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The reactivity of phenyl radicals in abstraction reactions toward some heteroaromatic compounds

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THE REACTIVITY OF PHENYL RADICALS IN ABSTRACTION REACTIONS TOWARD SOME HETEROAROMATIC COMPOUNDS

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The results summarized in this thesis represent an effort to obtain more information on the abstraction reaction of the phenyl radical toward alkyl substituted heteroaromatic compounds. The procedure of competitive reactions (1) was used because the measurement of the rates of reactions of free radicals in solution is experimentally difficult. In the competitive method two compounds compete for a reactive intermediate which is present in quite small concentration in comparison to the competing substrates.

Experimentally the same data are taken as in a kinetic study, except for the elimination of the time variable. The competitive method developed by Bridger and Russell (2-4) for the study of phenyl radicals was used to obtain data in the form of relative rates.

Comparison of the relative rates of abstraction of α-hydrogen atoms from various methyl-substituted heteroaromatic compounds has been used as a measure of the stability of the resultant hetero benzylic type radicals.

LITERATURE REVIEW

The first systematic investigation of the abstraction reactions of the phenyl radical was carried out by Russell and Bridger (2-4). Most studies with phenyl radicals have dealt with homolytic arylation (5-19) although other workers have also done some investigations on the abstraction reactions of the phenyl radical (6, 14, 19-25). The two most frequently used phenyl radical generators are phenylazotriphenylmethane (PAT) and benzoyl peroxide. Thermal decomposition of benzoyl peroxide not only gives benzene but also benzoic acid and complicated products. Bridger (2-4) has shown that PAT is the most ideal generator of phenyl radicals.

The thermal decomposition of PAT in a mixture of two solvents may be represented by the following equations:

$$Ph\text{-}N{=}N\text{-}CPh_3 \longrightarrow Ph\cdot + N_2 + Ph_3C\cdot \qquad (1)$$

$$Ph\cdot + CCl_4 \xrightarrow{4k(Cl)} PhCl + Cl_3C\cdot \qquad (2)$$

$$Ph\cdot + RH \xrightarrow{\Sigma n_i k_i(H)} PhH + R\cdot \qquad (3)$$

$$Ph_3C\cdot + Cl_3C\cdot + R\cdot \longrightarrow \text{non-radical products}, \qquad (4)$$

where Ph = C_6H_5,

RH = an organic compound capable of transferring hydrogen atoms to the phenyl radical,

k(Cl) = rate constant for abstraction reaction at a single carbon-chlorine bond of carbon tetrachloride,

$k_i(H)$ = rate constant for abstraction at a carbon-hydrogen bond of order (type) i,

and n_i = number of carbon-hydrogen bonds of order (type) i.

The kinetic expressions may be reduced to

$$\frac{\Sigma n_i k_i(H)}{4k(Cl)} = \frac{(PhH)(CCl_4)}{(PhCl)(RH)} \qquad (5)$$

where (PhH) and (PhCl) are the amounts of benzene and chlorobenzene formed from solutions containing (CCl_4) and (RH) molar concentrations of carbon tetrachloride and hydrocarbon RH.

Three assumptions involved in the derivation of equation 5 are: (a) Reactions 2 and 3 are each of the same molecularity in phenyl radical concentration and unimolecular in the concentration of substrate. (b) Reactions 2 and 3 are the only source of chlorobenzene and benzene respectively. (c) The ratio of the concentration of carbon tetrachloride and the hydrogen containing substrate remains constant during reaction. Assumptions (a) and (b) have been experimentally tested and shown to be valid by Bridger (2-4), (c) may be controlled by proper experimental conditions so that any change in concentration of carbon tetrachloride or hydrocarbon is negligible. This is done experimentally by using only a 0.1 M solution of PAT in a solvent composed of equimolar amounts of carbon tetrachloride and hydrocarbon.

The decomposition of PAT in pure carbon tetrachloride has been shown to always yield some benzene (2, 4). The benzene

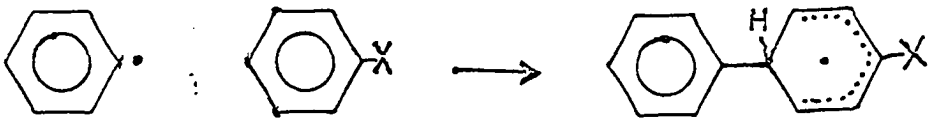
has been ascribed to a cage reaction. The yield of benzene does vary slightly with initial PAT concentration, although it does not approach zero at infinite dilution, so that a second route to benzene involving a reaction of some radical with PAT itself or one of its decomposition products has been proposed. That this yield of benzene can be used as a correction factor has been justified by Bridger (2-4) in the fact that the yield of benzene did not significantly increase when the solvent was changed to pure chlorobenzene from carbon tetrachloride or when mixtures of carbon tetrachloride with diphenyl ether, biphenyl or triphenylamine were used.

The use of PAT rather than peroxides in the competitive reactions was shown to be favorable due to the high concentration of trityl radicals. The trityl radicals help prevent free radical chain processes by reacting with the trichloromethyl radicals and hydrocarbon radicals (20, 21).

Benzoyl peroxide has been used by Russian workers (23, 24) in measuring simultaneously the abstraction and homolytic arylation reactions of substituted aromatic compounds by the competitive method in carbon tetrachloride. Trosman and Bagdasaryan (23, 24) claim that by use of low concentrations of benzoyl peroxide, free radical chain processes have negligible effect on the relative rate constants. They determined that the radical chain reaction in an equimolar mixture of benzaldehyde and carbon tetrachloride only 0.00638 mole of

chloroform were obtained from 0.034 mole of benzaldehyde (23) and that therefore the effect on the RH/CCl_4 ratio was negligible.

The mechanism of aromatic phenylation (6-12) may be represented by



(6)

(7)

In the case where phenyl radical is generated from PAT, R· in equation 7 represents trityl radicals. Where the phenyl radical is generated from benzoyl peroxide, R· is usually a phenyl or benzoyloxy radical. Thus in the case of benzoyl peroxide, benzene can arise from the process of aromatic phenylation rather than completely from the desired abstraction of a side chain hydrogen atom. The use of dilute concentrations of benzoyl peroxide (0.01-0.04 M) may lessen the extent of benzene formation in reaction 7. The products of the reaction of benzoyl peroxide with benzene at this low concentration are known to include carbon dioxide, benzoic acid, biphenyl, dihydrobiphenyl, phenyl benzoate and isomers of tetrahydroquarterphenyl. Higher concentrations (0.04-0.10 M) give

isomeric quaterphenyls, phenylbenzoic acids and terphenyls (17). A comparison of the data obtained by Bridger and Russell (2-4) using 0.096 M PAT at 60° with that of Vazilevskii (22) using 0.01 M PAT at 60°C, and Trosman and Bagdasaryan (23, 24) using 0.01 M benzoyl peroxide at 100°C is shown in Table 1.

Table 1. Comparison of the phenyl radical reactivities of various workers in hydrogen abstraction reactions

Compound	Bridger (2, 4)		Vazilevskii (22)		Trosman and Bagdasaryan (23, 24)	
toluene	0.27[a]	(1)[b]	0.32[a]	(1)[b]	0.32[a]	(1)[b]
t-butylbenzene	0.11	0.407	0.11	0.344	0.16	0.50
tetramethylbutane	0.18	0.667	0.18	0.563		
cumene	0.93	3.44			0.825	2.58
diphenylmethane	1.40	5.18			1.05	3.28
p-xylene	0.79	2.92			0.95	2.96
p-chlorotoluene	0.29	1.07			0.255	0.80
p-nitrotoluene	0.22	0.81				0.80[c]

[a]Total Reactivity.

[b]Reactivity compared to value of toluene taken as one.

[c]Value obtained by competitive experiment using toluene and p-nitrotoluene.

Since this work is a continuation of work done by Bridger (2-4) further discussion of his results will be given in the discussion section of this work when needed.

RESULTS

The reactivities of a number of carbon-hydrogen bonds α to heteroaromatics have been determined toward phenyl radicals. Some of the ring systems investigated are shown in Figure 1. The technique, described in detail in the experimental section, involves the use of gas-liquid chromatography (GLC) to determine the amounts of benzene and chlorobenzene formed during the complete decomposition of 0.1 M solution of PAT at 60°C in a mixture of carbon tetrachloride and the heteroaromatic compound.

Definitions used in this thesis are:

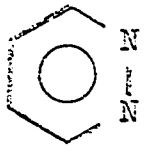
1. Total Reactivity, or reactivity per molecule, of compound RH is the reactivity toward phenyl radical relative to that of carbon tetrachloride, the reference solvent. It is defined by

$$\text{Total Reactivity} = \frac{\Sigma n_i k_i(H)}{4k(Cl)} = \frac{(CCl_4)(PhH - corr.)}{(RH)(PhCl)},$$

where corr. is the correction factor applied to benzene to account for benzene formed during the decomposition of the sample of PAT used in pure carbon tetrachloride. Mole ratios are used for carbon tetrachloride and the hydrogen-containing substrate. Yields of benzene and chlorobenzene are expressed in moles/mole PAT.

2. Reactivity per bond is that value obtained for reactivity after statistical corrections have been made for the

Figure 1. Structures of some of the ring systems investigated

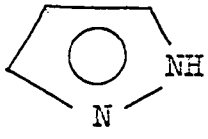


pyridazine

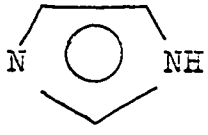
pyrimidine

s-tetrazine

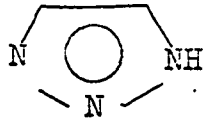
triazine



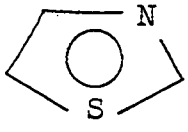
pyrazole



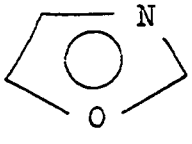
imidazole



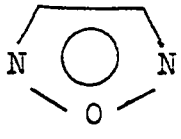
triazole



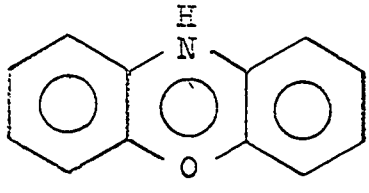
thiazole



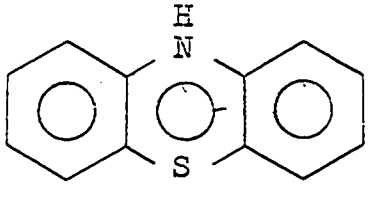
oxazole



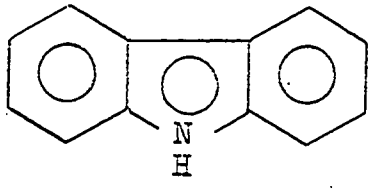
furazan



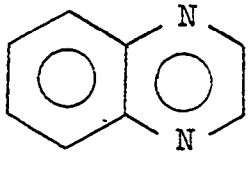
phenoxazine



phenothiazine



carbazole



quinoxaline

number of bonds in RH and CCl_4. For a carbon-hydrogen bond of type i it is equal to $k_i(H)/k(Cl)$.

