A Gas-Phase Study of the Ionic Alkylation of Benzocycloalkenes

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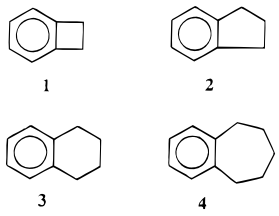
Since the early finding by Mills and Nixon of enhanced positional selectivities in the bromination of indan and tetralin derivatives,[1] the properties of benzocycloalkenes have been the subject of considerable interest. A small fused carbocyclic ring was found to direct the electrophilic substitution of the benzene nucleus to the β-position.[1,2] The effect (MN effect) was ascribed to partial π-electron localization resulting from the fusion of an angular strained ring.[3] Accordingly, the bond common to both rings was proposed to have a reinforced single-bond character. This concept has stimulated extensive experimental[4] and theoretical[5] investigations. Their conclusions were found either to support the manifestation of the MN effect[6] or to cast doubts on its existence.[7] The major focus of recent research has addressed the design and the structural elucidation of molecular frameworks where a mono-, bis-, or tris-annelated benzene nucleus was expected to display aromatic bond alternation.[8] Thus, in recent investigations the issue of the effect of a small ring on the structural features of a fused aromatic ring has superseded the original interest on the reactivity of the benzene nucleus. We turn to this latter point with the present report, although using a quite different approach.

It may be noted that the operation of the MN effect has been discussed in relation to either positional selectivities in electrophilic aromatic substitution reactions in solution or structural analysis in a crystal packing. In both cases there may be a major role played by the environment in affecting intrinsic molecular properties. In a series of studies we have obtained valuable insights into the reactivity of aromatic compounds toward ionic electrophiles by utilizing a radiolytic technique for the investigation of gaseous systems at atmospheric pressure.[9] In this environment, the lack of solvents, catalysts and counterions allows one to unveil the intrinsic features of the reaction under scrutiny by experimental means relying on the characterization of the neutral end products. By this methodology the reactivity of a benchmark substrate for the MN effect, benzocyclobutene (**1**), was studied in relation to the higher homologues, **2**, **3**, and **4**, using simple aromatic compounds, such as *o*-xylene (**5**) and mesitylene (**6**), as reference substrates.[10]



Me_2Cl^+ and Me_3C^+ were chosen as model reagents, both ions being known to promote an electrophilic aromatic substitution reaction in the gas phase. Me_2Cl^+, from the radiation induced ionization of MeCl and subsequent ion−molecule reactions, behaves as a selective methylating agent where the displacement of MeCl by the aromatic π system involves significant activation energies.[11] Me_3C^+, from the ionization/fragmentation of isobutane, is a mild electrophile, reacting as a Lewis acid with aromatic compounds.[12] The positional selectivity for the electrophilic substitution by Me_3C^+ is known to be highly sensitive to steric effects, inhibiting, to a large extent, the attack at a ring carbon that is ortho to a methyl group. The yields of the substitution products from the selected substrates are summarized in Table 1, where α and β denote the site of the entered alkyl group (Me or Me_3C) on the aromatic ring with respect to the cyclic alkyl substituent in the substitution products. The formation of the alkylation products is ascribed to a stepwise reaction pattern

