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MODEL CALCULATIONS ON THE ELECTROPHILIC REACTIVITY OF FUSED AROMATICS. INFLUENCE OF THE OH SUBSTITUENT

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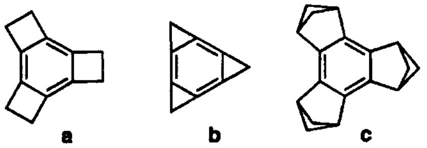
It is shown by MP2(fc)/6–31G//HF/6–31G* calculations on model systems that benzenes fused to carbocycles and possessing a β-hydroxy substituent exhibit a characteristic electrophilic regioselectivity, which is a linear function of the size of the annelated ring. This directive property, which determines the susceptibility of various positions within the aromatic fragment towards electrophilic substitution, is rationalized in terms of the degree of matching of two π-electron localization patterns, one occurring in the ground state of the molecule and the other in the transition structure (Wheland σ-complex formed by protonation). The overwhelming influence, however, is exerted by the OH group, which substantially activates its *ortho* positions. The role of hyperconjugation seems to be small but not negligible. The relevance of the present result in interpreting the Mills–Nixon effect is briefly discussed.**

INTRODUCTION

Structural effects of small rings annelated to an aromatic fragment have recently been extensively discussed.[1] Although there seems to be clear evidence for double-bond localization in the benzene fragment of benzocyclobutene,[2–4] biphenylene,[5–7] etc., supporting what is known as the Mills–Nixon effect,[8] some doubt has also been expressed as to whether the structural effects are large enough to be of significance.[9] In fact, experimental results were interpreted such as to conclude that the Mills–Nixon effect cannot be proved even in highly strained systems such as **a**, **b** and **c** (Scheme 1)[10,11] despite the ample theoretical[3,4,6,7,12–16] and experimental evidence[2,5,10,17,18] for double-bond fixation in such systems.

No matter how significant the extent of double-bond fixation corresponding to the preference of one Kekulé structure of benzene over the other is, what has to be accounted for is the fact that the β-position in 5-hydroxyindane is much more susceptible than the α site to electrophilic substitution.[8,9] The original explanation for this phenomenon was based on ground-state structural changes due to small-ring annelation: it was assumed that diazo coupling and bromination occurs at the *ortho* position joined to the hydroxylated carbon by a double



Scheme 1

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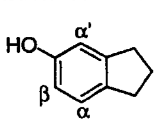
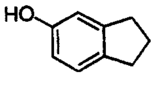
bond, indicating that I is the more stable one of the two Kekulé structures I and II.

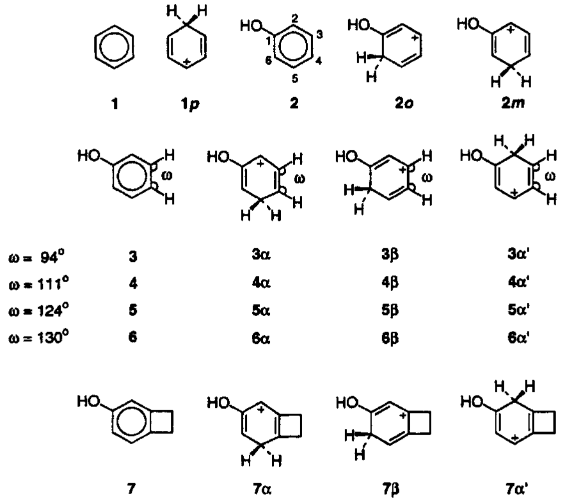


I



II

However, it is not the ground-state structure but rather the transition structure which mainly affects reactivity. It is therefore important also to consider the transition structure in order to explain the interrelation between structure and reactivity and to account for the selectivity that is observed even for systems with minor structural effects such as indane[19] or benzocyclobutene.[20] As a first step towards this goal in a previous study we analysed the electrophilic substitution of benzocycloalkanes,[21a] using protonation as model reaction and mimicking the strain induced by annelating rings by bending two vicinal CH bonds in benzene towards each other. This model reproduces the salient features of the real molecular systems in a transparent and satisfactory manner.[21b] As, in fact, Mills and Nixon[8] examined the electrophilic substitution of *β*-hydroxyindane, we have now extended this model study to include explicitly the OH group in a series of deformed phenols as depicted in Scheme 2. The numbering of atoms in all systems is that in phenol. These model systems have the distinct advantage that they are planar except for the protonated species, where an approximately sp^3-hybridized centre is introduced. Hence perturbation takes place in the plane of the molecule, thus being free of contamination by external conjugation or hyperconjugation. This approach gives an opportunity to investigate separately the effects of (i) the OH substituent, (ii) the ring strain induced by fused (cycloalkane) rings and (iii) hyperconjugation with the methylene group of the annelated carbocycle. The last aspect will be considered only qualitatively in a later stage. In this way we hope to shed some additional light on the Mills–Nixon hypothesis and, in particular, to obtain some insight into the interrelation of structural and energetic changes due to OH substitution and annelation.