3. Enhancement of reactivity is defined as reactivity per bond divided by the reactivity of the analogous paraffinic carbon-hydrogen bond.

The precision of the data varies, depending upon the reactivity of the compound under investigation. Using the range of duplicate or multiple determinations as a measure of precision, the relative error in total reactivities ranges between $\pm$ 3 to 15%. Errors are greater for unreactive compounds or those where the total yield of benzene and chlorobenzene is low due to the ease with which the phenyl radical adds to the heteroaromatic compound.

All data are summarized in tabular form on the following pages. Because some of the compounds were fairly insoluble in carbon tetrachloride the co-solvent used is also listed along with an indication of the correction factor for the sample of PAT used. Samples in which dimethyl sulfoxide (DMSO) was used as a co-solvent are corrected for the yield of benzene produced from the solvent, by using the value of 0.039 for the Total Reactivity of DMSO (2, 4).

Table 2. Reactivities of compounds toward the phenyl radical at 60°C

Reaction number	Compound	$\frac{(CCl_4)}{(RH)}$	Yield[a] benzene	Yield[a] chloro-benzene	Total yield[a]	Total reac-tivity[b]	Co-solvent
1a	Methylferrocene	1.06	0.110	0.485	0.603	0.270[c]	
1b		2.13	0.092	0.412	0.504	0.269[c]	Bromobenzene
1c		2.13	0.066	0.415	0.481	0.133[c]	Nitrobenzene
2a	10-Methylphenoxazine	2.45	0.370	0.396	0.766	2.04[d]	
2b		2.45	0.342	0.390	0.732	1.89[d]	
3a	N-Methylphenothiazine	3.60	0.190	0.416	0.606	1.29[d]	Bromobenzene
3b		3.60	0.204	0.414	0.618	1.42[d]	Bromobenzene
3c		3.73	0.145	0.468	0.613	0.827[d]	Sat. at 60°C
3d		1.24	0.186	0.240	0.426	0.750[d]	Nitrobenzene
4a	N-Methylcarbazole	1.38	0.0963	0.274	0.3703	0.278[d]	Nitrobenzene
4b		1.20	0.0807	0.258	0.3387	0.185[d]	Pyridine
4c		2.05	0.129	0.358	0.487	0.504[d]	Bromobenzene
4d		2.05	0.126	0.344	0.470	0.506[d]	Bromobenzene
5a	1-Methylpyrazole	0.995	0.114	0.584	0.698	0.124[d]	
5b		1.16	0.119	0.616	0.735	0.147[d]	

[a]Mole/mole PAT.

[b]$\frac{\Sigma n_i k_i(H)}{4k(Cl)} = \frac{(CCl_4)(PhH - corr.)}{(RH)(PhCl)}$.

[c]Corr. = 0.054.

[d]Corr. = 0.041.

Table 2. (continued)

Reaction number	Compound	$\frac{(CCl_4)}{(RH)}$	Yield benzene	Yield chloro-benzene	Total yield	Total reac-tivity	Co-solvent
6a	3(5)-Methylpyrazole	0.474	0.199	0.511	0.710	0.146[d]	
6b		0.474	0.197	0.506	0.703	0.146[d]	
7a	1-Methylimidazole	0.693	0.0412	0.290	0.331	0.0005[d]	
7b		0.693	0.0420	0.294	0.336	0.0024[d]	
8a	2-Methylbenzofuran	0.987	0.232	0.320	0.552	0.590[d]	
8b		0.987	0.232	0.318	0.550	0.575[d]	
9a	3-Methylfuran	0.548	0.0556	0.0895	0.1451	0.0894[d]	
9b		0.548	0.0528	0.0906	0.1434	0.0714[d]	
9c		0.548	0.0518	0.0956	0.1474	0.0619[d]	
9d		0.548	0.0444	0.0880	0.1324	0.0212[d]	
10a	3-Methylbenzofuran	0.963	0.0473	0.1205	0.168	0.0479[d]	
10b		0.963	0.0475	0.1150	0.163	0.0542[d]	
11a	2-Methylbenzothiophene	1.41	0.147	0.350	0.497	0.429[d]	
11b		1.96	0.129	0.438	0.567	0.392[d]	
12a	3-Methylbenzothiophene	0.838	0.1146	0.240	0.355	0.257[d]	DMSO
12b		0.870	0.1050	0.246	0.351	0.226[d]	
12c		0.870	0.1060	0.246	0.352	0.230[d]	
13a	2-Methylthiazole	0.685	0.218	0.412	0.630	0.294[d]	
13b		0.685	0.221	0.420	0.641	0.294[d]	

Table 2. (continued)

Reaction number	Compound	$\frac{(CCl_4)}{(RH)}$	Yield benzene	Yield chloro-benzene	Total yield	Total reac-tivity	Co-solvent
14a	2-Methylbenzothiazole	0.758	0.186	0.382	0.568	0.288[d]	
14b		0.758	0.185	0.383	0.568	0.285[d]	
15a	5-Methylthiazole	0.674	0.191	0.350	0.541	0.289[d]	
15b		0.674	0.188	0.346	0.534	0.286[d]	
16a	4-Methylthiazole	1.08	0.145	0.447	0.592	0.237[d]	
16b		1.08	0.128	0.423	0.551	0.222[d]	
17a	2-Methylbenzotriazole	1.32	0.036	0.310	0.346	-- [d]	
17b		0.461	0.0456	0.156	0.202	0.014[d]	
18a	1-Methylbenzotriazole	0.679	0.048	0.210	0.258	0.023[d]	Nitrobenzene
19a	2-Methylbenzimidazole	1.60	0.107	0.452	0.559	0.233[d]	DMSO
19b		1.60	0.127	0.459	0.586	0.300[d]	DMSO
20a	2-Methylbenzoxazole	0.676	0.146	0.403	0.599	0.176[d]	
20b		0.676	0.145	0.399	0.544	0.177[d]	
21a	Dimethyl s-tetrazine	2.06	0.0434	0.262	0.305	0.019[d]	
22a	3-Methylpyridazine	1.28	0.0787	0.520	0.599	0.0927[d]	
22b		1.28	0.0855	0.544	0.629	0.105[d]	
23a	4-Methylpyridazine	0.723	0.120	0.438	0.558	0.130[d]	
23b		0.723	0.125	0.456	0.581	0.133[d]	

Table 2. (continued)

Reaction number	Compound	$\frac{(CCl_4)}{(RH)}$	Yield benzene	Yield chloro-benzene	Total yield	Total reac-tivity	Co-solvent
24a	2-Methylpyrimidine	0.567	0.164	0.460	0.604	0.152[d]	
24b		0.567	0.167	0.450	0.617	0.159[d]	
25a	4-Methylpyrimidine	0.977	0.124	0.527	0.651	0.154[d]	
25b		0.977	0.129	0.537	0.666	0.160[d]	
26a	5-Methylpyrimidine	0.535	0.187	0.388	0.575	0.201[d]	
27a	4-Methylpyridine	0.814	0.139	0.512	0.651	0.156[d]	
27b		0.814	0.144	0.512	0.656	0.164[d]	
28a	2-Methylpyridine	0.546	0.174	0.400	0.574	0.182[d]	
28b		0.546	0.175	0.398	0.573	0.184[d]	
29a	3-Methylpyridine	0.560	0.197	0.424	0.621	0.206[d]	
29b		0.560	0.204	0.415	0.619	0.220[d]	
30a	2,4,6-Trimethyl-1,3,5-triazine	3.48	0.250	0.490	0.740	1.48[d]	DMSO
31a	2,3-Dimethylquin-oxaline	0.986	0.126	0.228	0.354	0.368[d]	Bromobenzene
31b		1.29	0.090	0.199	0.289	0.318[d]	Pyridine
31c		1.37	0.122	0.277	0.399	0.403[d]	Bromobenzene
32a	6,7-Dimethylquin-oxaline	2.51	0.101	0.248	0.349	0.607[d]	Bromobenzene
32b		0.935	0.114	0.123	0.237	0.555[d]	Bromobenzene

Table 2. (continued)

Reaction number	Compound	$\frac{(CCl_4)}{(RH)}$	Yield benzene	Yield chloro-benzene	Total yield	Total reac-tivity	Co-solvent
33a	Dimethylfurazan	0.800	0.213	0.570	0.783	0.242[d]	
33b		0.800	0.220	0.590	0.810	0.243[d]	
34a	2,2'-Dipyridylmethane	2.40	0.167	0.517	0.684	0.523[c]	
34b		2.34	0.161	0.524	0.685	0.535[d]	
35a	2,2'-Dibenzothiazolyl-methane	2.75	0.271	0.336	0.607	1.88[d]	
35b		2.75	0.285	0.335	0.620	2.00[d]	
36a	Diferrocenylmethane	6.72	0.167	0.337	0.504	2.51[d]	Sat. at 60°C, Bromobenzene
36b		6.72	0.168	0.341	0.509	2.52[d]	Sat. at 60°C, Bromobenzene
37a	2,2'-Difurylmethane	1.00	0.326	0.0977	0.424	2.78[c]	
38a	2-Furyl-2-thienyl-methane	1.24	0.336	0.139	0.475	2.53[c]	

DISCUSSION

Since it was known that radicals can be subject to solvent effects by complexing of the free radical with certain classes of compounds, especially aromatics, Bridger (2-4) determined that there were no special solvent effects in the abstraction reactions of phenyl radicals. In the present study it was necessary to use co-solvents because of the insolubility of some of the compounds in carbon tetrachloride. Some solvents used in this work appeared to have an effect on the total reactivity of certain compounds with the phenyl radical. It was found that nitrobenzene caused a significant decrease in the reactivity of methylferrocene compared to its reactivity in carbon tetrachloride alone or in a mixture of carbon tetrachloride and bromobenzene. The anomalous results with the nitrobenzene, in which the yield of benzene dropped but the yield of chlorobenzene remained about the same as that with the bromobenzene co-solvent, appears to be the result of the formation of a charge transfer complex with the methylferrocene or oxidation of the ferrocene to ferrocenium ion (26). Nitrobenzene is a good oxidizing agent readily forming the nitrobenzene radical anion (27). It has been shown that the phenyl radical from PAT reacts with the ferrocenium ion to form phenylferrocene but not with the neutral ferrocene molecule (28). Nitrobenzene also appears to give anomalous results with methylphenothiazine and methylcarbazole. These

results may also be due to oxidation of the compound or complex formation. In other words the nature of the hydrocarbon substrate is changed causing a change in the measured reactivity. This is not, therefore, a true solvent effect. Where the substrate is subject to hydrogen-bonding, the reactivity of the substrate has also been found to be subject to solvent effects (25, 29).

