THE SIGNIFICANCE OF THE BOND LENGTHS AND BOND ORDERS OF CONJUGATED UNSATURATED ORGANIC MOLECULES. THE ROLE OF HETERO-AROMATICITY IN THE TERTIARY STRUCTURES OF DNA

Vernon G. S. Box
Department of Chemistry, City College of the City University of New York, Convent Avenue @ 138th Street, New York, NY 10031, U. S. A.

Abstract - New criteria (based on X-ray crystallographic data) for assessing the presence of delocalization in conjugated π systems reveal that delocalization is not a widespread phenomenon in the ground states of many of these π systems. Instead, these molecules prefer to retain highly localized, independent, π systems. Thus, many explanations of the structural features and reactivities of these unsaturated organic molecules, based on their presumed delocalized ground states, must be critically reviewed. This is especially important for understanding the chemistry and properties of hetero-aromatic molecules.

INTRODUCTION

For many years organic chemists have been fascinated by the fact that true delocalization in molecules which contain conjugated π systems confers additional stability on these molecules. Indeed, so great is the appeal of this concept, that any π system which seems to be capable of delocalization is automatically assumed to be delocalized, unless strong evidence to the

contrary is provided. This situation is more acute in the consideration of aromatic molecules. Here, as long as any given molecule seems to satisfy Huckel's Rules,[1] that molecule is assumed to be truly delocalized and hence aromatic. The instances of "inhibition of resonance" by steric or other factors are viewed as being quite unusual[2] and any suggestion that a conjugated π system might not be truly delocalized is most often met with great scepticism.

Undoubtedly, there has been a need for the development of experimentally verifiable, non-theoretical criteria for establishing the presence of delocalization in conjugated systems. Many of the experimental attempts to identify delocalization in conjugated π molecules have involved the spectroscopic methods,[3] but the data generated are very often ambiguous. For over sixty years organic chemists have used molecular orbital theory[4] and Huckel's Rules for aromaticity[1,4] in considerations of the stereo-electronic features of molecules, and delocalization. Indeed, many people have come to regard molecular orbital theory as the physical basis of molecular bonding phenomena, rather than a human attempt to rationalize these phenomena. Huckel's Rules and HMO theory have been good guidelines for the assessment of the possibility of the existence of aromaticity in cyclic conjugated π systems, and the existence of delocalization in conjugated π systems. The many valuable results and insights generated by the molecular orbital theoretical treatment of truly delocalized π systems will undoubtedly continue to be meaningful. However, the users of the theory will benefit from the recognition of situations in which molecular orbital theory should be applied with great caution, or not at all.

This review will address the fact that many molecules which have been regarded as good examples of delocalized π systems (like unsaturated carbonyl compounds, polyenes, enols and enamines) are in fact not delocalized in their ground states. Thus, the validity of the molecular orbital theoretical studies of the "delocalized ground states" of these systems can be questioned. Fortunately, many of these molecular orbital

theoretical analyses can be valuable if the data is properly interpreted.

The Relationship Between Bond Type and Bond Order

During the development of the molecular graphics program STR3DI.EXE, an extensive review of the X-ray crystallographic data of several hundred organic molecules revealed some very definitive relationships between bond lengths and bond types.[5] Further, and quite coincidentally, it was also discovered that these bond length - bond type relationships could be correlated with, and were closely supported by, the carefully interpreted results of bond order calculations available from the well known area of VESCF-HMO theory.[5] These bond length/type/order relationships are shown below (Table 1).

The values of the bond lengths have been rounded. The numeric value of bond type (usually single, double, or triple) is obviously equal to the integral value of the VESCF-HMO calculated bond order.

Table 1.

Bond Type - Bond Length - Bond Order Relationships[5a]

Bond Type	Average Bond Length (pm)	Upper/Lower Bond Length Limit (pm)	Bond Order Range (ex VESCF-HMO)	Numeric Bond Type
C-C	154	165 - 143	< 1.5	1
C=C	134	143 - 125	1.5 to 2.5	2
C-O	140	150 - 130	< 1.5	1
C=O	122	130 - 113	1.5 to 2.5	2
C-N	148	158 - 138	< 1.5	1
C=N	129	138 - 120	1.5 to 2.5	2
C-S	188	201 - 175	< 1.5	1
C=S	164	175 - 152	1.5 to 2.5	2

In essence, the bonds in molecules which possess localized π bonds have calculated orders and lengths which lie within the relevant ranges for the appropriate (multiple) bonds (Table 1. above). Further, the bond lengths found in, and orders calculated for, the truly delocalized π systems definitively reveal the dominant bonding features in these systems. For example, a bond whose VESCF-HMO calculated order is 1.4 will be a true single bond even though the electron density between the bonded centers is greater than that found in a simple (ethane) single bonded system, and a

bond whose order is 1.6 will be a true double bond which is weaker than a double bond whose order is closer to (or greater than) 2.