Scheme 2

THEORETICAL PROCEDURE

The applied method should be practical enough to allow full geometry optimization of the studied systems and yet it should be rigorous enough to provide reliable results. Extensive calculations have shown that the SCF level of theory utilizing a basis set of $6-31/G^*$ quality yields reasonable structural parameters.[22] Since the energetic properties are crucial in the present study, the electron correlation should be explicitly taken into account. This can be achieved by single-point MP2(fc) calculations, where (fc) denotes frozen inner-core electrons in the course of computation of the correlation energy. The second order Møller–Plesset perturbation theory recovers most of the correlation energy. Possible imperfections of the adopted models are remedied to a large extent by the fact that the relative stability of Wheland σ intermediates[23] for *α*- and *β*-protonation sites implies cancellation of errors to a high degree. Two models are employed: $MP2(fc)/6-31G^*//HF/6-31G^*$ and $MP2(fc)/6-31G^{**}//HF/6-31G^*$. The latter wavefunctions performed very well in describing protonation processes in aromatics.[24] All computations were carried out by employing the Gaussian 92 program package[25] and all minima were verified by vibrational analysis.

RESULTS AND DISCUSSION

Structural properties

Annelated hydroxy compounds are modelled by bending two vicinal CH bonds in phenol toward each other. The CCH angles ω in the distorted phenols **3**–**6** are chosen such as to simulate four- ($\omega = 94°$), five- ($\omega = 111°$) and seven- membered carbocycles ($\omega = 124°$), and $\omega = 130°$ was chosen to describe even larger fused rings. In order to discuss structural changes imposed on the phenylene framework by protonation and annelation, the relevant $HF/6-31G^*$ structural parameters of phenol (**2**), its *ortho*- and *meta*-protonated forms (**2*o***) and (**2*m***), and of the model compounds **3**–**6** are collected in Table 1. Bond-length changes with respect to phenol are denoted by Δ_{prot} and Δ_{ann}, depending on whether they are induced by protonation (**2*o*** and **2*m***) or by annelation (**3**–**6**).

Table 1. Structural parameters and bond-distance changes Δ_{ann} and Δ_{prot} caused by annelation and protonation, respectively, for phenol (**2**), *o*- and *m*-protonated phenol (**2*o*** and **2*m***) and for distorted phenol **3**–**6**, as calculated by the HF/6–31G* model (distances in Å, angles in degrees)

Molecule	Bond	Distance	Δ_{ann}	Δ_{prot}	Bond angles	
2	C(1)—C(2)	1·386	—	—	C(1)—C(2)—C(3)	119·7
	C(2)—C(3)	1·387	—	—	C(2)—C(3)—C(4)	120·6
	C(3)—C(4)	1·383	—	—	C(3)—C(4)—C(5)	119·1
	C(4)—C(5)	1·389	—	—	C(4)—C(5)—C(6)	120·6
	C(5)—C(6)	1·382	—	—	C(5)—C(6)—C(1)	120·9
	C(1)—C(6)	1·388	—	—	C(6)—C(1)—C(2)	119·5
	C(1)—O	1·353	—	—	C(1)—O—H	110·6
	O—H	0·947	—	—	C(6)—C(1)—O	122·5
2*o*	C(1)—C(2)	1·390	—	0·004	C(1)—C(2)—C(3)	118·1
	C(2)—C(3)	1·373	—	−0·014	C(2)—C(3)—C(4)	124·1
	C(3)—C(4)	1·436	—	0·053	C(3)—C(4)—C(5)	119·0
	C(4)—C(5)	1·336	—	−0·053	C(4)—C(5)—C(6)	121·9
	C(5)—C(6)	1·488	—	0·106	C(5)—C(6)—C(1)	115·1
	C(1)—C(6)	1·486	—	0·098	C(6)—C(1)—C(2)	121·7
	C(1)—O	1·287	—	—	C(1)—O—H	114·6
	C(6)—H	1·090	—		C(6)—C(1)—O	114·0
	O—H	0·955	—	—	H—C(6)—H	104·8
2*m*	C(1)—C(2)	1·422	—	0·036	C(1)—C(2)—C(3)	123·9
	C(2)—C(3)	1·398	—	0·011	C(2)—C(3)—C(4)	118·5
	C(3)—C(4)	1·359	—	−0·024	C(3)—C(4)—C(5)	121·4
	C(4)—C(5)	1·471	—	0·082	C(4)—C(5)—C(6)	116·4
	C(5)—C(6)	1·479	—	0·097	C(5)—C(6)—C(1)	121·4
	C(6)—C(1)	1·348	—	−0·040	C(6)—C(1)—C(2)	118·4
	C(1)—O	1·337	—	—	C(6)—C(1)—O	127·2
	C(5)—H	1·094	—	—	C(1)—O—H	113·5
	O—H	0·950	—	—	H—C(5)—H	103·3
3	C(1)—C(2)	1·404	0·018	—	C(1)—C(2)—C(3)	115·5
	C(2)—C(3)	1·364	−0·023	—	C(2)—C(3)—C(4)	122·6
	C(3)—C(4)	1·441	0·058	—	C(3)—C(4)—C(5)	120·9
	C(4)—C(5)	1·366	−0·023	—	C(4)—C(5)—C(6)	116·6
	C(5)—C(6)	1·399	0·017	—	C(5)—C(6)—C(1)	122·0
	C(6)—C(1)	1·387	−0·001	—	C(6)—C(1)—C(2)	122·3
	C(1)—O	1·355	—	—	C(6)—C(1)—O	116·6
	O—H	0·947	—	—	C(1)—O—H	110·7
2	C(1)—C(2)	1·391	0·005	—	C(1)—C(2)—C(3)	117·9
	C(2)—C(3)	1·379	−0·008	—	C(2)—C(3)—C(4)	121·6
	C(3)—C(4)	1·392	0·009	—	C(3)—C(4)—C(5)	120·1
	C(4)—C(5)	1·381	−0·008	—	C(4)—C(5)—C(6)	119·6
	C(5)—C(6)	1·387	0·005	—	C(5)—C(6)—C(1)	120·5
	C(6)—C(1)	1·389	0·001	—	C(6)—C(1)—C(2)	120·9
	C(1)—O	1·354			C(6)—C(1)—O	117·0
	O—H	0·947	—	—	C(1)—O—H	110·7
5	C(1)—C(2)	1·387	0·001	—	C(1)—C(2)—C(3)	120·4
	C(2)—C(3)	1·385	−0·002	—	C(2)—C(3)—C(4)	120·3
	C(3)—C(4)	1·387	0·004	—	C(3)—C(4)—C(5)	118·7
	C(4)—C(5)	1·386	−0·003	—	C(4)—C(5)—C(6)	121·4
	C(5)—C(6)	1·385	0·003	—	C(5)—C(6)—C(1)	119·3
	C(6)—C(1)	1·385	−0·003	—	C(6)—C(1)—C(2)	119·8
	C(1)—O	1·287	—	—	C(6)—C(1)—O	122·6
	O—H	0·947	—	—	C(1)—O—H	110·6
6	C(1)—C(2)	1·384	−0·002	—	C(1)—C(2)—C(3)	121·7
	C(2)—C(3)	1·391	0·004	—	C(2)—C(3)—C(4)	119·5
	C(3)—C(4)	1·385	0·002	—	C(3)—C(4)—C(5)	118·0
	C(4)—C(5)	1·392	0·003	—	C(4)—C(5)—C(6)	122·8
	C(5)—C(6)	1·382	0·0	—	C(5)—C(6)—C(1)	118·7
	C(6)—C(1)	1·384	−0·004	—	C(6)—C(1)—C(2)	119·3
	C(1)—O	1·352	—	—	C(6)—C(1)—O	122·9
	O—H	0·947	—	—	C(1)—O—H	110·6

