The Quantitative Electrophilic Reactivity of Annulenes. Part 2.[1] Partial Rate Factors for Hydrogen Exchange of Azulene, Cycl[3,2,2]azine, Indolizine, *N*-Methylisoindole, Indole, and Pyrrolo[2,1-*b*]thiazole, and Attempted Exchange in *trans*-9,10-Dimethyldihydropyrene: the Dramatic Effect of Creating Aromaticity in the Transition State for Electrophilic Substitution, and the Importance of Valence Bond Theory

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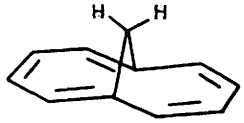
We have determined the rates of acid-catalysed detritiation of the 1-positions of azulene and cycl[3,2,2]azine in Aristar acetic acid at 70 °C. From the known exchange rate ratio between this acid and trifluoroacetic acid at 70 °C (1.58×10^8), the partial rate factors for exchange under the latter (standard) conditions are 9.93×10^{13} and 4.34×10^{13}, respectively, yielding corresponding σ^+ values of −1.60 and −1.56. From the literature rates of deuteriation of indolizine (1- and 3-position), *N*-methylisoindole (1-position), indole (3-position), and 6-methylpyrrolo[2,1-*b*]thiazole (7- and 5-position), partial rate factors under standard conditions may be calculated as 1.95×10^{16}, 9.93×10^{16}, 6.62×10^{17}, 5.52×10^{13}, 1.19×10^{17}, and 1.68×10^{18}, respectively. The corresponding σ^+ values are −1.86, −1.94, −2.04, −1.57, −1.95, and −2.08. *N*-Methylisoindole appears to be the most reactive aromatic compound known. The extreme reactivity of these compounds (indole apart) is attributed to creation of aromaticity in their respective transition states, and is reflected in very small methyl substituent effects as required by the reactivity–selectivity principle. Decomposition at higher acidities prevented determination of rate data for any other sites in azulene or cycl[3,2,2]azine but *maximum* σ^+ values for the 2- and 5—8-sites in indolizine may be estimated from literature data to be −1.57 and −1.30, respectively. The reactivity of the 3-position of indole is less than that of the 2-position in pyrrole (σ_2^+ −1.70) as in acetylation. In acetic acid at 50 °C *trans*-9,10-dimethyldihydropyrene underwent decomposition at a rate comparable to that of detritiation and no reliable rate data could be determined. Valence Bond Theory provides an easily visualized explanation of positional reactivities. It shows the origin of the reactivity of the most reactive site, and accounts for the relative reactivities of *N*-methylisoindole, indolizine, and cycl[3,2,2]azine, and the positional reactivities in each of the latter two molecules as well as in azulene and 6-methylpyrrolo[2,1-*b*]thiazole. It accounts for differences in methyl substituent effects in some of the title molecules, for the predominant 1-substitution in formylation of imidazo[1,2-*a*]pyridine (previously considered anomalous), for the exclusive 3-bromination of 2-phenyl-2*H*-indazole, and shows that nitration of thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine must take place at the 2- and not the 1-position recently reported. It also accounts for the 1-substitution in azupyrene, and the protonation of pyrrolo[1,2-*b*]pyridazine at C-1 in contrast to both theoretical (MO) predictions and the results for the isomeric azaindoles.

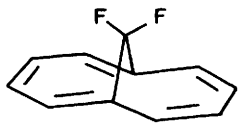
To date there has been only one study of the quantitative electrophilic reactivity of an annulene. Detritiation and desilylation of 1,6-methano[10]annulene (I) and its 11,11-difluoro derivative (II) yielded the partial rate factors and σ^+ values given in Table 1. The data showed that the annulene (I) was much more reactive than naphthalene to which it is formally similar (for detritiation,[2] σ_1^+ −0.35; σ_2^+ −0.25). Two factors may contribute to this. First, the annulene is not planar and therefore there is a loss of ground state resonance so that the energy barrier to achieving the transition state for reaction is smaller.[1] Secondly, in naphthalene benzenoid character is lost on going to the transition state which is not the case for the annulene, and this is reflected in the localization energies which predict both the 2- and 3-position in (I) to be significantly more reactive than the 1-position of naphthalene.[3] [The correlation between localization energies for naphthalene and (I) (calculated for the non-planar model by the SPO method)[3] predicts σ_3^+ for (I) to be −0.67. This is probably too high since the difference $\sigma_2^+ - \sigma_3^+$ for (I) should be greater than that for (II) because of the difference in inductive effects of CH_2 *versus* CF_2.]