Bridger and Russell (2-4) have shown that most substituents have small effects on the reactivities of α-hydrogen atoms toward phenyl radicals. They found that the following substituents, nitro, methylsulfinyl, acetyl, cyano, carbomethoxy, carboxyl, and chloro have an activating influence of less than fourfold whereas phenyl or vinyl substituents activate by about tenfold. The amino and mercapto groups had large effects on reactivity with enhancements of 31-40 and 11-14 respectively.

These substituents were assumed to stabilize the incipient alkyl radical by resonance of the type

$$\text{>}\ddot{\text{N}}-\dot{\text{C}}\text{H}_2 \leftrightarrow \text{>}\dot{\overset{\oplus}{\text{N}}}-\ddot{\text{C}}\overset{\ominus}{\text{H}}_2$$

$$-\ddot{\underset{\cdot\cdot}{\text{S}}}-\dot{\text{C}}\text{H}_2 \leftrightarrow -\dot{\overset{\oplus}{\underset{\cdot\cdot}{\text{S}}}}-\ddot{\text{C}}\overset{\ominus}{\text{H}}_2 \qquad (8)$$

A series of heterocyclics with methyl substituted on nitrogen is given in Table 3 with the relative enhancement of reactivity compared to a normal alkane. The effect on the rate enhancement can be seen as an involvement of the electron pair on nitrogen in delocalization through the phenyl rings. The

Table 3. Relative rate enhancement of some N-methyl substituted heterocycles

Reaction number	Substituent Z	Rate enhancement[a] 1° hydrogen Z-CH_3
	Alkyl[b]	(1)
2	10-phenoxazine	55.5
3	N-phenothiazine	38.4
4	N-carbazole	14.3
	N-pyrrole[c]	8.6
5	1-pyrazole	3.84
7	1-imidazole	.04

[a]Reactivity of an α-carbon-hydrogen bond relative to a molecule of carbon tetrachloride divided by the reactivity of the same bond type in a normal alkane.

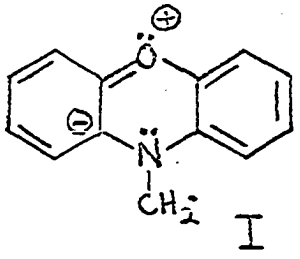
[b]Reactivity of 1° hydrogen in a normal alkane taken as $\frac{k\alpha(H)}{4k(Cl)} = 0.0117$, reference 4.

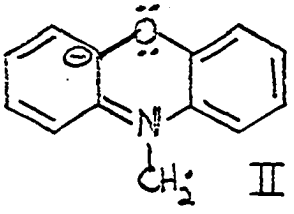
[c]Reference 4.

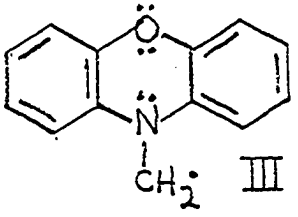
more the electron density of the p-orbital on nitrogen is decreased by conjugation the less the stabilization of the incipient alkyl radical due to such structures as 8. The nature of sigma and pi radicals and their relative stability has been discussed by Symons (30).

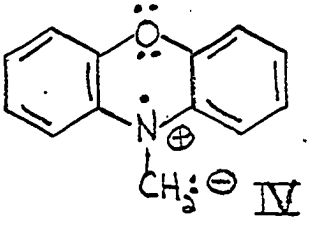
If the conformation of 10-methylphenoxazine is planar some of the resonance structures that can be drawn for the

incipient radical are

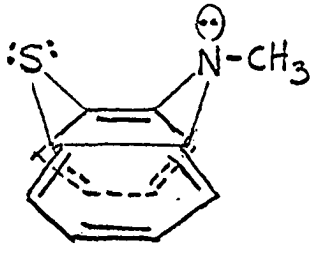

I


II


III


IV

Resonance structures such as I would tend to counteract those of II and therefore make IV a large contributor to the overall picture of the incipient alkyl radical. The structure of N-methylphenothiazine has been found to be a folded structure with an angle of $145 \pm 5^{\circ}$ between the planes of the phenyl rings, the molecule being folded along a line between nitrogen and sulfur (31). This stereochemistry would thus make conjugation of the electron pair on nitrogen to the rings less likely.

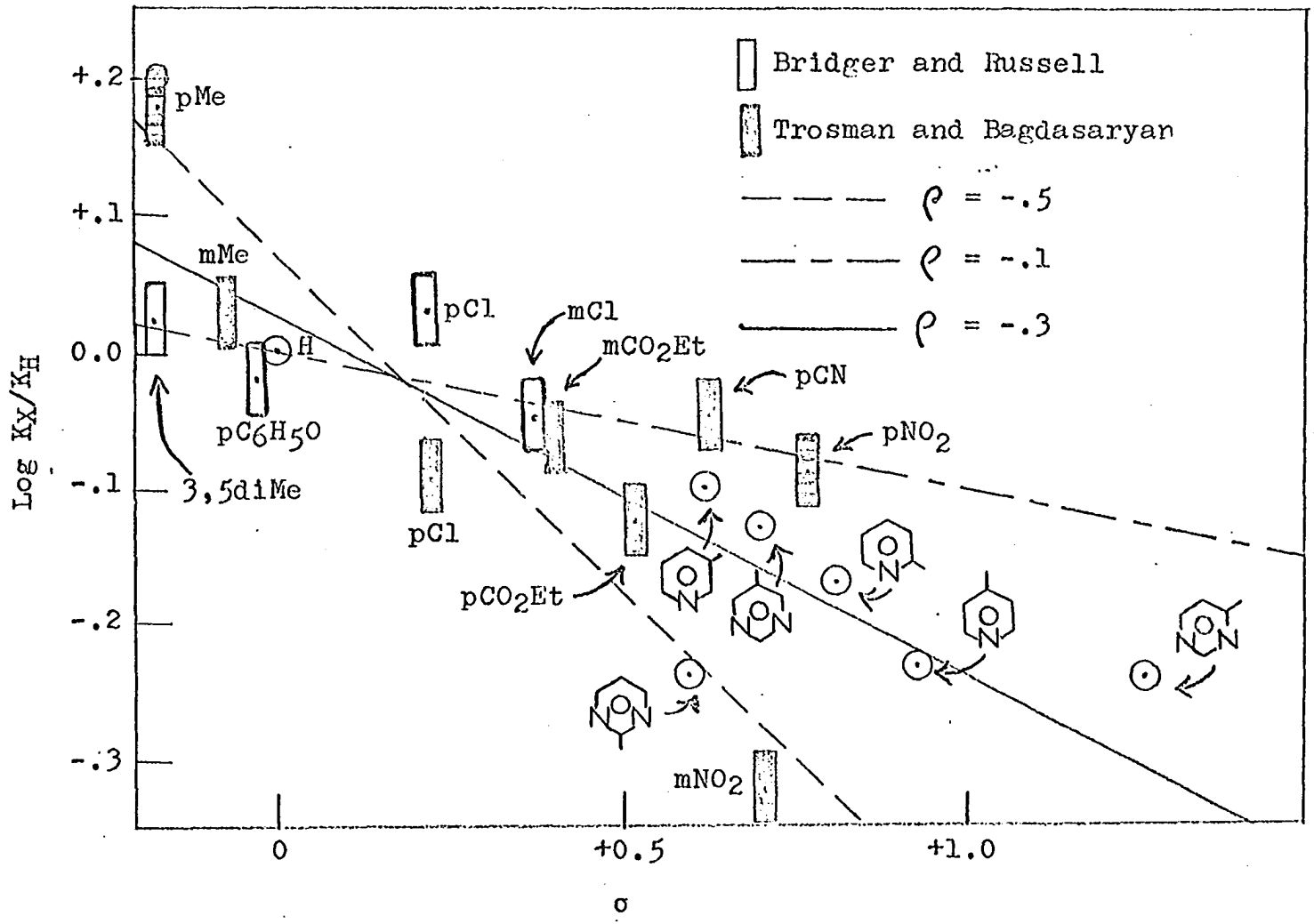


Carbazole is a planar molecule and would be expected to have delocalization of the nitrogen electron pair. However the involvement of the electron pair in delocalization over the phenyl rings would not be as important as delocalization of the nitrogen electron pair for the stabilization of indole or pyrrole. The rate enhancement due to pyrrole in N-methylpyrrole 8.6, is not much higher than that of a phenyl ring 7.7. Considering the stability of pyrrole as to the degree of aromaticity and electron delocalization, the electron density on nitrogen should still be significant. For pyrazole and imidazole, both pyridine and pyrrole structures may be drawn which show electron density removed from the methyl substituted nitrogen. Of the six reasonable resonance structures which can be written for both pyrazole and imidazole, there are four structures for imidazole in which the substituted nitrogen has a positive charge, and only three such structures for pyrazole. Chemically and physically imidazole is also more stable than pyrazole. Variable Electronegativity Self Consistent Field calculations (VESCF) have been done on imidazole and pyrazole (32, 33) giving the charge density on the substituted nitrogens as +0.35 and +0.344 respectively. This difference in charge density is not much, and it is possible that the adjacent nitrogen in pyrazole may have an effect on the reactivity of the neighboring methyl group. This will be considered later in the discussion of the six membered ring

nitrogen heterocycles.