Table 2. Structural parameters and bond-distance changes Δ_t and Δ_t(add) relative to phenol (**2**) of protonated distorted phenols ***nα***, ***nβ*** and ***nα'***$_0$ (***n*** = **3**–**6**) as calculated by the HF/6–31G* model (distances in Å, angles in degrees)

Molecule	Bond distance		Δ_t	Δ_t(add)	Bond angles	
3α	C(1)—C(2)	1·426	0·040	0·054	C(1)—C(2)—C(3)	119·1
	C(2)—C(3)	1·381	-0·006	-0·012	C(2)—C(3)—C(4)	121·3
	C(3)—C(4)	1·410	0·027	0·034	C(3)—C(4)—C(5)	122·9
	C(4)—C(5)	1·454	0·065	0·059	C(4)—C(5)—C(6)	112·0
	C(5)—C(6)	1·487	0·105	0·114	C(5)—C(6)—C(1)	124·3
	C(6)—C(1)	1·360	-0·028	-0·041	C(6)—C(1)—C(2)	120·4
	C(1)—O	1·340	—	—	C(6)—C(1)—O	117·9
	C(5)—H	1·094	—	—	C(1)—O—H	114·3
					H—C(5)—H	103·7
4α	C(1)—C(2)	1·428	0·042	0·041	C(1)—C(2)—C(3)	121·7
	C(2)—C(3)	1·388	0·001	0·003	C(2)—C(3)—C(4)	119·8
	C(3)—C(4)	1·368	-0·015	-0·015	C(3)—C(4)—C(5)	122·4
	C(4)—C(5)	1·464	0·075	0·074	C(4)—C(5)—C(6)	114·4
	C(5)—C(6)	1·484	0·102	0·102	C(5)—C(6)—C(1)	122·4
	C(6)—C(1	1·349	-0·039	-0·039	C(6)—C(1)—C(2)	119·3
	C(1)—O	1·337	—	—	C(6)—C(1)—O	126·8
	C(5)—H	1·094	—	—	C(1)—O—H	113·5
					H—C(5)—H	103·6
5α	C(1)—C(2)	1·420	0·034	0·037	C(1)—C(2)—C(3)	124·5
	C(2)—C(3)	1·401	0·014	0·009	C(2)—C(3)—C(4)	118·3
	C(3)—C(4)	1·358	-0·025	-0·020	C(3)—C(4)—C(5)	121·0
	C(4)—C(5)	1·475	0·086	0·079	C(4)—C(5)—C(6)	117·0
	C(5)—C(6)	1·477	0·095	0·100	C(5)—C(6)—C(1)	121·2
	C(6)—C(1)	1·348	-0·040	-0·043	C(6)—C(1)—C(2)	118·1
	C(1)—O	1·336	—	—	C(6)—C(1)—O	127·3
	C(5)—H	1·094	—	—	C(1)—O—H	113·5
					H—C(5)—H	103·2
6α	C(1)—C(2)	1·417	0·031	0·034	C(1)—C(2)—C(3)	125·9
	C(2)—C(3)	1·408	0·021	0·015	C(2)—C(3)—C(4)	117·5
	C(3)—C(4)	1·356	-0·027	-0·022	C(3)—C(4)—C(5)	120·3
	C(4)—C(5)	1·481	0·092	0·085	C(4)—C(5)—C(6)	118·3
	C(5)—C(6)	1·474	0·092	0·097	C(5)—C(6)—C(1)	120·6
	C(6)—C(1)	1·347	-0·041	-0·044	C(6)—C(1)—C(2)	117·5
	C(1)—O	1·336	—	—	C(6)—C(1)—O	127·6
	C(5)—H	1·094	—	—	C(1)—O—H	113·5
					H—C(5)—H	103·1
3β	C(1)—C(2)	1·404	0·018	0·022	C(1)—C(2)—C(3)	113·5
	C(2)—C(3)	1·353	-0·034	-0·037	C(2)—C(3)—C(4)	126·3
	C(3)—C(4)	1·501	0·118	0·111	C(3)—C(4)—C(5)	121·2
	C(4)—C(5)	1·320	-0·069	-0·076	C(4)—C(5)—C(6)	117·4
	C(5)—C(6)	1·501	0·119	0·123	C(5)—C(6)—C(1)	117·3
	C(6)—C(1)	1·502	0·114	0·097	C(6)—C(1)—C(2)	124·3
	C(1)—O	1·284	—	—	C(6)—C(1)—O	123·1
	C(6)—H	1·089	—	—	C(1)—O—H	114·8
					H—C(6)—H	104·8
4β	C(1)—C(2)	1·394	0·008	0·009	C(1)—C(2)—C(3)	116·6
	C(2)—C(3)	1·367	-0·020	-0·024	C(2)—C(3)—C(4)	124·6
	C(3)—C(4)	1·445	0·062	0·062	C(3)—C(4)—C(5)	120·0
	C(4)—C(5)	1·331	-0·058	-0·061	C(4)—C(5)—C(6)	120·2
	C(5)—C(6)	1·492	0·110	0·111	C(5)—C(6)—C(1)	115·8
	C(6)—C(1)	1·491	0·103	0·099	C(6)—C(1)—C(2)	122·5
	C(1)—O	1·286	—	—	C(6)—C(1)—O	113·6
	C(6)—H	1·090	—	—	C(1)—O—H	114·7
					H—C(6)—H	104·8