Table 1. Electrophilic substitution of 1,6-methano[10]annulene (I) and 11,11-difluoro-1,6-methano[10]annulene (II)

Compound	Position	*f* (detritiation)	*f* (desilylation)	σ^+ (detritiation)
(I)	2	1.03×10^6	9 270	−0.80
(II)	2	3 750	20.2	−0.41
	3	161		−0.25



(I)



(II)

The number of 'aromatic' annulenes continues to increase as does interest in them, as evidenced by regular I.U.P.A.C. Symposia on Novel Aromatics. This indicates a need to increase the body of basic quantitative reactivity data for molecules of

Table 2. Exchange rate data for tritium exchange in the 1-positions of azulene and cycl[3,2,2]azine in acetic acid

Aromatic	Reaction	T/°C	10^7k/s^{-1}	f	σ^+
Azulene	Detritiation	25	920		
Azulene	Detritiation	45	6 800		
Azulene	Detritiation	70	59 500[a]	9.93×10^{13}	−1.60
Azulene	Tritiation	25	1 200		
Cycl[3,2,2]azine	Detritiation	70	26 000	4.34×10^{13}	−1.56
Cycl[3,2,2]azine	Tritiation	25	361		

[a] Value by extrapolation from the data at the lower temperatures.

revealed and has enabled us to account for, or reinterpret, some data in the literature for electrophilic substitution of non-benzenoid aromatic compounds.

Results and Discussion

AristaR acetic acid was used as the exchange medium, and previous work had shown that at 70 °C, detritiation in this acid is $10^{8.2}$ times slower than in anhydrous trifluoroacetic acid.[9,*] In acid media significantly stronger than this, both molecules underwent appreciable decomposition. For [1-^{3}H]cycl[3,2,2]-azine rate coefficients for detritiation could be measured directly at 70 °C, but for [1-^{3}H]azulene the exchange was considered too fast to measure reliably, so rate coefficients were measured at 25 and 45 °C, the value at 70 °C being determined by extrapolation. In order to ascertain if rate coefficients could be determined for any other positions tritiation was carried out for each compound up to the point at which appreciable decomposition occurred, thereby preventing further meaningful measurements. No significant additional exchange was detected, which indicated that the next most reactive site in each molecule was at least 100 times less reactive than the most reactive one. The rate data are given in Table 2. These show that detritiation is slightly slower than tritiation (a similar result having been found earlier for exchange in pentamethylbenzene[10]), and that at 25 °C tritiation of azulene is 3.32 times faster than tritiation of cycl[3,2,2]azine, in excellent agreement with the rate ratio of 3.39 found by Thomas and Long.[4] The partial rate factors are calculated by multiplying the rate coefficient by the rate ratio (1.58×10^8) which applies between acetic acid and trifluoroacetic acid at 70 °C, and then dividing by 0.095×10^{-7} s^{-1}, the rate coefficient for detritiation of benzene.[11]

From the previously reported[5] rate coefficients for deuteriation of a range of annulenes (and indole) in D_2O–dioxane at 50 °C, including azulene, and our partial rate factor for the latter, we are able to calculate partial rate factors and σ^+ values for all the compounds (Table 3). In so doing we make the assumption (not strictly correct) that the ρ factor for exchange in D_2O–dioxane at 50 °C is the same as for exchange in trifluoroacetic acid at 70 °C. However since the compounds are all fairly close in reactivity and very much more reactive than benzene the error introduced by this assumption is very small and is unlikely to produce an error in σ^+ of $> \pm 0.02$.

Table 3. Partial rate factors and σ^+ values for standard conditions for detritiation (TFA; 70 °C), and methyl substituent effects

				Methyl substituent effect	
Compound	Position	f	σ^+	Factor	Position
Indolizine	1	1.93×10^{16}	−1.86		
Indolizine	3	9.93×10^{16}	−1.94		
1-Methylindolizine	3	3.86×10^{17}	−2.01	3.89	*meta*
2-Methylindolizine	1	1.52×10^{17}	−1.96	7.85	*ortho*
2-Methylindolizine	3	8.83×10^{17}	−2.05	8.89	*ortho*
3-Methylindolizine	1	7.45×10^{16}	−1.93	3.85	*meta*
1,2-Dimethylindolizine	3	5.52×10^{18}	−2.14	55	*ortho* × *meta*
2,3-Dimethylindolizine	1	7.72×10^{17}	−2.05	40	*ortho* × *meta*
Indole	3	5.52×10^{13}	−1.57		
N-Methylindole	3	6.90×10^{13}	−1.58		
2-Methylindole	3	8.00×10^{14}	−1.70	14.5	*ortho*
N,2-Dimethylindole	3	1.38×10^{15}	−1.73	20.0	*ortho*
N-Methylisoindole	1	6.62×10^{13}	−2.04		
6-Methylpyrrolo-[2,1-*b*]thiazole[a]	7	1.19×10^{17}[b]	−1.95	?	*ortho*
	5	1.68×10^{18}	−2.08	?	*ortho*