Experiments (18, 19) with substituted aryl radicals indicate that the phenyl radical is a neutral species, and therefore the influence of polar contributions to the transition state should be small (34, 35). In the application of the Hammett equation to the reactivities of substituted toluenes, Bridger and Russell (2, 4) obtained a ρ-value of ca.-0.1 confirming the unimportance of polar contributions to the transition state. In their Hammett plot, p-xylene was excluded because its reactivity is apparently governed by its lower bond dissociation energy. Trosman and Bagdasaryan (24) have also constructed a Hammett plot from abstraction reactions of the phenyl radical generated from benzoyl peroxide and have obtained a ρ-value of -0.5. Their reactivities for p-xylene and p-nitrotoluene agree well with those of Bridger and Russell (2, 4). However Trosman and Bagdasaryan include the p-xylene in their plot and exclude p-cyanotoluene and p-nitrotoluene. Comparison of the two Hammett plots is given in Figure 2 along with points for two heterocyclic ring systems from this present work. Using the data from the Russian workers (24) together with Bridger's data (2) gives a ρ of ca.-0.3. Omitting p-xylene and m-nitrotoluene would give a value close to that of Bridger. The values of σ for the pyridines are those of Jaffe' (36) calculated from experimental data. The values of σ for the pyrimidines are theoret-

Figure 2. Hammett plot for reactions of phenyl radicals with substituted toluenes


Bridger and Russell
Trosman and Bagdasaryan
ρ = -.5
ρ = -.1
ρ = -.3
+.2
+.1
0.0
-.1
-.2
-.3
Log Kx/KH
pMe
mMe
H
pC6H5O
3,5diMe
pCl
pCl
mCl
mCO2Et
pCN
pNO2
pCO2Et
mNO2
0
+0.5
+1.0
σ

ical values calculated by Jaffe' (37) from molecular orbital considerations. Two experimentally calculated σ-values are listed for 2-pyridine, 0.81 and 0.40 (36). The theoretically calculated value given is 0.46 (37). The value of 0.81 is used in Figure 2. The values for an α-nitrogen substituent in an aromatic ring may not be amiable to a Hammett plot in the same way that ortho substituted benzenes are not amiable to a Hammett plot. Therefore, these values for the two heterocyclics were not used in computing the slope in Figure 2 but are plotted in the figure for comparison purposes.

The lone pair of electrons extending in the plane of the aromatic ring of compounds such as pyridine may be large enough to exert a steric effect on the position α to it. The steric requirements of the lone pair of electrons on nitrogen in amines has been considered to be about the same as an ordinary carbon-hydrogen bond to that of a methyl group (38-40) or to be smaller than that of a carbon-hydrogen bond (41-44).

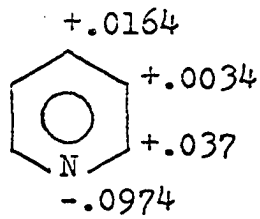
Substituents on the 2 and 6 positions of pyridine must be influenced in some way by the electron pair on the adjacent nitrogen. α-picoline has a boiling point ca. 15°C lower than β or γ-picoline. 2,6-Dimethylpyridine also has a substantially lower boiling point than other dimethylpyridines in which the α-position is free. The basicity of pyridine nitrogen is not affected much by two adjacent methyl groups but is

affected by two adjacent t-butyl groups (45).

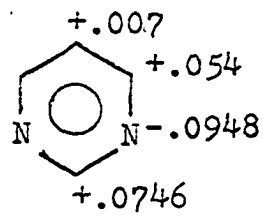
In first comparing the reactivities of substituted pyridines, pyrimidines, pyridazines, pyrazines, s-tetrazines and 1,3,5-triazine, it would seem that their reactivities do not depend too much on the number of nitrogens or their positions in the rings. Pyridine resonance structures would indicate that the α and γ-positions would have the least electron density and if the incipient benzyl radical is stabilized by electron density adjacent to it as in structures 8 then it would be expected that the methyl groups in these positions would be less reactive than in the β-position. Considering that the electron density at the α-position would be slightly lower than at the γ-position, a predicted order of reactivity would therefore be β>γ>α. However the order found for the three picolines was β>α>γ. Using bond dissociation energies (46) of the picolines, α = 75.5, β = 76.5 and γ = 77.5 kcal $mole^{-1}$, a predicted order of reactivity would be α>β>γ. It should be noted that the reactivity of the β-position is always predicted and found to be greater than the γ-position.

The charge densities calculated for the ring carbons and nitrogens in the unsubstituted parent six membered ring nitrogen heteroaromatics by VESCF molecular orbital calculations (47) gives actual numbers which can be compared rather than individual resonance structures, each of whose weight or importance is difficult to estimate. These charge densities

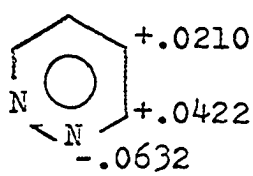
are given next to the ring position in the following structures.



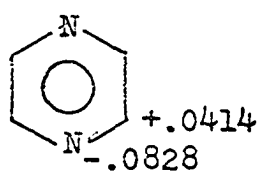
pyridine



pyrimidine



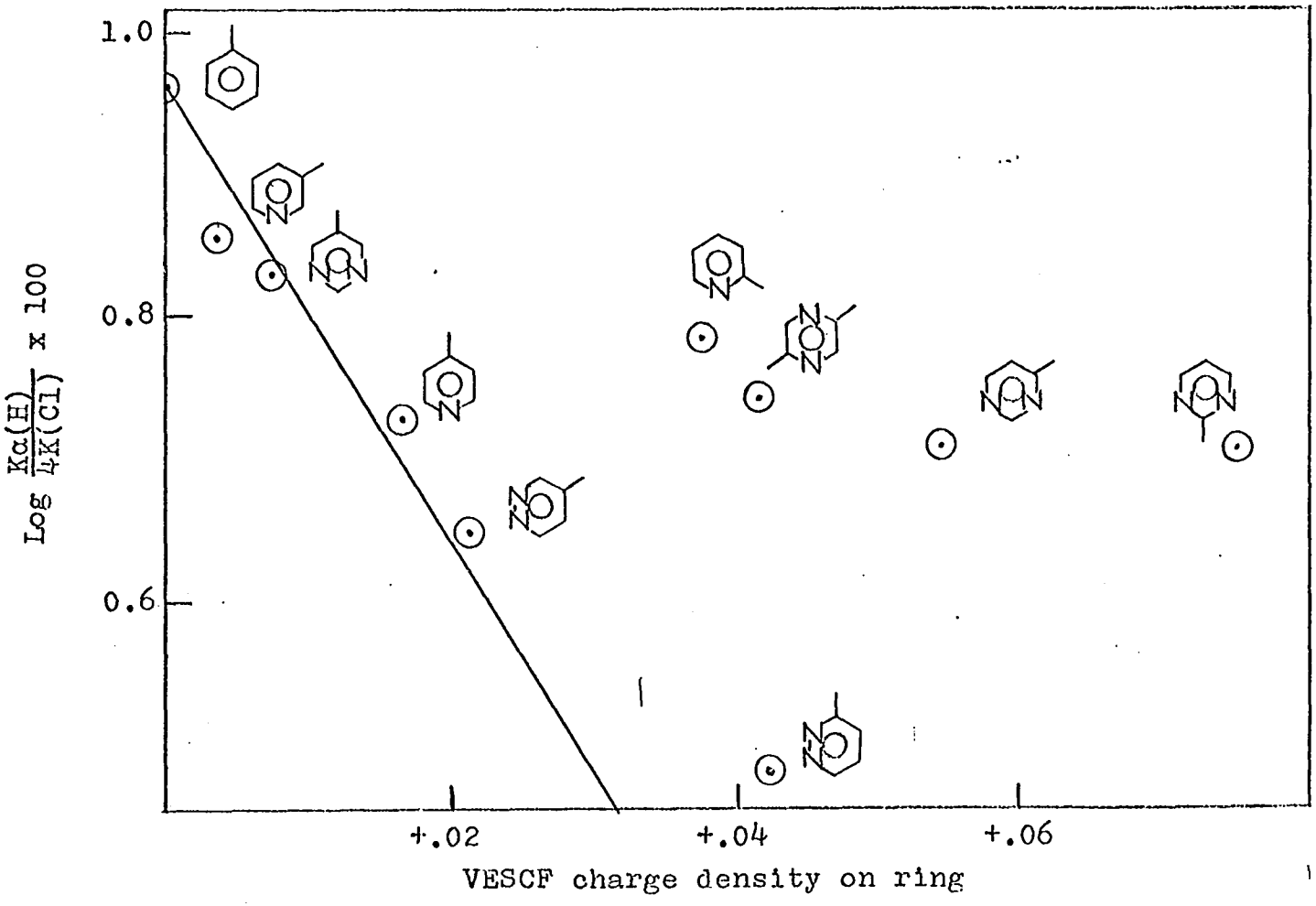
pyridazine



pyrazine

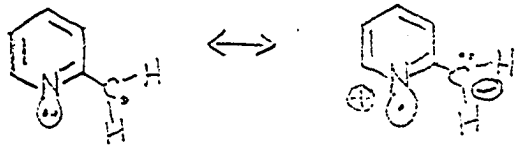
As can be seen from these structures the electron density on the nitrogens is less where there are two nitrogens in the ring. As can be predicted from resonance structures, nitrogens in the one and three positions reinforce each other while nitrogens <u>ortho</u> or <u>para</u> to each other do not reinforce each other. In Figure 3 is given a plot of these VESCF charge densities against the reactivity of α-hydrogens in methyl groups substituted on the corresponding ring positions. Although it would be best to compare reactivities with the charge density calculated for individual methyl substituted heterocycles this information is not available. It may be possible that substitution of a methyl group on these ring

Figure 3. Comparison of the reactivities of methyl substituted six membered ring nitrogen heteroaromatic compounds with VESCF charge density at the ring carbon of the parent heteroaromatic ring