continued

Table 2 (*cont.*)

5*β*	C(1)—C(2)	1·387	0·001	0·005	C(1)—C(2)—C(3)	119·5
	C(2)—C(3)	1·378	−0·009	−0·016	C(2)—C(3)—C(4)	123·1
	C(3)—C(4)	1·433	0·050	0·057	C(3)—C(4)—C(5)	118·4
	C(4)—C(5)	1·340	−0·049	−0·056	C(4)—C(5)—C(6)	123·1
	C(5)—C(6)	1·486	0·104	0·109	C(5)—C(6)—C(1)	114·6
	C(6)—C(1)	1·482	0·094	0·095	C(6)—C(1)—C(2)	121·2
	C(1)—O	1·287	—	—	C(6)—C(1)—O	114·4
	C(6)—H	1·090	—	—	C(1)—O—H	114·6
					H—C(6)—H	104·8
6*β*	C(1)—C(2)	1·385	−0·001	0·002	C(1)—C(2)—C(3)	121·0
	C(2)—C(3)	1·384	−0·003	−0·010	C(2)—C(3)—C(4)	122·2
	C(3)—C(4)	1·431	0·048	0·055	C(3)—C(4)—C(5)	117·6
	C(4)—C(5)	1·344	−0·045	−0·050	C(4)—C(5)—C(6)	124·6
	C(5)—C(6)	1·483	0·101	0·106	C(5)—C(6)—C(1)	114·0
	C(6)—C(1)	1·478	0·090	0·094	C(6)—C(1)—C(2)	119·3
	C(1)—O	1·287	—	—	C(6)—C(1)—O	120·6
	C(6)—H	1·090	—	—	C(1)—O—H	114·5
					H—C(6)—H	104·9
3*a*′	C(1)—C(2)	1·501	0·115	0·116	C(1)—C(2)—C(3)	110·6
	C(2)—C(3)	1·470	0·083	0·083	C(2)—C(3)—C(4)	124·0
	C(3)—C(4)	1·384	0·001	0·005	C(3)—C(4)—C(5)	121·4
	C(4)—C(5)	1·414	0·025	0·030	C(4)—C(5)—C(6)	119·2
	C(5)—C(6)	1·382	0·0	0·003	C(5)—C(6)—C(1)	120·7
	C(6)—C(1)	1·396	0·008	0·003	C(6)—C(1)—C(2)	124·1
	C(1)—O	1·289	—	—	C(6)—C(1)—O	123·1
	C(2)—H	1·090	—	—	C(1)—O—H	114·7
					H—C(2)—H	105·5
4*a*′	C(1)—C(2)	1·492	0·106	0·103	C(1)—C(2)—C(3)	113·1
	C(2)—C(3)	1·480	0·093	0·098	C(2)—C(3)—C(4)	122·9
	C(3)—C(4)	1·344	−0·039	−0·044	C(3)—C(4)—C(5)	120·3
	C(4)—C(5)	1·426	0·037	0·045	C(4)—C(5)—C(6)	121·9
	C(5)—C(6)	1·376	−0·006	−0·009	C(5)—C(6)—C(1)	119·1
	C(6)—C(1)	1·393	0·005	0·005	C(6)—C(1)—C(2)	122·7
	C(1)—O	1·288	—	—	C(6)—C(1)—O	123·7
	C(2)—H	1·090	—	—	C(1)—O—H	114·6
					H—C(2)—H	105·1
5*a*′	C(1)—C(2)	1·485	0·099	0·099	C(1)—C(2)—C(3)	115·7
	C(2)—C(3)	1·491	0·104	0·104	C(2)—C(3)—C(4)	121·5
	C(3)—C(4)	1·335	−0·048	−0·049	C(3)—C(4)—C(5)	118·8
	C(4)—C(5)	1·438	0·049	0·050	C(4)—C(5)—C(6)	124·6
	C(5)—C(6)	1·372	−0·010	−0·011	C(5)—C(6)—C(1)	117·9
	C(6)—C(1)	1·389	0·001	0·001	C(6)—C(1)—C(2)	121·5
	C(1)—O	1·287	—	—	C(6)—C(1)—O	124·4
	C(2)—H	1·091	—	—	C(1)—O—H	114·6
					H—C(2)—H	104·7
6*a*′	C(1)—C(2)	1·481	0·095	0·096	C(1)—C(2)—C(3)	117·0
	C(2)—C(3)	1·498	0·111	0·110	C(2)—C(3)—C(4)	120·8
	C(3)—C(4)	1·334	−0·049	−0·051	C(3)—C(4)—C(5)	118·0
	C(4)—C(5)	1·445	0·056	0·056	C(4)—C(5)—C(6)	126·0
	C(5)—C(6)	1·370	−0·012	−0·014	C(5)—C(6)—C(1)	117·3
	C(6)—C(1)	1·387	−0·001	0·0	C(6)—C(1)—C(2)	120·9
	C(1)—O	1·286	—	—	C(6)—C(1)—O	124·7
	C(2)—H	1·094	—	—	C(1)—O—H	114·6
					H—C(2)—H	104·5

