^+$, and $8H^+$. Upon heating in 96% sulfuric acid solution, acids **1**, **2**, and **3** underwent a series of transformations leading to the formation of the protonated lactone $11H^+$ (Scheme I, Table II). In this medium citraconic acid exists as the protonated anhydride $4H^+$ and therefore the formation of $11H^+$ must involve ring opening of the former, promoted by the little water present in the medium, to give $1H^+$. Under these conditions reversible proton transfer from oxygen to carbon would give rise to protonated itaconic acid ($3H^+$) via the short-lived C-protonated intermediate $9H^+$. The lactonization reaction would be explained from $3H^+$ through a simple intramolecular conjugate addition to the terminal olefin. Because of the high activation energy associated with C-protonation, the overall process requires heating at 140 °C for several hours to reach a moderate degree of transformation (see Table II). This is consistent with the observed quantitative transformation of protonated itaconic acid ($3H^+$) into $11H^+$ upon heating at only 100 °C during shorter periods of time. The occurrence of this comparatively faster transformation also explains why protonated itaconic acid ($3H^+$) is not even detected during the conversion of $4H^+$ into the lactone $11H^+$.

In good agreement with the above observations, when mesaconic acid (**2**) was dissolved in 96% sulfuric acid and the solution heated at 100 °C the formation of protonated citraconic anhydride ($4H^+$) took place. However, heating at 140 °C afforded the protonated lactone $11H^+$ as expected.

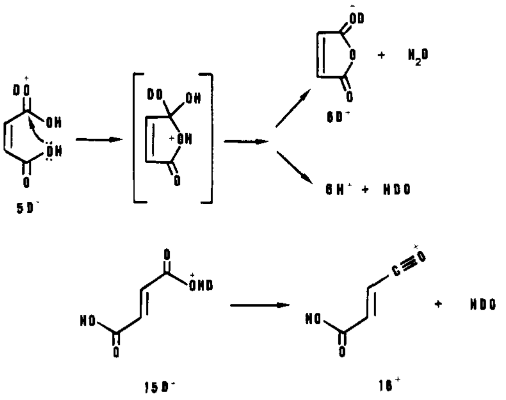
Whatever the origin of the species $11H^+$, its heating in concentrated sulfuric acid resulted in the appearance of increasing amounts of protonated acetic acid, whose formation can be rationalized by equilibration between the species $11H^+$ and $3H^+$, trapping of the intermediate C-protonated ion $9H^+$ by water and subsequent retro-aldol type reaction of the protonated hydroxy acid $12H^+$.

When protonated citraconic anhydride ($4H^+$) was heated at 140 °C in sulfuric acid containing 50% oleum, a quantitative transformation into the protonated sulfonated anhydrides $13H^+$ and $14H^+$ was observed. Under these conditions there is no water available in the medium to effect the anhydride ring opening and so sulfonation of the intermediate olefin $8H^+$, resulting from the deprotonation of $10H^+$, takes place. In the same medium, protonated itaconic anhydride ($8H^+$), directly generated from itaconic acid (**3**), underwent the transformation into $13H^+$ at room temperature, indicating again that the rate-determining step in the conversion of $4H^+$ into $13H^+$ is the C-protonation to $10H^+$. Further sulfonation of $13H^+$ to afford $14H^+$ was promoted by prolonged heating or using neat oleum as reaction medium (data not given).

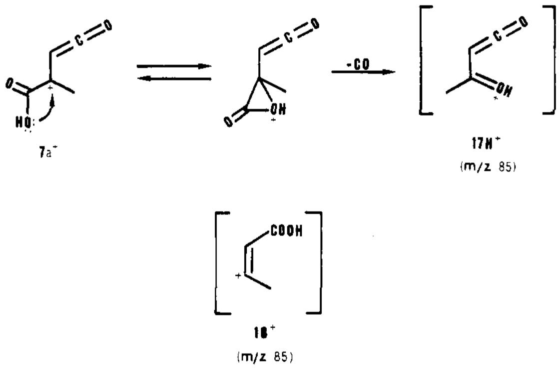
All the above cations were submitted to ultraviolet irradiation and found to be stable, except in the case of protonated mesaconic acid ($2H^+$). This compound dissolved in concentrated sulfuric acid was clean and quantitatively converted at room temperature into the anhydride $4H^+$. Under similar conditions experiments carried out in the dark showed no appreciable degree of trans–cis isomerization.