1.0
0.8
0.6
Log Ka(H)/4K(Cl) x 100
+.02
+.04
+.06
VESCF charge density on ring

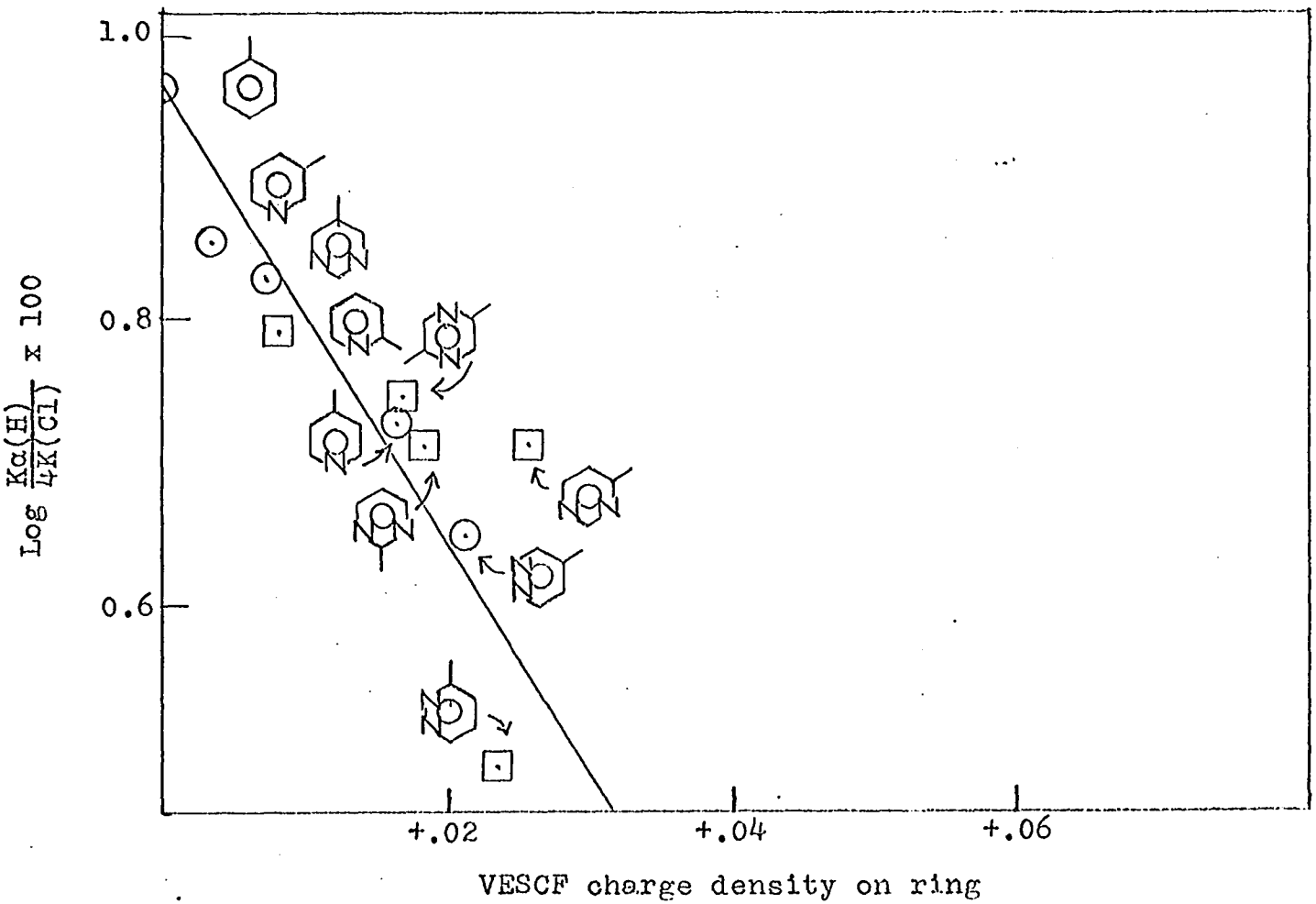
systems could cause a large enough perturbation to change the magnitude of the charge densities from those of the unsubstituted ring system.

In Figure 3 all compounds in which a methyl group is not adjacent to a ring nitrogen fall on a straight line, i.e. these compounds' reactivities correlate with the charge density on the ring carbon with the substituent. All other compounds not on this line have a methyl group adjacent to one or two ring nitrogens. There appears to be a correlation with charge density on nitrogen for these compounds which have a methyl group adjacent to a ring nitrogen. If for these compounds three tenths of the charge density of adjacent nitrogens is added to the charge density at the substituted ring carbon then these compounds fall on approximately the same line as the compounds in which there is no proximity of methyl groups and nitrogens. This can be seen in Figure 4. These results may be fortuitous but they suggest the slight possibility of an unusually stabilized radical which can be represented by structures such as:

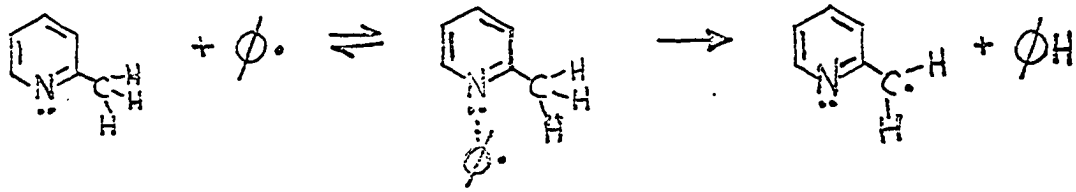


In any event there is apparently some sort of an ortho effect operating wherein rate enhancement is proportional to negative

Figure 4. Comparison of the reactivities of methyl substituted six membered ring nitrogen heteroaromatic compounds with VESCF charge density at the ring carbon of the parent heteroaromatic ring after correction for methyl groups adjacent to ring nitrogens


1.0
0.8
0.6
Log Kα(H)/4K(Cl) x 100
+.02
+.04
+.06
VESCF charge density on ring

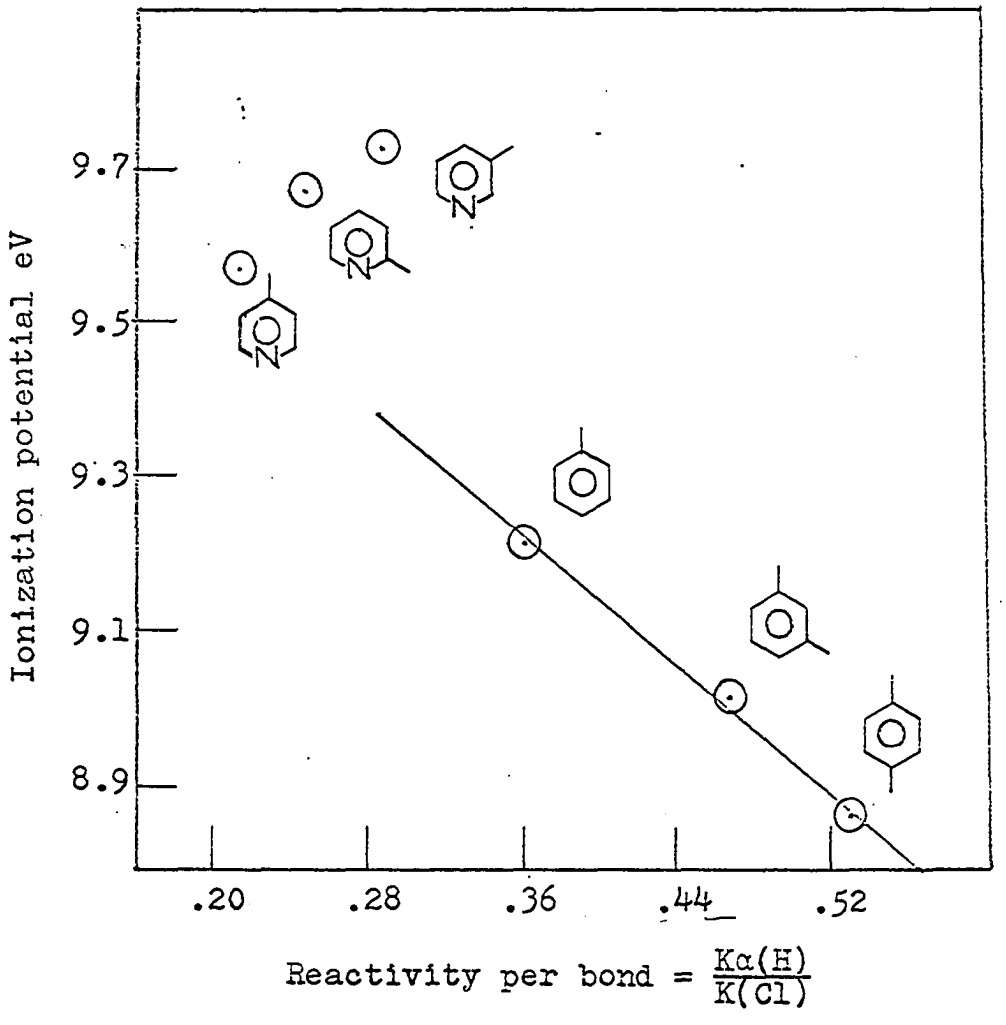
charge density on the ortho nitrogen atom. This effect does not seem to involve the $\widetilde{\pi}$-system since there is no evidence of an analogous para effect. The phenyl radical does have some tendency to attack centers of high electron density (see Figure 2) and the ortho effect may be connected with this. Complex formation may also be involved as shown below.



Higasi et al. (48) has suggested from the study of the ionization potential of methyl substituted pyridines from electron impact data that an electron from the nitrogen lone pair is lost rather than from the $\widetilde{\pi}$-system. Photoionization results appear to confirm this (49).

Ionization potential is related to bond dissociation energies and it is therefore interesting to compare ionization potential with reactivity results. This is done in Figure 5. The ionization potentials are those of Higasi et al. (48) from electron impact data. Because of the nature of electron impact data it is only possible to compare the results of one worker (49). In the benzene series the ionization of the first electron is assumed to be from the $\widetilde{\pi}$-electrons. The higher reactivity in the compounds with the lower ionization potential probably reflects the stability of the resulting

Figure 5. Comparison of reactivities per bond of some methyl benzenes and methyl pyridines with their ionization potential


Ionization potential eV
9.7
9.5
9.3
9.1
8.9
.20
.28
.36
.44
.52
Reactivity per bond = Kα(H) / K(Cl)

benzyl radical with the π-system. No reasonable correlation exists with the methyl pyridines due to the fact that the ionization potential is a measure of the loss of an electron from the nitrogen lone pair and not the π-system.