The data in Table 1 reveal that larger bond alternation is induced by protonation than by the angular deformation. This is not surprising since much higher energies are involved in protonations of the benzene fragment [*ca* 200 kcal/mol^{-1} (1 kcal = 4·184 kJ)][24] than in angular deformations of the phenol CH bonds (see below) and since the creation of an sp^3 centre by protonation obviously perturbs the π-bond localization pattern.[21] Bond alternation induced by fusion of four- and five-membered rings as modelled by the CCH angles ω of 94° and 111°, however, is also significant and far from being negligible. Owing to rehybridization, fusion with a small ring produces a lengthening of the *ipso* bond and a shortening of the *ortho* bonds.[3,6,21,26] It is also interesting that the model systems conclusively show that the in-plane angular strain can produce bond fixation within the aromatic unit. Stanger[27] argued that in true fused molecular systems bond alternation should be negligibly small owing to the appearance of bent bonds within the annelated carbocycle. However, a careful high-level *ab initio* analysis of bent bonds in highly strained polyannelated benzenes has shown that the main conclusions derived from studies of the model systems hold generally.[28] Finally, annelation of smaller carbocycles produces a significant sharpening of the apical C(1)—C(2)—C(3) and C(4)—C(5)—C(6) bond angles, which in **3** assume values of 115·5° and 116·6°, respectively. This finding indicates a spillover of the angular strain from the small ring to the aromatic fragment. Obviously, the aromatic moiety undergoes significant changes upon fusion, which in turn have important chemical consequences.

As a model for the transition structure in electrophilic substitution we use the Wheland σ complex of proton attack ***nα***, ***nβ*** and ***nα'***. Although being an intermediate corresponding to a minimum on the potential energy surface, this should be an appropriate substitute for the transition structure which for a gas-phase protonation may be unrealistic and difficult to locate. Geometric parameters of these protonated species where ***n*** = 3, 4, 5, 6 are given in Table 2. Total bond-length changes Δ_t relative to phenol (**2**) are compared with the sums Δ_t(add) of bond-length changes Δ_{ann} and Δ_{prot} caused by fusion and protonation. Full agreement between Δ_t and Δ_t(add) would imply that the two events protonation and annelation are completely independent. Deviations from additivity, on the other hand, indicate interference between these two effects. The largest differences between Δ_t and Δ_t(add) are found in ***3α*** and ***3β***, which is certainly caused by the significant angular strain of the four-membered ring. One concludes by extrapolation that the deviation from additivity would be even larger for an annelated three-membered ring. It is also interesting that the sum of absolute deviations $|\Delta_t - \Delta_t(\text{add})|$ is higher in ***3α*** than in ***3β*** (0·055 vs 0·042Å), while the sum of deviations of the C—C—C benzene ring angles from the ideal 120° value is smaller in ***3α*** than in ***3β*** (17·8° vs 23·6°). These observations bear some relevance for the interpretation of directive properties in electrophilic reactions of fused small rings.

Table 3. Total molecular energies *E* (in a.u.) of benzene (**1**), phenol (**2**) and deformed phenols **3**–**6** and of their protonated forms calculated by different models

Molecule	HF/6–31G*	MP2(fc)/6–31G*//HF/6–31G*	MP2(fc)/6–31G**//HF/6–31G*
1	−230·70314	−231·45648	−231·50459
1p	−231·01469	−231·74814	−231·80103
2	−305·55806	−306·48890	−306·54051
2o	−305·89172	−306·80230	−306·85929
2m	−305·86343	−306·77979	−306·83668
3	−305·49870	−306·43543	−306·48875
4	−305·55134	−306·48271	−306·53332
5	−305·55695	−306·48771	−306·53954
6	−305·55080	−306·48220	−306·53411
3α	−305·79426	−306·71989	−306·77855
4α	−305·85511	−306·77222	−306·82925
5α	−305·86284	−306·77929	−306·83622
6α	−305·85768	−306·77459	−306·83161
3β	−305·83732	−306·75304	−306·81121
4β	−305·88727	−306·79773	−306·85482
5β	−305·88936	−306·80044	−306·85750
6β	−305·88161	−306·79369	−306·85085
3α'	−305·82421	−306·74304	−306·80199
4α'	−305·88286	−306·79469	−306·85188
5α'	−305·89127	−306·80182	−306·85884
6α'	−305·88641	−306·79719	−306·85428

Intuitive conclusion that the protonated form **3*β*** is less stable than **3*β*** would be erroneous, however (see below).