The application of these new criteria for delocalization to many simple conjugated π systems has led to several important results.[5]

a) It was demonstrated that amides are truly delocalized π systems (whose bond orders and bond lengths lie within the ranges for double bonds), but simple enol ethers, enamines and esters have localized n and π orbitals (no n-π* delocalization) and the lengths and orders of their bonds fall within the relevant ranges for single and double bonds. Consequently, it was suggested that the enhanced nucleophilic reactivities of enols and enamines (in comparison with simple alkenes) were due mainly to transition state phenomena.

b) Delocalization in cyclic conjugated π systems was examined and this led to the formulation of new criteria for aromaticity. Since these criteria are based on bond lengths and bond orders, the "aromatic" status of any molecule can be verified experimentally (by X-ray crystallographic and similar structural studies), or by reliably calculated bond orders.

c) It was shown that substituent induced polarization of the enamine functionality could lead to true n-π* delocalization in that system, but that enols and their neutral derivatives could not be so influenced. Similarly, it was shown that there are heterocyclic molecules which satisfy Huckel's Rules, but which are not aromatic in their unsolvated ground states. However, suitably substituted derivatives of some of these molecules, whose electron densities have been significantly polarized, can become truly delocalized and hence aromatic.

The discussion below will apply these new criteria for delocalization to some other important π systems and will use both bond length data (obtained from X-ray crystallographic and other studies) and the VESCF-HMO calculated bond lengths and orders of some model compounds.[5c] All of the calculated bond lengths will be enclosed in brackets to distinguish them from experimentally determined values.

Since molecular mechanics programs often return bond lengths which are slightly different from those revealed by X-ray crystallography, the bond length and bond order data from these VESCF-HMO calculations were closely examined. Thus, it became apparent that the bond orders generated for unsymmetrical heterocycles which have more than one heteroatom in their rings are not always congruent with their associated bond lengths. In analyzing the bond lengths and the bond orders for the nitrogen containing heterocycles discussed below, the following data must be remembered:

a) an isolated C=N double bond, in a simple imine, is 129 pm long,

b) the C=N bonds of pyridine are 134 pm long and have orders of 1.66,

c) bond orders greater than 1.5 should be obtained for C-C bonds which are shorter than about 143.2 pm, and for C-N bonds which are shorter than 137.6 pm.

These data will enable us to recognize inconsistent bond order/bond length pairs among those presented herein, and the significance of these anomalous data can then be weighed.

DISCUSSION

Delocalization in Some Simple π Molecules

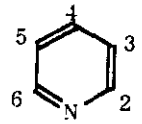
In order to create a frame of reference within which the ideas below can be examined, let us first review the structural, electron density distribution and bond order data of pyridine and benzene, two truly delocalized aromatic molecules.[5] Then, since most heterocyclic molecules possess conjugated π bonds, we shall examine the reality of delocalization in non-aromatic molecules which possess conjugated π bonds.

a) Pyridine and Benzene

The lengths of the C-C bonds of benzene and pyridine are about 139-140 pm, and the orders of these bonds are about 1.66, indicating that each of these bonds is a true double bond. Similarly, the C=N bonds of pyridine have orders of 1.66 (and are 134 pm long). The double bonds of these molecules are weaker than those of isolated alkenes or imines (which have bond orders closer to 2 and much shorter bonds) because of the attenuated electron

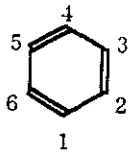
density in each double bond (there are six π electrons for six π bonds). Thus, each ring atom of benzene and pyridine (for which we include the lone pair as an "atom or group") must be recognized to be tetravalent and pentacoordinated (not pentavalent). Further, there is formal π bonding between every pair of neighbouring atoms in benzene, pyridine and every other truly aromatic molecule. The pentacoordination of the ring atoms in aromatic systems is the most important physical feature that distinguishes aromatic molecules from all others.