The bond dissociation energies found by Roberts and Scwarc (46) for the picolines were determined by the pyrolysis method (50). If the pyrolysis reaction measured is truly that of an initial bond fission, then the difference in order of reactivity of the three picolines from that expected from bond dissociation energies can be explained. The bond dissociation energy of the β and δ-picolines reflects the stability of the benzylic radical which depends upon the π-system. The bond dissociation energy of the α-picoline reflects one or both of two possible effects. First the steric effect of the nitrogen lone pair on the α-methyl group would result in non-bonded interactions which would result in a lowering of the bond dissociation energy. Second, the bond dissociation energy reflects the stability of the benzylic radical by interaction with the nitrogen lone pair. This argument of course relies upon predictions about reactivity through resonance structures and M.O. calculations, and the fact that electron withdrawing groups reduce the reactivity of the benzylic hydrogens, if only slightly, as can be seen from the Hammett plot. It would seem, however, that this reasoning would be justified by the large number of reactions which can be explained in organic

chemistry through the use of resonance and M.O. predictions. It is still possible, however, that this reasoning might not be valid in the present case.

The reversal in the reactivity of the α and β-positions from that expected from bond dissociation energies might also be due to steric effects. In the dissociation

there are no steric problems in the formation of products other than the possibility of steric acceleration mentioned above. However in the abstraction of hydrogen from the α-position of picoline, the neighboring nitrogen lone pair might present steric problems for the approaching phenyl radical.

When the reactivity of trimethyl-1,3,5-triazine was measured the high results were unexpected. However in view of the previous discussion and a comparison of the reactivity per bond of trimethyltriazine with hexamethylbenzene, 0.656 and 0.692 (2) respectively, the result is no longer surprising.

The reactivities of some fused ring compounds were measured and the results indicate that a phenyl ring fused to a heterocycle has negligible effect on the reactivity of a methyl group attached to the heterocycle. The heterocycle also appears to have little effect on the methyl group attached to the phenyl ring. The exception to this is the

case of 2-methylfuran and 2-methylbenzofuran where the latter is twice as reactive. Comparison of the reactivities per bond is given in Table 4.

In the furans and the thiophenes and their benzo derivatives the two position is always more reactive than the three position. The opposite has been found by Hunt (51) in the case of pyrrole and indole, where the two position of pyrrole has the greater reactivity while in indole the three position is the most reactive. It is hard to establish which positions

Table 4. Reactivities of some heteroaromatic compounds

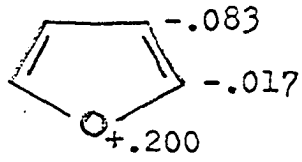
Compound	Reactivity per bond[a]
2-Methylfuran	.31[b]
2-Methylbenzofuran	.78
3-Methylfuran	.08
3-Methylbenzofuran	.07
2-Methylthiophene	.58[b]
2-Methylbenzothiophene	.55
3-Methylthiophene	.32[b]
3-Methylbenzothiophene	.32
2-Methylthiazole	.39
2-Methylbenzothiazole	.38
2,5-Dimethylpyrazine	.21[b]
2,3-Dimethylquinoxaline	.24
Mesitylene	.37[b]
6,7-Dimethylquinoxaline	.39
Toluene	.36[b]

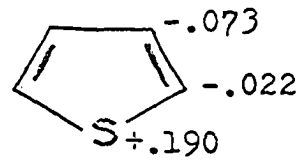
[a]Reactivity per bond = $\frac{k\alpha(H)}{k(Cl)}$.

[b]Reference 2.

in pyrrole, furan and thiophene have a higher electron density than others, and if there is a difference in charge density between the two and three positions. Molecular Orbital calculations on these five membered rings are not as clear cut as those of the six membered rings of the benzene type. These calculations give various results depending on what parameters are thought to be important in doing the calculations. Some examples of the various results are given below.

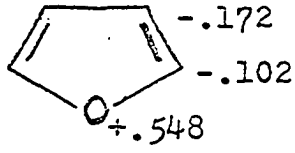
Sappenfield and Kreevoy (52)



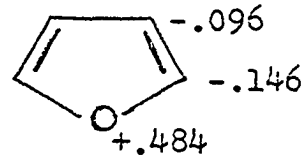


Orloff and Fitts (53)

Huckel Method

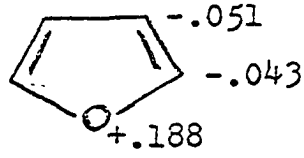


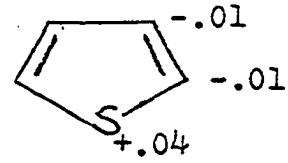
SCF-LCAO-MO Method

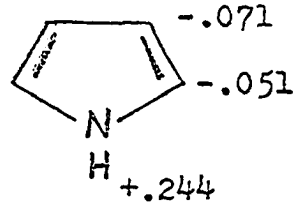


Brown and Coller, discussion in ref. (52)

VESCF







All of the calculations predict a higher negative charge distribution on the three position than the two position. Chemically the two position has been found to be the most reactive for substitution by electrophilic reagents in pyrrole, furan and thiophene. Of course the reactivity of this position is correlated well with resonance structures which predict the relative stabilities of the intermediate σ-complex. In M.O. theory the reactivity toward electrophilic reagents is predicted mathematically by delocalization energies (52) and not by relative charge distribution. The most reactive sites for electrophilic reagents in indole, benzofuran and benzothiophene are the two, three and three positions respectively.

The high reactivity of the methyl groups toward phenyl radicals in the two position of thiophene, furan and their benzo derivatives might be due to the same type of ortho effect as found in the six membered ring nitrogen heterocycles. The ortho effect could be due to stabilization of the incipient heterobenzylic radical through the non-bonding electron pair or complex formation, as discussed previously. This ortho effect would then explain the difference in reactivity of the methyl substituted benzofurans and benzothiophenes as compared to the methyl substituted indoles. The nitrogen in pyrrole and indole not having a non-bonding pair of electrons to interact with either the methyl group or the phenyl radical.

If the ortho effect is due to complex formation of the phenyl radical with the non-bonding electron pair it could possibly explain the low total yield of benzene and chlorobenzene from 3-methylfuran, 3-methylbenzofuran and 3-methylbenzothiophene. Complex formation of the phenyl radical could result in the preferential attack of the phenyl radical on the two position of the ring when there is no methyl substituent on this position for abstraction of a hydrogen atom.

The reactivities of a few compounds containing a methylene group bridging two heteroaromatic rings have been measured. The rate enhancements of the heteroaromatic rings on the methyl and methylene groups relative to a normal alkane are given in Table 5. In going from one phenyl ring to two, there appears to be no enhancement. In the case of the 2-pyridyl group, the addition of a second ring causes a decrease in enhancement. For the 2-benzothiazolyl group there is only a slight enhancement on the addition of a second ring. The thiazole ring can be thought of in terms of both its pyridine and thiophene like structures. It is interesting that the 2-benzothiazolyl group enhancements fall just slightly less than half way between the 2-thienyl and the 2-pyridyl group enhancements. The enhancement appears to be doubled when two thiophene, furan or ferrocene groups are present. Why there should be this difference in enhancement by these aromatic rings is not obvious.

Table 5. Relative rate enhancement of heteroaromatic rings on methyl and methylene groups

Substituent Z	Rate enhancement[a] $Z\text{-}CH_3$[b]	Z_2CH_2[c]
Phenyl	7.7[d]	7.6[d]
2-Thienyl	12.5[d]	23.1[d]
2-Pyridyl	5.2	2.9
2-Benzothiazolyl	8.1	10.6
2-Furyl	7.1[d]	15.3
Ferrocenyl	7.7	13.7
2-Furyl, 2-thienyl	--	13.9

[a]Reactivity of an α-carbon-hydrogen bond relative to a molecule of carbon tetrachloride divided by the reactivity of the same bond type in a normal alkane.

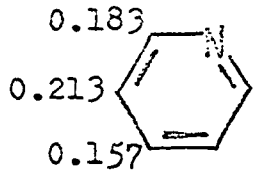
[b]Reactivity of a 1° hydrogen in a normal alkane taken as $\frac{k\alpha(H)}{4k(Cl)} = .0117$, reference 4.

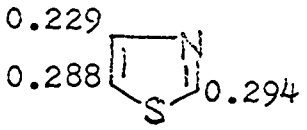
[c]Reactivity of a 2° hydrogen in a normal alkane taken as $\frac{k\alpha(H)}{4k(Cl)} = .091$, reference 4.

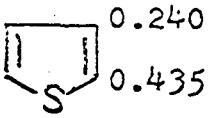
[d]Reference 2.

As was pointed out above, thiazole can be thought of in terms of both its pyridine and thiophene like structure. The methylthiazoles have about the same boiling points and odors as the picolines. The reactivity of methyl groups substituted at different positions on thiazole is compared to that of

pyridine and thiophene below.







EXPERIMENTAL

Melting points and boiling points are uncorrected. Compounds studied are grouped approximately according to the order in Table 2.

Chemicals

Distillation was relied upon for the purification of liquids. In one case, preparative gas-liquid chromatography was used. Solids were purified by recrystallization and column chromatography. All liquids and low melting solids were checked for volatile impurities. The identities of compounds were checked by NMR. In the following descriptions per cent purity refers to mole per cent unless otherwise specified.

Methylferrocene was prepared by the method of Benkeser and Bach (54) and purified by alumina column chromatography using petroleum ether (b.p. 35-37°) to give methylferrocene, m.p. 36-38°C. It was >99% by GLC after drying.

N-Methylphenothiazine was prepared by the method of Burger and Schmalz (55) and purified by alumina column chromatography using petroleum ether (b.p. 35-37°) to give after vacuum drying at 80°C, colorless needles m.p. 99-100°C.

10-Methylphenoxazine was prepared by the method of Gilman and Moore (56) and purified by alumina column chromatography using benzene, followed by vacuum distillation b.p. 151-154°C/3 mm. This gave an almost colorless solid m.p. 36-37°C.

N-Methylcarbazole was prepared by the method of Stevens and Tucker (57) and purified by alumina column chromatography with petroleum ether (b.p. 35-37°). After vacuum drying at 80°C, a product with m.p. of 87-88° was obtained.