Energetic properties

Total molecular energies of the molecules depicted in Scheme 2 as calculated by the HF/6–31G*, MP2(fc)/6–31G*//HF/6–31G* and MP2(fc)/6–31G**//HF/6–31G* models. denoted by M(I.), M(II.) and M(III.), respectively, are given in Table 3. The results show that as in undistorted phenol, where due to the *o*-, *p*-directing property of the OH group [$E(\mathbf{2o})$ is lower than $E(\mathbf{2m})$], protonation of the distorted phenols **3–6** is more favourable in β than in α positions with two notable exceptions: $E(\boldsymbol{n\alpha'})$ is lower than $E(\boldsymbol{n\beta})$ for $\boldsymbol{n} = \mathbf{5}$, **6**. This findings deserve a closer examination. Plots of the energy differences $E(\boldsymbol{n\alpha}) - E(\boldsymbol{n\beta})$ and $E(\boldsymbol{n\alpha'}) - E(\boldsymbol{n\beta})$ estimated by model M(III.) against the CCH angle ω are shown in Figure 1. Two parallel straight lines are obtained, which can be expressed by

$$E(\boldsymbol{na}) - E(\boldsymbol{n\beta}) = C(a) - 0{\cdot}22\omega \text{ (in kcal mol}^{-1}) \quad (1)$$

where a stands for α or α' and the additive constants assume the values $C(\alpha) = 43{\cdot}5$ and $C(\alpha') = 26{\cdot}4$ kcal mol^{-1}. The correlation coefficients in both cases are $r = 0{\cdot}99$. These results will be interpreted on the basis of homodesmic reactions,[29,30] which previously proved useful in interpreting the selectivity in electrophilic substitution reactions in fused aromatics.[21] Consider, for instance, the protonated species $\boldsymbol{n\alpha}$. From the corresponding set of the homodesmic reactions we obtain the relationship

$$E(\boldsymbol{n\alpha}) + E(\mathbf{2}) = E(\mathbf{2m}) + E(\boldsymbol{n}) + E_{\text{intf.}}(\boldsymbol{n\alpha}) \quad (2)$$

where $\boldsymbol{n} = \mathbf{3}$–**6** and $E_{\text{intf.}}(\boldsymbol{n\alpha})$ denotes the interference between annelation and protonation, i.e. the deviation from strict additivity of these two almost independent events. Introducing the proton affinity $PA(\mathbf{2})_m = E(\mathbf{2}) - E(\mathbf{2m})$ of the *meta* position of phenol and the strain energy $E_s(\boldsymbol{n}) = E(\boldsymbol{n}) - E(\mathbf{2})$ of the distorted phenol, equation (2) can be written as

$$E(\boldsymbol{n\alpha}) - E(\mathbf{2}) = -PA(\mathbf{2})_m + E_s(\boldsymbol{n}) + E_{\text{intf.}}(\boldsymbol{n\alpha}) \quad (3)$$

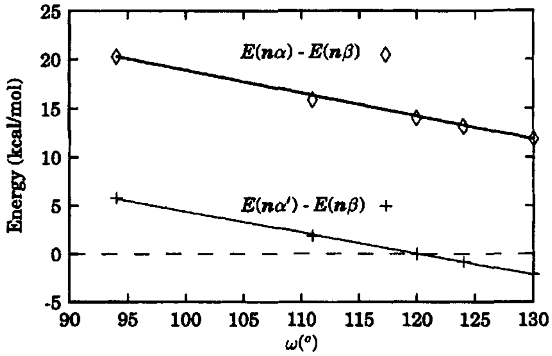


Figure 1. Energy differences $E(\boldsymbol{n\alpha}) - E(\boldsymbol{n\beta})$ and $E(\boldsymbol{n\alpha'}) - E(\boldsymbol{n\beta})$ for α, α' and β proton attack in phenol (**2**) and distorted phenols **3–6** as a function of the CCH angle ω, as calculated by the MP2(fc)/6–31G**//HF/6–31G* model

Hence the energy of the α-protonated and distorted phenol $\boldsymbol{n\alpha}$ relative to that of phenol is given by the corresponding PA plus the sum of $E_s(\boldsymbol{n})$ and $E_{\text{intf.}}(\boldsymbol{n\alpha})$, which together describe the effect of annelation. $E_s(\boldsymbol{n})$ embodies the angular strain, the aromaticity defect caused by bond fixation and the increased H···H repulsion of the C—H bonds involved in the bending deformation. This repulsion energy is certainly an undesirable feature of the model systems since it does not occur in the true fused molecules. However, the strain energy $E_s(\boldsymbol{n})$ disappears when the relative stabilities of the α and β positions are considered in the protonation process. Thus, for protonated forms $\boldsymbol{n\beta}$ the relationship analogous to equation (3) reads

$$E(\boldsymbol{n\beta}) - E(\mathbf{2}) = -PA(\mathbf{2})_o + E_s(\boldsymbol{n}) + E_{\text{intf.}}(\boldsymbol{n\beta}) \quad (4)$$