[a] Incorrectly described in the literature as the 2-methyl compound with exchange at the 1- and 3-position. [b] Owing to a typographical error, the reported[5] rate coefficient was too large by 10^5.

this type, so that the contribution of each particular structural aspect to the reactivity may be more realistically assessed. We present in this paper rate data for detritiation of azulene and cycl[3,2,2]azine (**VIII**) in AristaR acetic acid, and hence have determined their partial rate factors under standard conditions (detritiation in anhydrous trifluoroacetic acid at 70 °C). Second-order rate coefficients for detritiation of these molecules in acetic acid of unknown purity were reported by Thomas and Long,[4] but partial rate factors could not be determined from this work, nor was it clear if exchange could be measured for other than the most reactive sites in each molecule. From the exchange data we have obtained, and previously reported rates of deuteriation of azulene, indolizine, *N*-methylisoindole, and indole, and various of their methyl derivatives in D_2O–dioxane, and also of 2-methylpyrrolo[2,1-*b*]thiazole under the same conditions,[5] we are able to determine partial rate factors and hence σ^+ values for all these compounds and analyse the data in terms of current theories of electrophilic aromatic substitution. Previously we have found the (generally neglected) Valence Bond Theory to be particularly successful in accounting for the positional reactivites in strained aromatics (benzcyclobutene, indane, biphenylene, triptycene, fluoranthene),[6] and in heterocycles (quinoline, isoquinoline, benzo[*b*]furan, benzo[*b*]thiophene),[7] and for both the substituent effects and positional reactivities in polycyclic aromatics (naphthalene, phenanthrene, anthracene).[8] In the present work the importance of the method is further

* In principle this factor will depend upon the reactivity of the aromatic compound. However compounds whose rate coefficient can be measured in acetic acid will all be of fairly similar reactivity, so the error introduced by using a constant value will be trivial.

Table 4. Positional reactivity indices for electrophilic substitution of azulene

Method[a]	Positions 1(3)	2	4(8)	5(7)	6	Order
π-Densities, HMO	1.173	1.047	0.855	0.986	0.870	1 > 2 > 5 > 6 > 4[b]
π-Densities, SCF	1.049	0.997	0.908	1.034	0.938	1 > 5 > 2 > 6 > 4
π-Densities, PP	1.096	0.979	0.879	1.049	0.948	1 > 5 > 2 > 6 > 4
π-Densities, VESCF	1.061	1.004	0.937	1.009	0.961	1 > 5 > 2 > 6 > 4
π-Densities, ω-techniques	1.118	1.048	0.905	0.976	0.916	1 > 2 > 5 > 6 > 4
Free valence	0.48	0.42	0.482	0.429	0.454	4 > 1 > 6 > 5 > 2[c]
Localization energy L_r^+	1.924	2.362	2.551	2.341	2.930	1 > 5 > 2 > 4 > 6
Localization energy L_r^w	0.598	1.072	1.425	1.093	1.525	1 > 2 > 5 > 4 > 6
Super-delocalizability	0.817	0.481	0.337	0.490	0.326	1 > 5 > 2 > 4 > 6
Brown's Z_r values	1.667	1.523	1.536	1.578	1.523	1 > 5 > 4 > 2 = 6

[a] All values taken from ref. 12. [b] In ref. 13, markedly different values are given for the 4-, 5-, and 6-position but the order remains the same. [c] Atom polarizability values give a similar, and incorrect order.

The main features of the results are as follows:

Azulene.—The σ^+ value for the 1-position gives a clear indication of just how reactive the molecule is, and it is worth noting that no polycyclic aromatic hydrocarbon has a σ^+ value exceeding −1.0. Azulene is very much more reactive than 1,6-methano[10]annulene, and the reason for the high reactivity is discussed below. Since exchange in the next most reactive site in azulene (most probably the 2-position) could not have taken place at a rate exceeding one hundredth of that of the 1-position we may place an upper limit on its σ^+ value of −1.37.