pyridine



bond	bond length (pm)[3,5c]	bond order[5c]
1 - 2	134.0 (134.4)	1.654
2 - 3	139.5 (139.8)	1.675
3 - 4	139.4 (140.0)	1.661

benzene



bond	bond length (pm)[4b,5c]	bond order[5c]
1 - 2	140 (140.0)	1.667

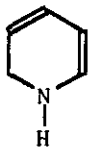
The initial processes in the reactions of benzene and pyridine are undoubtedly identical to those analogous processes in the reactions of alkenes, and in both cases must involve either attack by the aryl/alkene π electron density on an electrophile, or the attack of a nucleophile on the aryl/alkene lowest unoccupied π* molecular orbital. During the subsequent transformations of the reaction complex, or intermediate, the reaction paths of benzene and pyridine diverge from that of a simple alkene. The aryl-derived intermediate undergoes structural modifications directed toward restoring the aromaticity of the parent system, whereas the alkene-derived intermediate (not driven by as powerful a thermodynamic imperative) reacts otherwise. This is true for all electrophilic and nucleophilic reactions of suitably substituted derivatives of benzene, pyridine and the

alkenes.

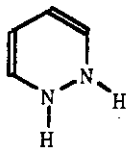
Benzene, pyridine and their derivatives can therefore be regarded as special alkenes, distinguished from simple alkenes and other non-aromatic molecules by the pentacoordinated nature of each of their ring atoms and a dramatic thermodynamic imperative to retain their very stable electronic structures.

b) Conjugated, Non-Aromatic π Molecules

Since most heterocycles contain conjugated π bonds, it will also be valuable to examine the features of some simple conjugated molecules in order to identify those features which indicate the presence, or absence, of true delocalization. Thus, we shall not only be able to recognize delocalized aromatic systems, but also delocalized non-aromatic molecules.



(1A)



(1B)

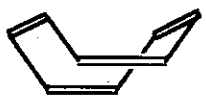
The issue of delocalization in non-aromatic, conjugated π systems like (1) has not been resolved because experimental data have not been invoked to provide convincing support for, or against, this premise. Fortunately, the structural features of some simple molecules, especially cyclooctatetraene (2) provide us with the criteria that we need to resolve these issues, in addition to confirming the validity of the new concepts of delocalization stated above.

The C-C single bond lengths in cyclooctatetraene[6] are 146 pm, shorter than that of 1,3-butadiene[3] (148 pm). There is no possibility of delocalization in cyclooctatetraene because the dihedral angles between the π bonds are about 65° in the stable conformation of this molecule. Further, any delocalization would be very unfavourable since a highly unstable "anti-aromatic" (4N π electron) species would be generated.[7] Thus, the length of the single bond of cyclooctatetraene is not an indication of partial, or

full, delocalization in this molecule.

The length of the C2-C3 single bond of cyclooctatetraene (as for 1,3-butadiene) is determined by the fact that the orbitals involved in the bond formation process are sp2 hybrids, which lie closer to their respective nuclei than sp3 hybrids. Thus, the greater electronegativity of the sp2 hybridized C2 and C3 atoms lead to a shorter C2-C3 bond.

cyclooctatetraene (2)



bond	bond length (pm)[6,5c]		bond order[5c]
1 - 2	134	(134.3)	1.981
2 - 3	146	(149.5)	1.136

The lengths of the single bonds of cyclooctatetraene are well within the range of normal C-C single bonds, and its double bonds have lengths and orders which are identical with those of an isolated C=C double bond. These data are the defining features of a highly localized π system.

It is also important to note that the bond lengths and VESCF-HMO calculated bond orders of the neutral conjugated alkenes[3,8] and carbonyl compounds, for example cis- and trans-retinal,[9] also show that these molecules are highly localized species.