Therefore,

$$E(\boldsymbol{n\alpha}) - E(\boldsymbol{n\beta}) = E_{\text{intf.}}(\boldsymbol{n\alpha}) - E_{\text{intf.}}(\boldsymbol{n\beta}) + [PA(\mathbf{2})_o - PA(\mathbf{2})_m] \quad (5)$$

follows, where the term in brackets is a constant, being 14·1 and 14·2 kcal mol^{-1} for the M(II.) and M(III.) model, respectively. Similarly, for the difference between $E(\boldsymbol{n\alpha'})$ and $E(\boldsymbol{n\beta})$ energies, one has

$$E(\boldsymbol{n\alpha'}) - E(\boldsymbol{n\beta}) = E_{\text{intf.}}(\boldsymbol{n\alpha'}) - E_{\text{intf.}}(\boldsymbol{n\beta}) \quad (6)$$

Here, the term corresponding to the last term in equation (5) has disappeared since PA is related to the *ortho* position in both cases. The form of equations (5) and (6) immediately explains the difference in the additive term in the straight lines shown in Figure 1, which is given by the difference in *PA*s related to the *ortho* and *meta* sites in phenol. Since this difference is as high as *ca* 14 kcal mol^{-1}, it follows that the OH substituent considerably amplifies the discrimination between α and β sites in electrophilic reactions relative to the parent fused hydrocarbon.[21a]

In connection with the selectivity observed for electrophilic substitution in β-hydroxyindane the difference, $E(\boldsymbol{n\alpha'}) - E(\boldsymbol{n\beta})$ is of particular interest. According to equation (6), this difference is given by the difference in the corresponding interference energies. According to the definition of $E_{\text{intf.}}$ in equation (2), a negative sign signifies a cooperative interaction between annelation and protonation, whereas a positive sign is indicative of an antagonism between the two different events taking place in the same molecule. From the data in Table 4, it is seen that $E_{\text{intf}}(\boldsymbol{n\alpha})$ and $E_{\text{intf.}}(\boldsymbol{n\alpha'})$ are positive for $\omega < 120°$ and negative for

Table 4. Interference energies $E_{\text{intf.}}(n\alpha)$ (in kcal mol^{-1}) for α and β proton attack in distorted phenols **3**–**6** as calculated by models M(II.) and M(III)[a]

	$E_{\text{intf.}}(n\alpha)$		$E_{\text{intf.}}(n\beta)$		$E_{\text{intf.}}(n\alpha')$	
CCH angle $\omega(n)$	M(II.)	M(III.)	M(II.)	M(III.)	M(II.)	M(III.)
94	5·8	3·6	−2·6	−2·3	3·7	3·4
111	0·8	0·2	−1·0	−1·8	0·9	0·1
124	−0·5	−0·3	0·5	0·5	−0·4	−0·4
130	−1·0	−0·8	1·2	1·2	−1·0	−0·9

[a] M(II.) = MP2(fc)/6-31G*//HF/6-31G*; M(III.) = MP2(fc)/6-31G**//HF/6-31G*

$\omega > 120°$, whereas the opposite is true for $E_{\text{intf.}}(n\beta)$. This is consistent with the interpretation of the MN effect based on the compatibility of two π-electron localization patterns, one triggered by protonation and the other caused by changes in the σ framework induced by annelation. For to $\omega < 120°$ the negative sign of $E_{\text{intf.}}(n\beta)$ and the positive signs of $E_{\text{intf.}}(n\alpha')$ and $E_{\text{intf.}}(n\alpha)$ correspond to compatibility in the case of β protonation and to counteraction of ground-state (annelation) and transition-structure (Wheland intermediate) π-localization patterns in the case of α protonation. Thus, interference between annelation and protonation favours β protonation for $\omega < 120°$, as is seen from the relative stabilities $E_{\text{intf.}}(n\alpha') - E_{\text{intf.}}(n\beta)$ of the α' and β protonation products plotted in Figure 1. For large annelated rings ($\omega > 120°$), however, the α' position should exhibit a higher reactivity towards electrophilic substitution, provided that other intramolecular interactions, such as hyperconjugation, do not change the picture. It is very important to realize that the strain energy enters into consideration only indirectly, through the π-bond fixation in the ground state. This is obvious from the fact that E_s disappeared in equations (5) and (6).

The finding that the sum of the CCC angle deviations from 120° is larger in the benzene ring of **3**β than in **3**α could imply a higher angular strain in **3**β and a lower reactivity towards electrophilic substitution, i.e. a higher value for $E(3\beta)$ than for $E(3\alpha)$. However, from Figure 1, it is seen that $E(n\alpha) - E(n\beta)$ is always positive and from equations (5) and (6) it is seen that this is mainly due to the effect of the OH substituent, which activates the *ortho* position relative to benzene, whereas the *meta* position remains virtually unchanged.[24] As pointed out before, the difference between the α and α' positions is due to the difference in *PA* values of the *ortho* and *meta* positions of phenol (**2**). Finally, the fact that the interference energies $E_{\text{intf.}}(n\alpha)$ and $E_{\text{intf.}}(n\alpha')$ are nearly identical explains why the two straight lines in Figure 1 are parallel, and the negative slope of these lines is easily understood from the fact that $E_{\text{intf.}}(n\alpha)$ and $E_{\text{intf.}}(n\alpha')$ decrease with increasing ω, whereas $E_{\text{int.}}(n\beta)$ increases.