Reactivity indices for azulene[12] are shown in Table 4 and apart from free valence (usually an unsatisfactory parameter) each indicates that the 1-position should be the most reactive. However the values of both the electron densities and the positional reactivity order vary widely from method to method, and indeed some positions are predicted to be activated while others would be deactivated. None of the methods indicates the origin of the high reactivity of the 1-position. In view of these shortcomings we considered it worthwhile to see if Valence Bond Theory provides any better understanding, or a positional reactivity order comparable to those given above. In using this method here and subsequently we utilize the following well established requirements.

(i) Formation of an aromatic sextet in the transition state will be very favourable, whilst formation of an anti-aromatic structure will be unfavourable.

(ii) Positions adjacent to very reactive sites will also be activated, but to a lesser degree, through secondary relay. In Valence Bond terms this is represented by *meta*-bridged intermediates, *e.g.* (**III**) for benzene. Conversely, positions adjacent to very unreactive sites will also be deactivated but rather less so.

(**III**)

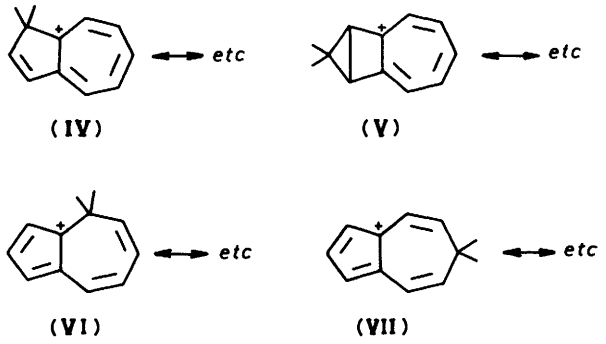
(iii) The maximum delocalization of charge will be favoured.

Substitution at the 1-position of azulene involves the canonical form (**IV**) which now contains an aromatic 6π seven-membered ring (with seven canonical forms). This is therefore exceptionally stable, so accounting for the very high reactivity of the 1-position. (Previous major reviews[14] stress only the ability to delocalize the positive charge, rather than the 6π-ring created in the transition state.) The 2-position should also be fairly reactive, through the stability of the structure (**V**). By contrast, reaction at the 4- or 6-position produces an anti-aromatic 4π five-membered ring [(**VI**), (**VII**)]. These positions will therefore be very unreactive, and the 5-position will also be unreactive but rather less so as a result of the secondary effect. In benzenoid chemistry, delocalization of charge to *para*-positions is more effective than to *ortho*-ones and if one may treat azulene in a comparable manner, then (**VII**) will be a more important canonical form than (**VI**) making 6-substitution more difficult than 4-substitution. In summary, this simple approach yields the reactivity order 1 > 2 > 5 > 4 > 6, comparable to those in Table 4 obtained by more sophisticated methods, but requiring very little effort. But especially interesting is our finding that this method can be applied to a large number of molecules, a few of which are described in this paper.

Table 5. Positional reactivity indices for electrophilic substitution of cycl[3,2,2]azine

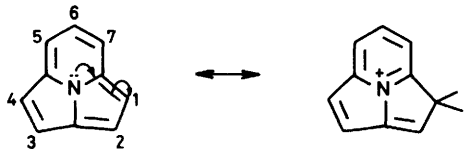
Method[a]	Positions 1(4)	2(3)	6	5(7)	Order
π-Densities, HMO	1.118	1.047	1.010	1.002	1 > 2 > 6 > 5
Localization energy L_r^+	2.108	2.253	2.402	2.291	1 > 2 > 5 > 6

[a] Calculations in an earlier paper[16] gave different values but used the wrong value of *h* for N having a lone pair in a *p*-orbital.



Cycl[3,2,2]*azine.*—This is slightly less reactive than azulene which is consistent with π-electron density, or localization energy calculations (Table 5)[15] which may be compared with those in Table 4 for similar methods. It will be seen that the

methods disagree as to the order for the least reactive sites (and the same was true for azulene, where 'crossing' also occurs) but each predicts the 1-position to be the most reactive. To find the *reason* for this high reactivity we again turn to Valence Bond Theory. Substitution at position 1 produces the intermediate (**VIIIa**) which now contains a 6π pyridinoid ring, absent in the ground state. The intermediate, and hence the transition state, is therefore of comparable aromaticity to the ground state, leading to the very high reactivity. The 2-position will also be fairly reactive through involvement of structure (**IX**). By contrast, reaction at the 5-position produces two anti-aromatic five-membered rings (**X**) so this will be unfavourable. The 6-position will be also unreactive by the secondary effect, but less so. This method therefore produces the order 1 > 2 > 6 > 5, the same as the π-density calculations, but very simply and with greater understanding.