These bond length features, which indicate localization of π bonds, must also be present in the structures of non-aromatic, conjugated heterocyclic molecules, like (1) above and other structurally intriguing heterocycles to be described below, and will be extremely valuable criteria in enabling us to appreciate their true structural features.

c) Dipyridyls and Biphenyls

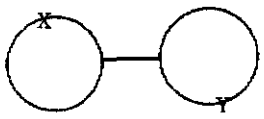
The dipyrdiyls (3) are an especially interesting group of molecules because their non-planar conformations must result in the molecules having two sets of "localized" molecular orbitals (one for each ring), while their planar conformations could allow inter-ring delocalization which would "blend" these "localized" molecular orbitals into one global molecular orbital. If the two aromatic rings were participants in a truly delocalized system then

the inter-ring bond should be considerably shorter than a single bond and would normally be expected to show the length and physical characteristics of a double bond.

The important structural features of the dipyridyls, two aromatic rings linked together, are also found in molecules like the dibenzofurans and the azaphenanthrenes and so it must be valuable to resolve issues of inter-ring delocalization in these compounds. Fortunately, the structurally similar biphenyls have been extensively investigated and are excellent models for these molecules.

In the solid phase, the two aromatic rings of biphenyl[10] (4) are coplanar and the bond linking them is 148 pm long (longer than the single bond of cyclooctatetraene). The X-ray crystallographic data[10] for other non-ortho-substituted biphenyls, in which the aromatic rings are not coplanar, show that this inter-ring bond is usually 148-151 pm long. These bond lengths show that the inter-ring bonds in planar and non-planar biphenyls are true single bonds. In the ground state, the π systems of the two linked aromatic rings are independent of each other, even when the rings are coplanar, and there is no global delocalization.

The biphenyls which are not substituted in the ortho-positions show free rotation about the inter-ring bond,[2] as would be expected for a true single bond. Biphenyls which are suitably substituted at their ortho positions can show restricted rotation about the single bond, but this restricted rotation is well known to be mediated by steric interactions,[2] and is not a result of a delocalization phenomenon.



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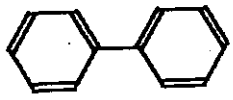

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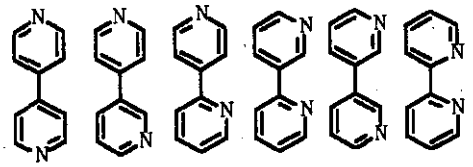
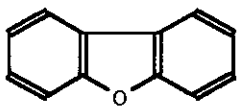


(3)

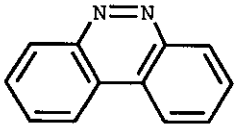
These important structural features of the biphenyls must also be encountered in the dipyridyls and all other hetero-aromatic molecules of general structure (5).

d) Dibenzofuran

Dibenzofuran (6) can be regarded as a biphenyl-derived molecule which should be highly stable, since the central ring looks like a moiety which obeys Huckel's Rules. The X-ray crystallographic data for dibenzofuran[12] shows that the length of the bond joining the two benzenoid rings is 148 pm and so is a single bond. Indeed, the lengths of the C-O bonds are 140 pm, similar to the C-O bonds of simple aliphatic ethers. Thus, the central ring of dibenzofuran has no feature which could suggest delocalization, or aromaticity, in that moiety. The oxygen's lone pairs are very highly localized and the two benzenoid rings are quite independent of each other.



(6)



(7)

e) 9,10-Diazaphenanthrene

9,10-Diazaphenanthrene (7) has the features of a biphenyl whose two rings have been further linked together. The central ring is a six-membered heterocycle which one would assume must have features similar to those of pyridazine (see below). However, the X-ray crystallographic data for 9,10-diazaphenanthrene[11] shows that the bond is about 143.6 pm long (just within the 143.2 pm lower limit of the length of a C-C single bond) and hence is either a true single bond, or at best a very weakly delocalized π bond. Further, the N=N bond is 129.2 pm long (identical with the length of an isolated N=N bond), and the C-N bonds are about 139.6 pm (within the 137.6 pm lower limit of the length of a C-N single bond). Thus, there is very little delocalization between the two benzenoid rings, or in the central ring. The molecule's geometry clearly indicates that the combined stability of two independent benzene rings is greater than the stability of the globally delocalized π system.