These results are based on the assumption that annelation can be modelled by bending two vicinal CH bonds towards each other. We therefore include in Table 5 some results for the real annelated system β-hydroxybenzocyclobutane (**7**) and its protonated forms **7**α, **7**β and α'. The bond-distance changes Δ_t relative to phenol (**2**), for which we use the same numbering of atoms as for **2** (Scheme 2) for the sake of comparison, are in very good agreement with the data for the corresponding

Table 5. Total molecular energies E (in a.u.) of benzocyclobutane (**7**) and its protonated forms and bond-distance changes Δ_t (in Å) relative to phenol (**2**)[a]

Parameter	**7**	**7**α	**7**β	**7**α'
E				
HF/6-31G*	−382·41971	−382·73538	−382·76622	−382·75960
MP2/6-31G**	−383·67828	−383·98349	−384·00836	−384·00400
Δ_t				
C(1)—C(2)	0·009	0·057	0·004	0·112
C(2)—C(3)	−0·013	−0·012	−0·021	0·092
C(3)—C(4)	0·000	−0·016	0·058	−0·045
C(4)—C(5)	−0·014	0·075	−0·064	0·028
C(5)—C(6)	0·013	0·112	0·120	0·004
C(6)—C(1)	0·004	−0·043	0·116	0·001

[a] Numbering of atoms as in phenol (**2**).

model systems **3**, **3*a***, ***β*** and ***a'***, except for the annelated bond C(1)—C(6) in **7** and its protonated forms, which is, as expected, less susceptible to bond-distance changes than the corresponding bond in **3**. From the total energies E in Table 5, the differences between the energies of the σ complexes for α and β protonation and for α' and β protonation, respectively, are calculated as $\Delta E(\alpha-\beta)=15{\cdot}6\ \mathrm{kcal\,mol^{-1}}$ and $\Delta E(\alpha'-\beta)=2{\cdot}8\ \mathrm{kcal\,mol^{-1}}$. Although smaller than the corresponding values $\Delta E(\alpha-\beta)=20{\cdot}5\ \mathrm{kcal\,mol^{-1}}$ and $E(\alpha'-\beta)=5{\cdot}8\ \mathrm{kcal\,mol^{-1}}$ for the model systems, they reflect exactly the same ordering of reactivity towards substitution for the various ring carbons. Thus we may conclude that the model is well suited for the problem at hand, and that the conclusions drawn from the result are reliable.

The present results are also supported by the existing chemical experience. Lloyd and Ongley[31] found that nitration, Friedel–Crafts acylation and hydrobromination of benzocyclobutene gave substitutions predominantly at the β-position. It was also shown that products of bromination[32] and the reactivity toward protodesilylation and also protodetritiation strongly favour the β site in indane, whereas there was virtually no such discrimination in tetralin.[33] Some more evidence can be found in a recent book.[34] Hence, the higher yields of β products in benzenes fused with small rings are in accordance with expectation based on the compability of ground-state and transition-structure π-localization patterns. A word of caution is necessary, however. In fused molecules a certain amount of hyperconjugation takes place between CH_2 groups of the carbocycle and the aromatic system. The effect of hyperconjugation can be qualitatively taken into account by considering the activation of α and β positions in *o*-xylene. Here, CH_2 groups are simulated by CH_3 groups. It appears that the β position is more favourable than the a position in *o*-xylene by only 0·7 kcal mol as estimated by both models M(II.) and M(III.). Since hyperconjugation is not suspected to vary with the size of the fused carbocycle, these values should be simply added to the energies $E(n\boldsymbol{\alpha})$, $E(n\boldsymbol{\alpha}')$ and $E(n\boldsymbol{\beta})$, assuming that additivity holds. As in energy differences this additive term disappears again, one concludes that hyperconjuation will change the $\beta:\alpha$ yield ratio very little. It should be kept in mind, however, that all our conjectures are valid strictly for protonation and that other electrophilic groups may behave somewhat differently, depending on their own electronic structure. The proton, on the other hand, defines a useful baseline in gauging electrophilic substitutions.

CONCLUSIONS

The present results and earlier evidence show persuasively that the orientation in electrophilic reactions of aromatics is affected by the annelated carbocycles much in the sense predicted by Mills and Nixon.[8] It appears that the discriminating property reflected in the energy difference $E(n\boldsymbol{\alpha})-E(n\boldsymbol{\beta})$ is a linear function (with negative slope) of the annelated ring size and is determined solely by the compatibility of ground-state and transition-structure effects, whereas the ring strain has only an indirect effect. We are confident that higher levels of theory may perhaps change some numbers slightly, but not the main conclusions. Support for this statement is provided by the fact that the M(II.) and M(III.) models give very similar results. It follows as a corollary that annelation of small rings to aromatic fragments has important chemical consequences. Concomitantly, if what has been observed is called 'effect,' it is a serious misrepresentation to say that the Mills–Nixon effect does not exist, regardless of the fact that in the original work the now outdated idea of fast kinetic equilibrium between the two Kekulé structures of benzene was used.[35] In addition, it is certainly true that the 'bicyclic ring strain effect'[10b] involves a large portion of the angular Baeyer strain which was originally used by Mills and Nixon as the main argument in rationalizing the electrophilic regioselectivity in indane.[8,9] To summarize, one can safely state that instead of the non-existent Mills–Nixon theory, there is an existing Mills–Nixon effect which embodies all changes in the physical and chemical behaviour of the aromatic fragment when annelated to small rings.

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