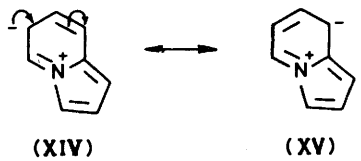
(VIII) (VIIIa)

(IX) (X)

We had hoped at commencement of this work to deduce information relating the reactivity and non-planarity of cycl[3,2,2]azine. The nitrogen in the planar form is sp^2 hybridized (and cannot therefore protonate) whereas in the non-planar form it is sp^3 hybridized (and can). The evidence shows that protonation only occurs at carbon,[4,17] so it is evidently fairly planar (as models also indicate). The inaccuracy of currently available MO calculations does not permit accurate conclusions. These predict the molecule to be less reactive than azulene, as observed, suggesting (but nothing more than that) the non-planarity of the ground state does not substantially increase the reactivity of the azine.

Indolizine.—This molecule (**XI**) is related to cycl[3,2,2]azine, and is more reactive at the comparable 1-positions by a factor of 445. Valence Bond Theory indicates the origin of this reactivity difference. The ground state for cycl[3,2,2]azine has two 10π-electron circuits whereas indolizine has only one, so the former compound should be the more stable. The exceptional reactivity of indolizine at the 1-and 3-position, like that at the 1-position of cycl[3,2,2]azine, derives from formation of the very stable 6π pyridinoid ring in the transition state (**XII**), (**XIII**); the 3-position is most reactive because there is greater delocalization of charge in (**XIII**).

(XI) (XII) (XIII)



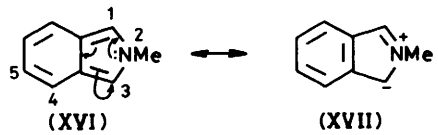
(XIV) (XV)

Rate coefficients (10^7 k/s^{-1}) for exchange at each position in indolizine in D_2SO_4 at 200 °C have been determined as follows:[18] >500 000(1,3); 1 300(2); 6(7); 4.6(5); 0.67(6); <0.1(8), so the overall positional reactivity order is 3 > 1 ≫ 2 ≫ 7 > 5 > 6 > 8, which may be compared with predictions of π-electron density, *viz.* 3 > 1 ≫ 2 > 5 > 7 > 6 > 8[18] (calculated either by the SCF method, or the HMO method using an auxiliary inductive parameter), and localization energies *viz.* 1 > 3.[19] The latter are clearly wrong, but the π-densities are quite good but do not indicate the origin of the reactivity differences and predict the 6- and 8-position to be deactivated; other π-density methods[15] give completely the wrong order. Valence Bond Theory is again very good here. As noted above the 1- and 3-position are very reactive because of the formation of the pyridinoid ring in the transition state, and the 2-position will be fairly reactive by secondary relay {*cf.* (**IX**) for cycl[3,2,2]azine}. By contrast, delocalization of charge into the six-membered ring (**XIV**), (**XV**) creates an anti-aromatic five-membered ring, so reaction at the 6- and 8-position will be unfavourable, especially at the 8-position since structure (**XV**) involves the maximum delocalization of charge. The 5- and 7-position will also be unreactive by the secondary effect (not so much as the 6- and 8-position) but it is not possible to distinguish the stabilities of the relevant canonical forms. The order predicted by the Valence Bond method is therefore the same as by the best of the π-electron density methods.

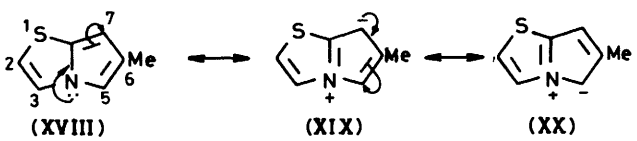
From the data above one may calculate maximum σ^+ values for the other positions in indolizine as −1.57 for the 2-position and −1.30 for the 5—8-positions. There may be a substantial error here (perhaps as much as 0.2 σ units) because the exchange conditions are so very different. Nevertheless it is clear that all positions are very reactive.