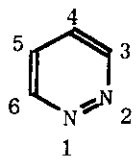
These analyses of the molecules (3), (4), (6) and (7) are of great

importance since they discredit the assumption that the more extensive a π system is, the greater will be its stability (since it would possess many more cannonical forms). The fact that there is no delocalization between the aromatic rings of compounds (4), (6) and (7) shows that this assumption is not always correct.

f) Pyridazine, Pyrimidine and Azobenzene

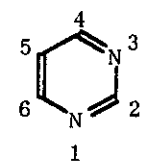
The chemistry and bond length data[3] for pyridazine (8) and pyrimidine (9) show that they are as strongly aromatic as pyridine.

pyridazine (8)



bond	bond length (pm)[3,5c]	bond order[5c]
1 - 2	133.0 (134.0)	1.603
2 - 3	134.1 (133.2)	1.711
3 - 4	139.3 (140.7)	1.629
4 - 5	137.5 (139.4)	1.696

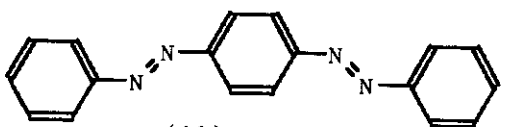
pyrimidine (9)



bond	bond length (pm)[3,5c]	bond order[5c]
2 - 3	133.3 (134.3)	1.663
3 - 4	134.8 (134.4)	1.645
4 - 5	138.4 (139.8)	1.671

These molecules provide excellent models for delocalized N=N and C=N bonds in hetero-aromatic systems and show that these delocalized bonds are longer than their localized analogues which are both about 129 pm long.

The X-ray crystallographic structure of the azobenzene (10) shows[13] that the C-N bonds are about 145 pm long, and the N=N bonds are about 123 pm.



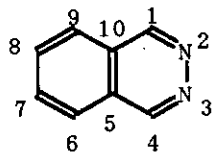
(10)

Since the C-N single bond is almost the same length as an isolated C-N bond (about 148 pm), then the bond lengths of the compound (10) indicate that there is no delocalization between the benzenoid rings and the N=N groups. The N=N bond of compound (10) is unusually short, much shorter than an isolated N=N bond in an azoalkane.

g) 1,3-Diazanaphthalene and 2,3-Diazanaphthalene

The X-ray crystallographic structure[14] of 2,3-diazanaphthalene (11) shows that C1-C10 and C4-C5 bonds of the hetero-aromatic ring are about 141 pm long and are similar in length to those in the benzenoid ring. The C=N bonds are 129.7 pm long, similar to the average length of an isolated C=N bond (129 pm) and considerably shorter than the C=N bonds of pyridine (134 pm) and pyridazine (8). The N=N bond is 137 pm long, longer than the N=N bond of pyridazine (8), and barely lies within the outer limit (138 pm) of the normal range of lengths for N=N (double) bonds. Thus, the molecule (11) is probably not aromatic since its π electron density is highly localized.

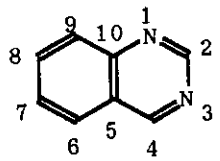
2,3-diazanaphthalene (11)



bond	bond length (pm)[14,5c]	bond order[5c]
1 - 2	129.1 (130.9)	1.825
2 - 3	137.3 (137.1)	1.447
3 - 4	129.7 (130.9)	1.825
4 - 5	140.7 (143.7)	1.462

Indeed, the VESCF-HMO calculated, unsolvated, ground state of the molecule (11) shows that the C-C bonds of the heterocyclic ring have bond lengths and orders suited to single bonds. Thus, all the data suggest that the heterocyclic moiety of the molecule (11) is, at best, only very weakly aromatic.

1,3-diazanaphthalene (12)



bond	bond length (pm)[3,5c]	bond order[5c]
1 - 2	130.7 (131.7)	1.789
3 - 4	130.7 (131.8)	1.776

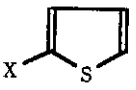
The X-ray crystallographic structural data of 1,3-diazanaphthalene[3] (12) show that the C2=N1 and C4=N3 bonds are about 131 pm long. When compared with pyrimidine (9) whose C=N bonds are 133 pm long, we must conclude that the C=N bonds of compound (12) are more localized and hence this molecule is less aromatic than pyrimidine. This increased localization is also

revealed by the VESCF-HMO calculated features of compound (12).

The X-ray crystallographic structural data of the hetero-aromatic molecules (11) and (12) enable us to recognize the very important fact that a heterocyclic moiety which is fused to a benzenoid, or another strongly aromatic, ring system will show greater localization of its π electron density and hence reduced aromaticity. Other examples of this phenomenon will be encountered below.

h) The Five-membered Ringed Hetero-aromatic Molecules.