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(10) Gaseous samples of known composition were prepared in sealed 0.13-L Pyrex vessels according to a well-established procedure. Typical components were as follows: 600−650 Torr of a bulk gas (MeCl to form Me_2Cl^+, or isobutane as the precursor of Me_3C^+), 10 Torr O_2 (a radical scavenger), 0.5−2 Torr of the aromatic substrate(s). TEA (0.7−1.0 Torr) was added in all experiments run in isobutane and in several experiments run in MeCl. Irradiations were performed in a 220 Gammacell (Nuclear Canada Ltd.) at the dose rate of $\sim 5 \times 10^3$ Gy h^{-1} for 3 h in a thermostated device. The radiolytic products were extracted from the vessel utilizing ethyl acetate as the solvent by repeated freeze−thaw cycles and analyzed by GC−MS using a Hewlett-Packard 5890 series II gas chromatograph in line with a quadrupole mass spectrometer, HP 5989B. The capillary columns and gas-chromatographic conditions were the following: (i) a 50-m long, 0.20-mm i.d. fused silica capillary column, coated with a 0.5-μm cross-linked methylsilicone film (HP PONA column), operated isothermally at 60 °C for 5 min and then heated at the rate of 3 deg min^{-1} to 120 °C and subsequently at 16 deg min^{-1} to 240 °C.; (ii) a 60-m long, 0.20-mm i.d. bonded-phase capillary column, coated with a 0.2-μm poly(ethylene glycol) film (Supelcowax 10M from Supelco Co.), operated at 100 °C for 2 min and then heated at the rate of 5 deg min^{-1} to 250 °C. MeCl, *i*-C_4H_{10}, and O_2 were research grade gases from Matheson Gas Products Inc. with a stated purity in excess of 99.95 mol %. **1** was obtained from 2-(2′-bromophenyl)ethyl bromide according to (a) Brewer, P. D.; Tagat, J.; Hergrueter, C. A.; Helquist, P. *Tetrahedron Lett.* **1977**, *52*, 4573 and (b) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184. Other compounds used as additives, as substrates or as reference compounds for GC−MS analyses were obtained from commercial sources or prepared according to established methods.

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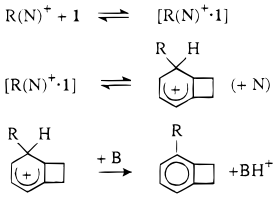
Table 1. Gas-Phase Reactions of Ionic Electrophiles with Benzocycloalkenes and Reference Aromatic Compounds

substrate	reagent ion	T (°C)	product distribution (%)[a] α	β	k_S/k_5[b]
1	Me_2Cl^+	25	26	74	–
1	Me_2Cl^+	80	26	74	0.17
1	Me_2Cl^+	120	25	75	0.17
2	Me_2Cl^+	25	56	44	–
2	Me_2Cl^+	80	55	45	0.85
2	Me_2Cl^+	120	57	43	0.82
3	Me_2Cl^+	25	60	40	–
3	Me_2Cl^+	80	63	37	1.7
3	Me_2Cl^+	120	63	37	1.6
4	Me_2Cl^+	25	67	32	–
4	Me_2Cl^+	80	62	38	3.2
4	Me_2Cl^+	120	61	39	2.8
5	Me_2Cl^+	25	56	44	1.0
5	Me_2Cl^+	80	57	43	1.0
5	Me_2Cl^+	120	58	42	1.0
6	Me_2Cl^+	80	–	–	9.3
6	Me_2Cl^+	120	–	–	7.2
1	Me_3C^+	120	35	65	0.56
2	Me_3C^+	120	4	96	0.84
3	Me_3C^+	120	0	100	1.3
4	Me_3C^+	120	0	100	1.5
5	Me_3C^+	120	0	100	1.0

[a] Reported values are the average of at least three experiments. Average error ±2%. [b] Values derived from competing reactions of S and **5** (*o*-xylene) for the gaseous electrophile. The standard equation $k_S/k_5 = ([P_S]/[P_5]) \times ([\mathbf{5}]/[S])$ was used, where P_S and P_5 are the overall alkylation products of S and **5**, respectively.