Results in Sulfuric Acid versus CIMS Data. As predicted by proton affinity–ionization energy correlations, the carbonyl oxygen is the thermodynamically favored site of protonation of carboxylic acids.[10] In fact, this was found indeed to be the case for protonations in solution at room temperature. The most common primary transformation of the ions $1H^+$, $2H^+$, and $3H^+$ in the gas phase is the loss of water either in CIMS,[6] fast atom bombardment (FAB) or field ionization (FI) mass spectrometry.[8] A close parallelism for this behavior is found in solution chemistry, where the protonated cis diacids $1H^+$ and, to a lesser extent, $5H^+$ were found[5] to undergo dehydration even in aqueous sulfuric acid. On the other hand, the trans isomer $2H^+$, protonated fumaric acid ($15H^+$),[5] and also the C_2–C_3 single-bonded $3H^+$ ion underwent dehydration at room temperature in sulfuric acid containing substantial amounts of free sulfur trioxide. The structure of the [$MH^+ - H_2O$] ions in MS is not well defined although it has been settled that they result from fragmentation of the protonated acids and not from protonation of the anhydride produced thermally in the ion source.[6] The CIMS data reported by Harrison[6] in the light of the results here presented allow us to propose different structures for the [$MH^+ - H_2O$] ions, depending on the cis or trans nature of the corresponding neutral precursor. Thus, dehydration of the protonated cis diacids would result in *direct* cyclization to the protonated anhydrides, while the protonated trans diacids *first* would give rise to the acylium ions and *then* to the protonated anhydrides. These different dehydration pathways do explain the isotopic effects found in the CD_4 CI mass spectra of maleic (**5**) and fumaric (**15**) acids,[6] where the ratio [$MD^+ - H_2O$]/[$MD^+ - HDO$] was found to be dramatically different, being lower in the case of **15** (see Scheme II). The existence of two isobaric ions whose structure depends on the stereochemistry of the parent diacid also justifies the different ability of these species to undergo further fragmentation. So, while the loss of carbon monoxide occurs in the series of the trans diacids to a high extent, it hardly takes place from the dehydrated cis isomers. We propose that the [$MH^+ - H_2O - CO$] ions arise from the acylium ions and have the structure $17H^+$, rather than the destabilized vinyl cation 18^+ proposed elsewhere[8] (Scheme III). The reluctance of protonated cis diacids to undergo subsequent loss of water and carbon monoxide is easily rationalized, since the second process requires a previous ring opening of the anhydride.

Scheme II



Scheme III



In summary, this study confirms the possibility of establishing fruitful correlations between CIMS and thermolysis in highly acidic solutions especially concerning the structural assessment of the fragmenting ions in the former and the use of fragmentation routes to predict the chemistry of the parent compounds under acidic conditions.

Experimental Section

Proton spectra were recorded at 60 MHz with a Hitachi Perkin-Elmer Model R-24 B NMR spectrometer. ^{13}C NMR spectra were recorded with a Bruker WP 80 SY NMR spectrometer using dioxane as external standard (capilar). ^1H and ^{13}C NMR chemical shifts (δ) are reported in ppm relative to TMS.

Neutral substrates used were commercial materials. Ions were prepared by slow addition, with efficient stirring, of the cooled substrate onto the mineral acid in an ice–water bath to give ca. 1 M solutions.

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(10) Benoit, F. M.; Harrison, A. G. *J. Am. Chem. Soc.* **1977**, *99*, 3980.

Ion solutions were heated in tightly closed NMR sample tubes by using a thermostated bath at the temperatures indicated in the text.

Irradiations were carried out by placing the ion solutions into quartz tubes surrounding a centrally positioned quartz cooling jacket (external diameter 55 mm) containing a 125-W medium pressure mercury lamp. The temperature was kept below 30 °C by means of a water bath.

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Registry No. **1**, 498-23-7; **1H**$^+$, 116664-83-6; **2**, 498-24-8; **3**, 97-65-4; **3H**$^+$, 116664-77-8; **4**, 616-02-4; **4H**$^+$, 116664-78-9; **8H**$^+$, 116664-79-0; **9H**$^+$, 116664-84-7; **11H**$^+$, 116664-80-3; **13H**$^+$, 116664-81-4; **14H**$^+$, 116664-82-5; CH$_3$CO$_2$H$_2^+$, 18639-92-4.