The effects of methyl substituents in indolizine are very small (f_o^{Me} and f_m^{Me} in detritiation of benzene are 220 and 6.1, respectively[20]) and this is consistent with the extreme reactivity of the molecule and the prediction of the reactivity–selectivity principle (*i.e.* the transition state is significantly nearer to the ground state). The 3-position is also activated more by the 2-methyl substituent than is the 1-position, which follows from the higher order of the 2,3-bond compared with the 1,2-bond, indicated by the Valence Bond structure (**XI**). This is also evident in the greater activation of the 3-position by 1,2-dimethyl groups than of the 1-position by 2,3-dimethyl groups.

N-*Methylisoindole.*—This compound (**XVI**) undergoes exchange at the 1-position, and is the most reactive compound given in Table 3; indeed its σ^+ value of −2.04 shows it to be the most reactive (unsubstituted) aromatic compound yet known. Both these features are explained by Valence Bond Theory.



(XVI) (XVII)



(XVIII) (XIX) (XX)

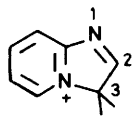
Reaction at the 1-position creates the exceptionally stable benzenoid ring in the transition state (**XVII**). This is not the case for 4- or 5-substitution so these positions will be much less reactive, and indeed there have been no reports of substitution at either of them; the principle of maximum delocalization of charge suggests that the 4-position would be the more reactive.

6-*Methylpyrrolo*[2,1-b]*thiazole*.—This molecule (**XVIII**) is also very reactive and this can be seen to be due to formation of a 6π five-membered aromatic (thiazole) ring in the transition states for 7- and 5-substitution (**XIX**), (**XX**). The 5- and 7-position are conjugated with both sulphur and nitrogen, and maximum delocalization from each should make the 5-position more reactive, as should the greater activation of methyl across the 5,6-bond, indicated by the Valence Bond structure (**XVIII**) to be of higher order. This is observed. Similar arguments account for the electrophilic substitution at sites, equivalent to the 5- and 7-position in (**XVIII**), which have been reported for imidazo[2,1-*b*]thiazole, imidazo[1,2-*a*]imidazole, pyrrolo[2,1-*b*]benzothiazole, imidazo[2,1-*b*]benzothiazole, imidazo[5,1-*b*]benzothiazole, pyrrolo[1,2-*a*]benzimidazole, pyrrolo[2,3-*a*]imidazole, imidazo[5,1-*b*]benzimidazole, and imidazo[2,1-*b*]-1,3,4-thiadiazole.[21]

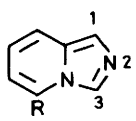
Indole.—The results provide the first σ^+ value for electrophilic substitution in indole. In acetylation the 2-position of pyrrole was found to be approximately twice as reactive as the 3-position in indole,[22] and this reflects the general pattern, *viz*. that benzo homologues are generally less reactive than the five-membered π-excessive heterocycles. For exchange the 2-position of pyrrole σ^+ has been determined[23] as *ca*. −1.70 so the value of −1.57 for the 3-position in indole from the present work is at least qualitatively consistent with the acetylation result. The small (*ortho*) activation of the 3-positions by 2-methyl in indole and *N*-methylindole are again consistent with the very high reactivity of the molecule.

Interpretation of the Reactivity of Other Heterocycles by the Valence Bond Method.—The Valence Bond method, emphasized in this paper, readily explains both the positional reactivities (and substituent effects) in a large number of heterocycles, and we give here a few examples taken from the recent literature where the method has been overlooked.

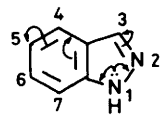
(i) *Nitration and bromination of imidazo*[1,2-a]*pyridine*. This goes exclusively in the 3-position[24] which follows from the formation of a 6π-pyridinoid transition state (**XXI**).



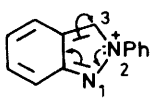
(**XXI**)



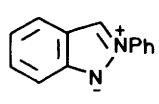
(**XXII**)



(**XXIII**)



(**XXIV**)



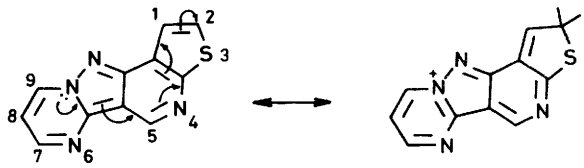
(**XXV**)

(ii) *Formylation of indolizine and imidazo*[1,5-a]*pyridine* (**XXII**; R = H). This goes primarily into the 3-position of the former, but 72% into the 1-position and only 28% into the 3-position of the latter.[25] These results were considered inconsistent and it was proposed that the preferential 3-substitution in indolizine must arise from co-ordination of the formylation electrophile with the bridgehead nitrogen.[25] However, 3-substitution in indolizine is the *predicted* result, confirmed by the hydrogen exchange data. Valence Bond Theory predicts that in imidazo[1,5-*a*]pyridine the 2,3-bond must be of higher order than the 1,2-bond; consequently deactivation by N-2 across the former bond will be considerably greater, and the observed results then follow. For (**XXII**; R = Me) substitution went 100% into the 1-position. This was not explained, but must certainly be a steric effect (from the 5-methyl group) to which acylations are particularly susceptible.