Scheme 1



(Scheme 1, showing the reaction sequence leading to the α alkylation product of **1**, R = Me, Me_3C, N = MeCl) that is well established from detailed mechanistic studies.[9]

The kinetic role of the individual steps in the overall sequence can be discussed as follows. The final step, namely the neutralization of the arenium ion by proton transfer to a base, if kinetically significant, should be affected by the presence and concentration of an added base. The fact that the addition of a strong base such as triethylamine (TEA, 0.3−0.8 Torr) does not affect either the isomeric product composition or the relative reactivities of the methylation reaction shows that this step is not rate-determining.[9] The alkylation of simple aromatics by Me_3C^+ ions is known to be reversible and affected by the presence of a base, so that all experiments have been performed in the presence of 0.7−1.0 Torr TEA, ensuring fast deprotonation of the charged intermediates. It may be concluded that, under the selected conditions, the rates of both alkylation reactions reflect the rate of the electrophilic attack. Indeed, if the collisional encounter of the reagents were the slow step of the reaction, nearly uniform intermolecular selectivities would be expected, being the collision rates nearly equal for the selected substrates.[13] The fact that at 120 °C the relative reactivity of **1** vs **4** spans a factor of 16 in the reaction with Me_2Cl^+ and a factor of 2.7 with Me_3C^+ speaks against a rate-determining collisional encounter. The relative reactivities are more widely spaced in the competition experiments run at 80 °C. The low volatility of the substrates at 25 °C prevented reliable and reproducible reactivity values to be obtained from the competition experiments performed. The markedly higher reactivity in the methylation by Me_2Cl^+ displayed by mesitylene, highly activated toward electrophiles, supports the view that the rate of the reaction is determined by the rate of the electrophilic attack. From the relative reactivity data there appears to be a regular increase in reactivity as the polymethylene chain is lengthened, the reactivity of *o*-xylene falling between those of **2** and **3**. A conformational advantage due to the favorable alignment of the C−H bonds at the side-chain α-carbons of **2** and **3** which are almost perpendicular to the aromatic π-system, thereby facilitating C−H hyperconjugation, has been suggested to account for the relative reactivities observed in solution (**2**, **3** > **5**).[2] Obviously, such an effect does not seem to play a major role in the gas phase where the relative reactivity appears to depend on the number of carbon atoms on the fused ring, providing increasing stabilization in the product ion as their number increases, probably by a combination of hyperconjugation, inductive and polarization effects.[14] The most relevant result, however, regards the intramolecular selectivity for the attack at the α and β positions of the aromatic ring. In the Me_2Cl^+ reaction, a MN orientation favoring the β position is in fact found only in the methylation of **1**. The other annelated benzenes, **2**−**4**, display an isomeric distribution of the substitution products (Table 1) that is barely different from that of *o*-xylene.

The present gas-phase data show that the MN hypothesis may be only justified for the first member of the investigated series (which, incidentally, was not an original MN substrate). Moreover, the absence of a noticeable temperature dependence of the observed α/β distributions suggests that the intramolecular selectivities observed arise from a difference in activation entropies rather than in activation energies, once again at variance with the original MN hypothesis. Also, the expectation that the relative rates for the formation of the methylated α- and β-arenium ions might reflect the relative stability of the α and β protonated species, as reported in a recent theoretical study, is not fulfilled.[6b] The α/β selectivity ratio from the Me_3C^+ reaction with **1** shows a very similar isomeric distribution as the methylation products. The agreement, however, is probably fortuitious. Indeed, the attack of the encumbered Me_3C^+ ion at the α position experiences an unfavorable steric relationship with the ortho methylene group. In its absence, the α position might have displayed a higher reactivity. The opposition of steric hindrance to ortho attack is responsible for the exclusive β-substitution product obtained from *o*-xylene (Table 1) and for the unreactivity of mesitylene. The substantial yield of the α substitution product from the *tert*-butylation of **1** and the still significant, though smaller, yield from **2** suggest that the ortho methylene group of the fused ring in these two terms exerts a reduced steric effect with respect to a freely rotating methyl group.

In conclusion, the gas-phase electrophilic attack by alkylating ions on benzocycloalkenes, involving interaction of isolated species, has shown an α/β selectivity ratio conforming to the MN effect only for the first member of the series investigated in this study (**1**). Any positional selectivity diverging from that of *o*-xylene displayed by the higher homologues in electrophilic reactions run in solution thus appears to reflect specific medium effects.

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