1-Methylpyrazole was prepared from 46.1 g. of methylhydrazine (Matheson, Coleman, and Bell) and 220 g. of 1,1,3,3-tetraethoxypropane (Eastman Kodak Company) by placing the two together with 100 ml. of glacial acetic acid, 10 ml. of conc. HCl, and 10 ml. of water in a round bottom flask equipped with stirrer and condenser. The reaction was heated carefully whence it slowly turned red and formed a precipitate. The reaction then became very exothermic and boiled vigorously and had to be controlled by an ice bath. After the reaction had stopped, the solution was refluxed two more hours. It was then added to water. The excess acetic acid was neutralized with sodium bicarbonate, and the organic layer extracted with ether, dried, and fractionally distilled to give 1-methylpyrazole b.p. 127°C. It gave a picrate m.p. 148°C and was >99% pure by GLC (58).

3(5)-Methylpyrazole (Aldrich Chemical Company) was fractionally vacuum distilled. The fraction used was >98% pure by GLC.

1-Methylimidazole (K & K Chemical Company) was fractionally vacuum distilled. The fraction used was >98% pure by GLC.

2-Methylbenzofuran was prepared by the method of Adams and Rindfusz (59). It was vacuum distilled three times b.p. 93-94°/20 mm. to give a sample 97% pure by GLC.

3-Methylbenzofuran was prepared by the method given in Organic Synthesis (60). It was distilled to give >99% pure material b.p. 195-197°C.

3-Methylfuran was prepared by the method of Burness (61). It was twice distilled to give a product of >99% purity with a b.p. of 65-66°. It was used immediately after distillation as it turns yellow on standing.

2-Methylbenzothiophene (2-methylthianapthene) was prepared by the method of Shirley and Cameron (62). The compound was purified first by vacuum distillation b.p. 135-150°C/ 80 mm. then by fractional crystallization to give a fraction melting at 51-52°C.

3-Methylbenzothiophene (3-methylthianapthene) was prepared by the method of Werner (63). The compound was purified by several vacuum distillations at 25 mm. b.p. 125-127°C. The impure compound tended to turn yellow on standing which may have been due to a trace of thiophenol being present. The last fractional distillation gave material which remained colorless and which was >99% pure by GLC. No thiophenol or phenylthiopropanone could be detected by GLC.

2-Methylthiazole was prepared by Hantzsch's method (64). In the final distillation of the compound the 2-methylthiazole

appeared, by examination with GLC, to be codistilling slowly with ethanol from the reaction mixture. The lower boiling distillates were, therefore, combined and mixed together with some anhydrous ether. Anhydrous hydrogen chloride was then passed into the cooled solution until no more hydrochloride precipitated. The hydrochloride was then filtered, air dried, and then made basic with a very concentrated and cold solution of potassium hydroxide while keeping the mixture cold with an ice bath. The methylthiazole was extracted with anhydrous ether (alcohol free), dried over solid potassium hydroxide and distilled to give material of 97% purity by GLC with a b.p. of 126-127°C.

2-Methylbenzothiazole (Eastman Kodak Company) was >99% pure by GLC.

4-Methylthiazole was prepared, using the method of McLean and Muir (65), by reduction of 2-chloro-4-methylthiazole with zinc. The 2-chloro-4-methylthiazole was prepared using the method of Tscherniac (66). Distillation gave 98% pure 4-methylthiazole by GLC with a b.p. of 131-132°C.

5-Methylthiazole was prepared by using slight modifications of two other preparations. First 2-amino-5-methylthiazole was prepared by a modification of McLean and Muir's method (65). The exact procedure was as follows. To a solution of 58 g. of freshly distilled propionaldehyde in 250 ml. of anhydrous ether was added in small portions, 250 g. of

dioxane-bromine complex while cooling the mixture in an ice bath. The dioxane-bromine complex was added in small portions so that the bromine color of the solution would disappear before the next addition. After addition of the dioxane-bromine complex was complete, the solution was allowed to stir for one hour. The reaction mixture was then placed in a separatory funnel and washed with 100 ml. of water, and with sodium bicarbonate solution. The wet ethereal solution of bromopropionaldehyde was then added directly to another flask containing 76 g. of thiourea and allowed to stir for three hours. The ethereal solution was then filtered from solids and neutralized by shaking with a solution of potassium carbonate. The ethereal solution was dried over anhydrous sodium sulfate and the ether evaporated to give 80 g. of crude 2-amino-5-methylthiazole. The crude aminothiazole was diazotized in sulfuric acid and reduced by means of hypophosphorous acid using the method of Ganapathi and Venkataraman (67). The exact procedure used is as follows. The crude 2-amino-5-methylthiazole (80 g.) was dissolved in a strong solution of sulfuric acid (200 ml. conc. H_2SO_4 + 200 ml. water). The sulfuric acid solution was then cooled to -20°C. With stirring, a solution of 48 g. of sodium nitrite in 200 ml. of water was added very slowly (over 2 hrs.) to the sulfuric acid solution by means of a capillary tubing extending below the surface of the sulfuric acid solution. During this time, the temperature

was kept below or near -20°C. After the addition was complete the solution was allowed to stir at -20°C for another half hour, and then 150 ml. of 50% hypophosphorous acid was added slowly at -20°C. After the addition, the mixture was allowed to stir at -20°C for one hour and then slowly allowed to warm to room temperature over several hours. The solution was then cooled again and very slowly and carefully neutralized and made basic with concentrated potassium hydroxide while keeping the contents cool. The water solution containing the free 5-methylthiazole was then steam distilled. The thiazole comes over in about the first 200 ml. of water. This steam distillate was then saturated with potassium carbonate and the oily layer separated and dried over solid potassium hydroxide. The product was then fractionally distilled to give 5-methylthiazole, b.p. 141-142°C, >97% pure by GLC.

1-Methylbenzotriazole and 2-methylbenzotriazole were prepared, separated and purified by the method of Krollpfeiffer et al. (68). The 2-methylbenzotriazole distilled at 103-104°C/15 mm. and was >99% pure by GLC. The 1-methylbenzotriazole was further purified by shaking an ethereal solution with potassium hydroxide solution to remove unreacted benzotriazole. This gave, after recrystallization, 1-methylbenzotriazole with a m.p. of 65°C.

2-Methylbenzimidazole (Eastman Kodak Company) was recrystallized from ethanol and vacuum dried to give a product

of m.p. 175-176°C.

2-Methylbenzoxazole (Eastman Kodak Company) as received was >99% pure by GLC.

Dimethyl s-tetrazine was a sample prepared and purified by Dr. Kanaka while at this laboratory.

3-Methylpyridazine was prepared from 3-methyl-6-chloropridazine by the hydrogenation method of Jones et al. (69). The 3-methyl-6-chloropridazine was prepared by the method of Overend and Wiggins (70). Vacuum distillation gave >99% pure 3-methylpyridazine by GLC, b.p. 88-90°C/12 mm. The 3-methylpridazine was used soon after distilling as it turns yellow on standing in air.

4-Methylpyridazine was prepared by the method of Mizzoni and Spoerri (71). Vacuum distillation gave 4-methylpridazine >99% pure by GLC, b.p. 103-105°/13 mm. The 4-methylpyridazine was used soon after distilling as it turns yellow on standing in air.

2-Methylpyrimidine was prepared by hydrogenation of 4,6-dichloro-2-methylpyrimidine by the method of Smith and Christensen (72). The 4,6-dichloro-2-methylpyrimidine was prepared by the method of Boarland and McOmie (73). The 2-methylpyrimidine distilled at 136-137°C and was >97% pure by GLC.

4-Methylpyrimidine was prepared by the procedure given in Organic Synthesis (74). It distilled at 140-141°C and was

>98% pure by GLC.

5-Methylpyrimidine (K & K) was purified by preparative GLC on a column of 30% polypropyleneglycol, UCON oil on 80-100 mesh firebrick, using an Aerograph Model A-90-P Manual Temperature Programmed G. C. instrument. The pure 5-methylpyrimidine crystallized as a low melting solid of approximately 30°C upon collection. The preparative GLC separation gave >99% pure material by GLC.

4-Methylpyridine (4-picoline) (Eastman Kodak Company) showed a minimum purity of 98% by GLC after fractionation.

3-Methylpyridine (3-picoline) (Matheson Coleman & Bell) showed a minimum purity of 95% by GLC after fractionation.

2-Methylpyridine (2-picoline) (Matheson Coleman & Bell) showed a minimum purity of 99% by GLC after fractionation.

2,4,6-Trimethyl-1,3,5-triazine was prepared by the method of Grundman and Weisse (75). The compound was distilled three times from sodium, b.p. 154-156°C, m.p. 55-56°C and had a minimum purity of 97% by GLC.

2,3-Dimethylquinoxaline (Eastman Kodak Company) was recrystallized from ethanol and after vacuum drying gave a m.p. of 105-106°C.

6,7-Dimethylquinoxaline (Aldrich Chemical Company) was treated with charcoal and then chromatographed on an alumina column with petroleum ether (b.p. 35-36°C) to give pure colorless crystals with a m.p. of 100-101°C after vacuum drying.

Dimethylfurazan (Aldrich Chemical Company) was fractionally distilled before use to give a minimum purity of 99%.

2,2'-Dipyridylmethane was prepared by the method of Sperber et al. (76). Vacuum distillation gave >99% pure compound by GLC of b.p. 102-103°C/0.5 mm. On standing the compound appears to air oxidize forming a crystalline solid. It was used directly after distillation and was redistilled before the second determination since it had stood some time.

2,2'-Dibenzothiazolylmethane was prepared by the method of Mills (77). The compound was recrystallized four times from ethanol to obtain colorless needles melting at 95-96°C. It was vacuum dried before use.

Diferrocenylmethane was prepared by modifications of other procedures in the literature. Acetylferrocene was prepared by the method of Hauser and Lindsay (78). This was then converted into ferrocenoic acid with sodium hypochlorite using a procedure similar to that in Organic Synthesis (79). Ferrocenoic acid was then converted to ferrocenoyl chloride by the method of Schlögl (80) and then converted into diferrocenyl ketone. This was then converted into diferrocenylcarbinol by the method of Schlögl and Mohar (81). The carbinol was then converted to the diferrocenylmethane by a method similar to that used before in converting ferrocenylcarbinol into methylferrocene (54). The diferrocenylmethane was purified by alumina column chromatography to give pure material melting at

149-150°C (81).

2,2'-Difurylmethane was prepared by the method of Dineili and Marini (82). Vacuum distillation gave 98% pure material by GLC with a boiling point of 72-73°C/10 mm. The compound was stored in Dry Ice until used as it decomposes on standing.