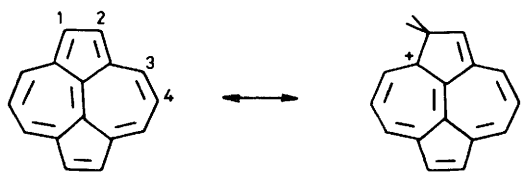
(iii) *Bromination of* 1H-*indazole* (**XXIII**) *and* 2-*phenyl*-2H-*indazole* (**XXIV**). The former gives the 3,5-dibromo derivative whereas the latter brominated readily (at room temperature) to give exclusively the 3-bromo derivative (and no substitution in the phenyl ring).[26] This was found puzzling but again Valence Bond Theory shows the result to be expected. 1*H*-Indazole brominates at the 3- and 5-position through normal conjugative electron release from nitrogen as shown in (**XXIII**) (a small amount of the 3,7-dibromo product could also have been expected). By contrast 2-phenyl-2*H*-indazole brominates very readily and exclusively at the 3-position because a benzenoid transition state is produced through the electron movements shown in (**XXIV**). Moreover, conjugation of the lone pair from N-2 onto N-1 also involves a very stable benzenoid canonical form (**XXV**), thereby making delocalization of the lone pair from N-2 into the phenyl ring very unfavourable.

(iv) *Nitration of thieno*[3″,2″:5′,6′]*pyrido*[4′,3′:3,4]*pyrazolo*-[1,5-a]*pyrimidine* (**XXVI**). This went into the thiophene ring (79%) and it was assumed (by analogy with the preferred β-site of substitution in benzo[*b*]thiophene) that it had entered the 1-position.[27] However the Valence Bond method indicates that formation of the aromatic 6π-pyrimidinoid canonical form (**XXVII**) in the transition state will outweigh all other considerations and therefore substitution will take place at the 2-position. This is also confirmed by the fact that methyl groups at either the 7- or 9-position (which can conjugate with the 2- but not the 1-position) caused the yield of the corresponding product to increase to 81%, which would not be the case if nitration occurred at the 1-position of the parent. It should also be noted that substitution at the β-position of benzo-[*b*]thiophene is only preferred to α-substitution in order better to preserve the benzenoid character of the six-membered ring. In (**XXVI**) however the six-membered ring adjacent to the thiophene ring is not benzenoid so this constraint does not apply anyway.

(v) *Electrophilic substitution in azupyrene* (**XXVIII**). Both hydrogen exchange and trifluoroacetylation take place at the 1-position of this molecule, whereas electron densities calculated by the MNDO method indicate that the 4-position should be the most reactive.[28] Valence Bond Theory predicts 1-substitution because a 6π aromatic ring is created in the transition state (**XXIX**).

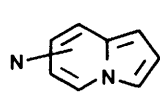


(**XXVI**) (**XXVII**)

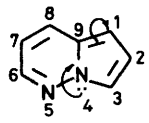


(**XXVIII**) (**XXIX**)

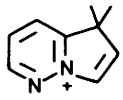
(vi) *Protonation of azaindoles* (**XXX**). These compounds protonate at nitrogen in the six-membered ring except for pyrrolo[1,2-*b*]pyridazine (**XXXI**) which protonates at C-1, a difference in behaviour which could not be rationalized.[29] We suggest that (**XXXI**) protonates at C-1 because this gives the structure (**XXXII**) which contains a 6π aromatic ring (as indeed does protonation of all the azaindoles), but in addition is one in which the N-4–C-9 bond is of high order. Since it is well established that this bond in pyridazine is of exceptionally high order,[30] structure (**XXXII**) should be particularly stable, and the observed behaviour follows. Application of the principle of maximum delocalization of charge to the conjugative withdrawal of electrons by N-5 from C-1 or C-3 indicates preferential protonation at C-1.



