Site Specific Gas-phase Protonation of 2-t-Butylmaleates and 2-t-Butylsuccinates upon Chemical Ionization: Stereochemical Effects and Kinetic Control

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An intense effect of steric hindrance on gas-phase protonation under chemical ionization (CI) conditions, reflected by a very high site specificity in chemical ionization mass spectrometry (CIMS) of isomeric ethyl methyl esters of 2-t-butylmaleic and 2-t-butylsuccinic acids, provides new direct evidence of kinetic control in the protonation process.

The question of whether gas-phase protonation under chemical ionization (CI) conditions is under kinetic or thermodynamic control has recently been referred to by several research groups.[1—3] The most direct method by which this problem has been dealt with is based on CI protonation of ambident substrates where there is a difference in the proton affinities (PA) of the competing sites, followed by attempted determination of the actual site of protonation with the aid of collisionally induced dissociation (CID) mass spectrometry. Preferable protonation at sites of lower PA is considered as evidence of kinetic control in the protonation process. Under thermodynamic control protonation will be preferred at the higher PA site.

Here we suggest an alternative way to attack this problem. CIMS behaviour of ambident substrates, where similar functional groups (having therefore similar proton affinities) differ only in their steric environment, may be indicative in this respect. A stereochemical effect in CIMS of such appropriately designed systems, reflected by high protonation site-specificity, will indicate kinetic control in the gas-phase protonation reaction.

NH_3-CI, isobutane-CI, and CH_4-CI mass spectra have been measured for the isomeric ethyl methyl 2-t-butylmaleates (**1**) and 2-t-butylsuccinates (**2**). The relative abundance of $[MH - MeOH]^+$ and $[MH - EtOH]^+$ ions listed in Table 1 show preferred loss of the alcohol molecule originating from the sterically hindered ester group adjacent to the bulky t-butyl substituent at position 2. This preference is extremely high under NH_3-CI and isobutane-CI conditions, lower upon CH_4-CI.

It has previously been shown that the CI- and CID-induced elimination of an alcohol molecule from the protonated molecular ions of maleates (and analogues) involves the hydrogen atom from the protonated ester group and the alkoxy from the non-protonated one, *via* a cyclic transition state (see Scheme 1).[4,5]

The predominant elimination of an alcohol originating from the sterically hindered ester group in (**1**) and (**2**) (both isomers in each system) suggests that initial protonation occurs under NH_3-CI and isobutane-CI almost exclusively (to a great extent also under CH_4-CI) at the carbonylic oxygen of the non-hindered ester group, and that proton is transferred to the adjacent alkoxy of the sterically hindered ester group followed by elimination of the alcohol molecule (ROH). This series of events is shown for (**1**) in Scheme 2.

The above results suggest that gas-phase protonation occurs in diesters (**1**) and (**2**) with a very high site-specificity under NH_3-CI and isobutane-CI conditions (somewhat lower under CH_4-CI), the non-hindered ester group being the preferred site of protonation. Since the two ester groups have similar proton affinities [possible difference due to size of the methyl and ethyl groups is levelled off by comparison of the isomers, (**1a**) with (**1b**) and (**2a**) with (**2b**)], the site-specificity is induced by the stereochemical difference between the two competing sites. Thus these results provide clear and direct evidence of kinetic control over the protonation reaction of (**1**) and (**2**). A thermodynamic control should lead to two MH^+ ions in each isomer and consequently to a comparable extent of elimination of the two alcohols.

To the best of our knowledge this is the first report of a stereochemical effect on the competition for proton between similar sites in an ambident molecule in the proton attachment step in CIMS. There have been reports of the effect of steric

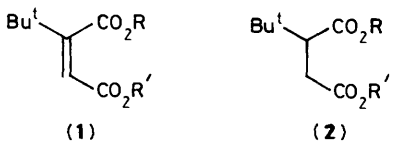
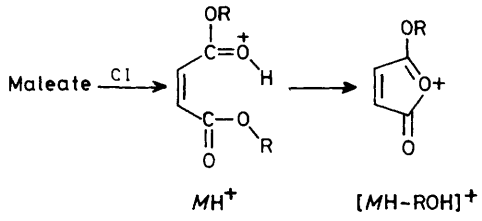
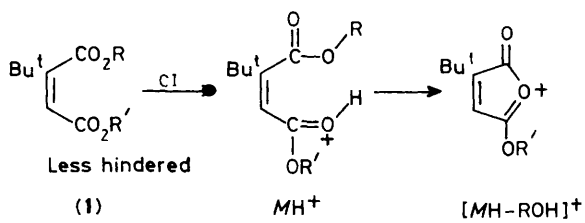


Table 1. Partial CIMS data for isomers (**1**) and (**2**).

	Isobutane-CI		NH_3-CI		CH_4-CI	
	$[MH - MeOH]^+$	$[MH - EtOH]^+$	$[MH - MeOH]^+$	$[MH - EtOH]^+$	$[MH - MeOH]^+$	$[MH - EtOH]^+$
(**1a**)	100	9	100	5	100	35
(**1b**)	5	100	<1	100	15	100
(**2a**)	100	6	49	<1	100	22
(**2b**)	3	100	4	43	14	100



Scheme 1



Scheme 2

hindrance on the rates of proton or other cation attachment rates measured by ion cyclotron resonance in monofunctional compounds.[6—8]

We thank the Lady Davis Foundation for a postdoctoral fellowship to A. W. This work was supported by the Fund for Promotion of Research at the Technion.

Received, 29th July 1988; Com. 8/03114B

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