2-Furyl-2-thienylmethane was prepared by the method of Goldfaro and Danyushevski (83). Two vacuum distillations at 73-74°C/4 mm. gave material of 95% purity by GLC. The compound was stored in Dry Ice until used as it decomposes on standing.

Carbon tetrachloride (Matheson analytical grade) was passed through silica gel and distilled through a Todd column. GLC showed less than 0.1% impurities.

Preparation of Phenylazotriphenylmethane

Phenylazotriphenylmethane (PAT) was prepared according to the procedure of Cohen and Wang (84), which also was used by Bridger (2).

The preparation of sample A of PAT used in this work is described as follows. N-phenyl-N'-tritylhydrazine was prepared by placing 156 g. of triphenylchloromethane (0.56 mole) and 1500 ml. of ether in a 3-liter flask equipped with reflux condenser, stirrer, and dropping funnel. Phenylhydrazine (111 ml., 1.12 mole) was added slowly during a period of one hour. The mixture was stirred five hours longer at room

temperature, filtered to remove phenylhydrazine hydrochloride, and then the ether evaporated at reduced pressure. The crude material was recrystallized twice from a methylene chloride-ethanol (1:1 by volume) mixture to give 90 g. (0.266 mole, 47.6% yield) of N-phenyl-N'-tritylhydrazine, m.p. 132-134°C (reported m.p. 134-135°C).

N-Phenyl-N'-tritylhydrazine (90 g.) in 1800 ml. of ether was stirred 6 hours at room temperature with 800 ml. of saturated aqueous sodium bicarbonate and 70 ml. of 30% hydrogen peroxide. The ether layer was separated, washed once with 5% aqueous sodium sulfate and dried over anhydrous sodium sulfate. The ether was removed at reduced pressure. The PAT was recrystallized by dissolving in 500 ml. of a mixture of methylene chloride-ethanol (1:1 by volume) and evaporating the solvent to approximately half the original volume by means of a vacuum rotary evaporator. During the evaporation, the heat loss from the solution kept the PAT near or below 0°C. When about half the original amount of solvent had been removed the PAT crystallized out. The PAT was then filtered, the filtrate discarded, and the PAT dried in a vacuum desiccator over paraffin shavings and calcium chloride. The yellow crystals of PAT contained some white solid so it was reoxidized. The impure PAT was dissolved in 2000 ml. of ether and stirred three hours at room temperature with 500 ml. of saturated aqueous sodium bicarbonate and 100 ml. of 30% hydrogen

peroxide. At the end of the first three hours another 100 ml. of 30% hydrogen peroxide was added, and the reaction allowed to stir for three more hours. The reaction mixture was worked up as above, the PAT being recrystallized twice and dried. This reaction yielded 24 g. of PAT, m.p. 111-112°C (decomposition). The decomposition of a 0.100 M solution of this material in carbon tetrachloride at 60°C resulted in yields of 4.1% benzene and 74.4% chlorobenzene.

Sample B used in four cases in this work was supplied kindly by J. D. Hunt and the benzene correction factor used for this sample of PAT was 5.4% benzene. Both samples of PAT were stored in a refrigerator at 5°C.

Analytical Methods

Decomposition procedure for competitive reactions

A solution of carbon tetrachloride and the hydrogen-containing substrate was made weighing each liquid to the nearest 0.2 mg. in a stoppered flask. If DMSO was used as a cosolvent, it was also weighed out with the other substrates. PAT was then weighed into an ampoule of about 10 ml. capacity, and enough of the solvent mixture was added to make the solution 0.100 M at room temperature. In most cases the PAT was weighed out so that a volume of 5 ml. of solvent mixture was used. In two cases where only very small amounts of compound

were available for study, 5-methylpyrimidine and dimethyl-s-tetrazine, an ampoule of 4 ml. volume was calibrated to a volume of 1 ml. PAT and compound were then weighed out into the ampoule and carbon tetrachloride added to make 1 ml. of solution at room temperature. The solution of azo compound was frozen in liquid nitrogen, evacuated to 1-2 mm., and thawed in order to remove gasses. The ampoule was then sealed while the frozen solution was maintained under vacuum. The sealed tubes were placed in an oil bath maintained at 60 $\pm$ 0.1°C for slightly more than ten half-lives of PAT (4 hours). Before gas chromatographic analysis, weighed solutions without PAT were checked by GLC for the presence of impurities which would interfere with the determination of the products. The samples containing PAT were also checked after decomposition of the PAT for interfering substances before a solution of internal standard was added to the reaction mixture.

Determination of benzene and chlorobenzene

Gas-Liquid Chromatography (GLC) was used for the quantitative determination of benzene and chlorobenzene. A Perkin-Elmer Vapor Fractometer Model 154-D was used for all GLC work. All columns were constructed of 1/4-inch O.D. metal tubing. Firebrick was treated with hexamethyldisilazane. Conditions used for GLC work appear below. The first two conditions mentioned are two used by Bridger (2) and are given Roman

numerals corresponding to his designations.

GLC conditions I (2) Two columns were used in series. A 1-meter, 3,3'-oxydipropionitrile (ODPN) column (85), 20% dry weight on 80/100 mesh firebrick, was followed by a 1-meter di-n-propyl tetrachlorophthalate column (86), 10% by weight on 80/100 mesh firebrick.

GLC conditions IV (2) Two 1-meter ODPN columns were used in series. Temperature was 78°C and flow rate was 70 cc./min.

GLC conditions A Two columns were used in series. A 1-meter picric acid-fluorene complex column (87) 30% by weight on 80/100 mesh firebrick, was followed by a 1-meter ODPN column. Temperature was 81°C and the helium flow rate was 60 cc./min. at ambient conditions.

Correction factors Correction factors given in Table 6 conform to the equation:

Moles A/Area A = (Moles B/Area B) x Correction Factor.

Gas chromatograms areas were measured with an Ott plainimeter.

Table 6. Correction factors for GLC

Compound A	Compound B	Correction factor
Benzene	Toluene	1.08
Chlorobenzene	Toluene	0.98
Benzene	Ethylbenzene	1.25
Chlorobenzene	Ethylbenzene	1.06

Retention times A list of approximate retention times appears in Table 7, at the end of this section. With the exceptions of internal standards and reaction products, no effort was made to determine retention times accurately with very dilute samples. Only those compounds are listed which had a reasonable retention time under the GLC conditions mentioned. All other compounds were not eluted. The use of conditions A also prevented the elution of basic nitrogen compounds.

GLC conditions for the analysis of benzene and chlorobenzene from each competitive reaction are listed in Table 8.

Table 7. Relative retention times of selected compounds

Compound	GLC conditions	Retention time[a] (min.)
Carbon tetrachloride	I IV A	0.52, 0.43, 0.42
Benzene	I IV A	(1.0)
Toluene	I IV A	1.84, 1.66, 2.00
Ethylbenzene	I IV A	3.30, 2.50, 3.18
Chlorobenzene	I IV A	3.78, 3.52, 4.25
1-Methylpyrazole	IV	ca. 13
3-Methylfuran	IV	ca. 0.6
2-Methylthiazole	IV	ca. 7.8
4-Methylthiazole	IV	ca. 6.6
5-Methylthiazole	IV	ca. 14
2-Methylpyridine	IV	ca. 7.3
3-Methylpyridine	IV	ca. 13
4-Methylpyridine	IV	ca. 13
2,4,6-Trimethyl-1,3,5-triazine	IV	ca. 8

[a]Retention times are relative to benzene. Actually observed retention times for benzene under conditions specified in the text for conditions I, IV and A were 5.0, 7.9 and 5.0 minutes respectively.

Table 8. Conditions for analysis of competitive reactions

Reaction no.	RH	Method of determination	
		Benzene	Chlorobenzene
1	Methylferrocene	IV	IV
2	10-Methylphenoxazine	IV	IV
3	N-Methylphenothiazine	IV	IV
4	N-Methylcarbazole	IV	IV
5	1-Methylpyrazole	IV	IV
6	3(5)-Methylpyrazole	IV	IV
7	1-Methylimidazole	A	A
8	2-Methylbenzofuran	IV	IV
9	3-Methylfuran	IV	IV
10	3-Methylbenzofuran	IV	IV
11	2-Methylbenzothiophene	IV	IV
12	3-Methylbenzothiophene	IV	IV
13	2-Methylthiazole	IV	IV
14	2-Methylbenzothiazole	IV	IV
15	5-Methylthiazole	IV	A
16	4-Methylthiazole	IV	IV
17	2-Methylbenzotriazole	IV	IV
18	1-Methylbenzotriazole	IV	IV
19	2-Methylbenzimidazole	IV	IV
20	2-Methylbenzoxazole	IV	IV
21	Dimethyl-s-tetrazine	IV	IV
22	3-Methylpyridazine	IV	IV
23	4-Methylpyridazine	IV	IV
24	2-Methylpyrimidine	A	A
25	4-Methylpyrimidine	IV	IV
26	5-Methylpyrimidine	IV	IV
27	4-Methylpyridine	A	A
28	2-Methylpyridine	IV, A	IV
29	3-Methylpyridine	A	A
30	2,4,6-Trimethyl-1,3,5-triazine	A	A
31	2,3-Dimethylquinoxaline	IV	IV
32	6,7-Dimethylquinoxaline	IV	IV
33	Dimethylfurazan	IV	IV
34	2,2'-Dipyridylmethane	IV, A	IV, A
35	2,2'-Dibenzothiazolylmethane	IV	IV
36	Diferrocenylmethane	A	A
37	2,2'-Difurylmethane	I	I
38	2-Furyl-2-thienylmethane	I	I

SUMMARY

The relative reactivities of methyl substituted heterocyclic and heteroaromatic compounds toward abstraction reactions by the phenyl radical were determined by the method of competitive reactions. Phenylazotriphenylmethane was used as the source of phenyl radicals in the competitive reaction with the substituted heterocyclic compounds and carbon tetrachloride.

Compounds having a methyl group on a ring carbon adjacent to a ring nitrogen, oxygen or sulfur having a non-bonding pair of electrons appeared to display an ortho effect with enhanced reactivity over that expected. Reactivity otherwise appeared to be correlated with electron density at the position of the methyl substituent. The reactivities of a few heteroaromatic diarylmethanes were also determined. The reactivities of methyl groups on phenyl and heteroaromatic rings appeared to be not much different than methyl groups in the corresponding positions of benzo fused heteroaromatic rings.

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