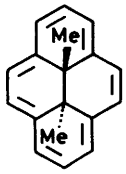
(**XXX**)



(**XXXI**)



(**XXXII**)



(**XXXIII**)

Attempted Exchange-rate Measurement in trans-9,10-*Dimethyldihydropyrene*.—The report that *trans*-9,10-dimethyldihydropyrene (DHP) (**XXXIII**) could be recovered in 88% yield from the reaction with deuteriated trifluoroacetic acid during 2 min at room temperature[31] led us to expect that, at much lower acidities, kinetic data could be obtained for exchange. The literature report indicated that all the aromatic protons exchanged, since their signals disappeared in the aromatic region of n.m.r. spectrum.

We therefore tritiated the compound in a mixture of 25 vol % trifluoroacetic acid in acetic acid during 42 h at 70 °C. However the mixture showed a quite rapid loss of the green colour (of DHP) and chromatography confirmed that a substantial amount of a pink decomposition product was produced. The identity of this by-product could not be ascertained on the amount of material available. Kinetics were carried out on the recovered, purified, and tritiated (partially or fully) material, using 40 vol % trifluoroacetic acid in acetic acid at 70 °C (Table 6). These showed an initial rapid loss of tritium which became replaced by a much slower loss of tritium, and during the slow portions of the runs the samples had largely lost their green colour. The rates of the fast reaction (determined by the usual back-extrapolation technique) were not reproducible, the coefficients varying from 8 100 × 10^{-7} s^{-1} to 13 800 × 10^{-1} s^{-1}, and these were not significantly altered by carrying out the reactions in the dark. The rate coefficient for the slow reaction was *ca.* 120 × 10^{-7} s^{-1}. The proportion of activity loss *via* the fast relative to the slow reaction also varied from 58 to 35%, the proportion being higher the slower the initial reaction. An additional feature is that the green colour of DHP causes *extreme* quenching (so much so that runs could only be carried out with *very* dilute solutions). The amount of quench correction needed for each sample during a run diminished with time, showing that DHP was being lost; subsequent experiments confirmed that the pink by-product was also a quencher, though a much less effective one. The amount of initial quenching also varied from run to run, being higher the greater the proportion of tritium loss proceeding *via* the fast reaction (and giving the 'slowest' fast reaction). The observed results are consistent with the following.

(i) Fast loss of tritium arises from a combination of exchange and decomposition of DHP.

(ii) Decomposition may be surface catalysed. This would cause it to be less important the higher the initial concentration of DHP. A higher initial concentration of the latter is shown by higher initial quenching.

(iii) The slow loss of tritium is due to exchange in the by-product.

In an event to circumvent or minimize these problems, runs were carried out in weaker media (Table 6). However, in both 15 and 25 vol % TFA in HOAc slowing of the kinetic runs and loss of green colour was observed. Furthermore in the latter medium, the pattern of correlation between percentage of initial quenching *versus* proportion of exchange *via* the fast and slow reactions *versus* magnitude of the initial rate was repeated. The differences in exchange rates for the fast runs between the different media were smaller than that which is normally obtained,[9] further indicating that abnormalities were present.

The most reliable result is probably that obtained in the least acidic medium (15 mol % TFA in HOAc) in which exchange normally occurs *ca.* 840 times faster than in acetic acid.[9] If we make the assumption that *all* the tritium loss in this medium is due to exchange, this gives a rate coefficient for the fast reaction in acetic acid as 0.55 × 10^{-7} s^{-1}. From the comparison with azulene we may calculate σ^+ as *ca.* −1.0. The true value cannot be greater than this and must be less because of the assumption which we make. Nevertheless it provides some indication of the upper limit of the reactivity of DPH, and is comparable with that for other 14-annulenes.[32]

Experimental

The general method for carrying out the kinetic studies have been described,[33] but was modified for detritiation runs at 25

Table 6. Detritiation of *trans*-9,10-dimethyldihydropyrene in trifluoroacetic acid–acetic acid at 70 °C

Vol % TFA in HOAc	10^7k(fast)/s^{-1}	10^7k(slow)/s^{-1}	Proportions of tritium loss *via* fast reaction (%)	Initial quenching (%)
15	460	10	51	38
25	1 150	21	58	43
25	1 280	21	54	39
40	8 200	120	65	53
40	9 600	Not measured	56	32
40	11 300	115	42	24
40	13 800	120	35	19

and 45 °C in that portions were withdrawn from a stock solution instead of sealed ampoules being used. Quench correction was carried out by adding a volume of pentamethylbenzene of known specific activity to each sample after the initial count had been obtained. Subtraction of this latter value from the total in the presence of pentamethylbenzene gave the count due to the latter. The ratio of this count to that which was obtained in the absence of the quencher gave the quench-correction factor.

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