Intraannular Functionalization of Macrocyclic Polyethers via Organolithium Intermediates

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1,3-Xylyl crown ethers substituted at the 2-position with an acidic (COOH, OH, SO$_2$H) or reactive (CHO) functional group can be synthesized from a common starting material by a generally applicable method that does not require the protection of these groups. 2-Bromo-1,3-xylyl crown ethers **1** react at −78 °C with *n*-butyllithium to yield the corresponding 2-lithio-1,3-xylyl crown ethers **2** without extensive cleavage of the polyether ring. Subsequent reaction with electrophilic reagents (dimethyl disulfide, *N,N*-dimethylformamide, CO$_2$, or SO$_2$) yielded the corresponding macrocycles **3–6**. Reaction of **2** with trimethyl borate, followed by hydrolysis and oxidation by hydrogen peroxide, provides an excellent alternative for the published synthesis of 2-hydroxy-1,3-xylyl crown ethers **8**. The single-crystal X-ray structures of 2-bromo-1,3-xylyl-18-crown-5 (**1b**) and 2-sulfino-1,3-xylyl-18-crown-5 (**6b**) reveal a restricted flexibility of the macroring in these 18-membered macrocycles. In **6b**, the macrocyclic cavity is filled by the SOH group, which is engaged in a bifurcated hydrogen bond with two ether oxygen atoms.

Introduction

Complexes of neutral molecules with macrocyclic receptors are thermodynamically much less stable than are complexes of crown ethers with charged guests.[1,2] One way to increase the complex stability would be the in situ conversion of a neutral guest into a (partially) charged species. This would provide additional electrostatic interactions in the complex between host and guest, as we have shown for the complexation of urea.[3] We have recently demonstrated that 1,3-xylyl crown ethers with an intraannular proton-donating group and a cavity large enough to encapsulate the guest molecule provide good ligands for the complexation of neutral guests such as urea or water via strong hydrogen bonds.[4] In an extension of this approach we were interested in developing a general and convergent synthetic procedure for the functionalization of crown ethers with different intraannular acidic substituents.

Various syntheses of crown ethers with intraannular acidic carboxyl or hydroxyl groups have been described previously. However, they all require the protection of the acidic substituent during the Williamson cyclization, which takes place under strongly basic conditions, and involve multistep processes with low overall yields. Various 2-carboxy-1,3-xylyl-3*n*-crown-(*n* − 1) ethers (*n* = 5–7 and 10) were obtained previously by Cram[5] starting from 2-(methoxycarbonyl)-1,3-bis(bromomethyl)benzene and this method was extended in our group for the preparation of larger macrocycles.[4]

The syntheses of 2-hydroxy-1,3-xylyl crown ethers have been also previously reported.[6] The major problem was finding a suitable protecting group for the hydroxyl function that would be stable under the strongly basic conditions of the Williamson macrocyclization and could be selectively removed under conditions that did not cleave the benzylic ether bonds. In the synthesis of 2-hydroxy-1,3-xylyl crown ethers, methoxymethyl,[6a] allyl,[6b] and methyl[6c] groups were reported for protection of hydroxyl function. The use of methoxymethyl and allyl groups was described for the synthesis of 2-hydroxy-1,3-xylyl crown ethers in which the 5-position was blocked by a methyl or a chloro substituent, respectively.[6a,b] Since substituents at the 5-position show a considerable effect on the complexation properties of the macrocycle and on the proton-donating ability of the OH group, 2-hydroxy-1,3-xylyl crown ethers with an unsubstituted 5-position are much more attractive, because they provide the possibility for

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(1) de Boer, J. A. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc.* **1982**, *104*, 4073.

(2) van Staveren, C. J.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5271.

(3) (a) Harkema, S.; van Hummel, G. J.; Daasvatn, K.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1981**, 368. (b) Aarts, V. M. L. J.; Geevers, J.; Reinhoudt, D. N.; Lengton, W.; Bos, M.; Uiterwijk, J. W. H. M.; Harkema, S. *Tetrahedron* **1987**, *43*, 617. (c) Uiterwijk, J. W. H. M.; Harkema, S.; Reinhoudt, D. N.; Daasvatn, K.; Den Hertog, H. J., Jr.; Geevers, J. *Angew. Chem.* **1982**, *94*, 462; *Angew. Chem. Suppl.* **1982**, 1100.

(4) Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuis, P. D. J.; van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035.

(5) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405.

(6) (a) Koenig, K. E.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 4018. Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553. (b) van der Leij, M.; Oosterink, H. J.; Hall, R. H.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3661. (c) Browne, C. M.; Ferguson, G.; McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703.

0022-3263/88/1953-5484$01.50/0