(13)



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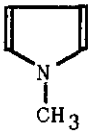


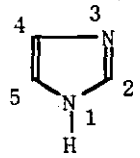
(15)

The non-aromaticity of furan (13) has been discussed[5] and this conclusion is strongly is supported by the bond length data for this molecule.[3,15] The lengths[3,16] of the C-S bonds and the C-C bonds of simple derivatives thiophene are within the ranges of lengths of the respective C=S and C=C (double) bonds and these, along with the bond order data from VESCF-HMO calculations, show that thiophene (14) is undoubtedly aromatic. The aromaticity of pyrrole (15) has been discussed[5] and is also supported by its bond length data.[3]

The bond lengths[3,17] of imidazole (16) indicate that this molecule is only weakly aromatic, if at all. The length of the N3-C4 indicates that it is at the smaller extreme of the range of lengths for C-N single bonds, and the length of the C5-N1 bond places this bond at the higher extreme of the range of lengths for C=N double bonds. Further, the length of the C4-C5 bond shows that it is highly localized. The VESCF-HMO calculated bond lengths for imidazole (16) are similar (between 0.3 and 1.0 pm longer) to those ascertained by the X-ray crystallographic study,[3] except for the calculated lengths of the N3-C4 bond (which is 1.7 pm shorter), and the C4-C5 bond (which is 2.0 pm longer). The calculated bond lengths (but not the bond orders) are closer to those predicted for an aromatic imidazole

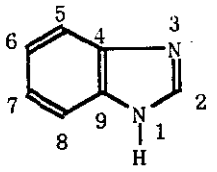
molecule, but still show that the calculated model of imidazole would only be weakly aromatic in its unsolvated ground state.

imidazole (16)



bond	bond length (pm)[3,5c]		bond order[5c]
1 - 2	134.9	(135.9)	1.553
2 - 3	132.6	(132.9)	1.727
3 - 4	137.8	(136.2)	1.567
4 - 5	135.8	(137.8)	1.783
5 - 1	136.9	(137.3)	1.462

benzimidazole (17)

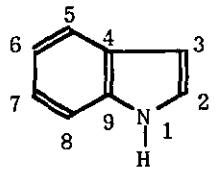


bond	bond length (pm)[5c]		bond order[5c]
1 - 2		(136.5)	1.537
2 - 3		(132.4)	1.767
3 - 4		(137.7)	1.476
4 - 5		(141.5)	1.542
5 - 6		(138.7)	1.754
6 - 7		(142.3)	1.568
7 - 8		(138.7)	1.757
8 - 9		(141.6)	1.533
9 - 1		(137.5)	1.420
9 - 4		(140.6)	1.602

The VESCF-HMO calculated bond lengths (and orders) for the heterocyclic ring of benzimidazole (17) are similar to those for imidazole, but these data indicate that there is more π localization in the heterocyclic moiety of benzimidazole than in imidazole. Thus, the heterocyclic ring of benzimidazole will undoubtedly be non-aromatic in its unsolvated ground state.

The bond lengths[3] and VESCF-HMO calculated bond orders of the heterocyclic moiety (the atoms N1, C2 and C3) of indole (18) also reveal that there is greater localization of the π electron density in this heterocyclic ring than in pyrrole.

indole (18)



(18)

bond	bond length (pm)[3,5c]		bond order[5c]
1 - 2	138.0	(137.4)	1.487
2 - 3	135.8	(138.2)	1.785
3 - 4	143.6	(142.4)	1.517
4 - 5	139.8	(142.0)	1.515
5 - 6	138.1	(138.4)	1.773
6 - 7	139.6	(142.4)	1.547
7 - 8	137.2	(138.4)	1.772
8 - 9	139.5	(142.0)	1.510
9 - 1	137.4	(137.1)	1.462

Indeed, both the bond order and the bond length criteria suggest that the heterocyclic ring of the indole structure is not aromatic in the unsolvated ground state of this molecule.

The Reality of Delocalization

The examples discussed above dramatically reveal that delocalization is not always a feature of the ground states of neutral, stable molecules which have conjugated π systems.

The absence of global delocalization in the aromatic molecules reviewed above (biphenyl, 9,10-diazaphenanthrene, and dibenzofuran) indicates that truly aromatic systems which engage in external delocalization in their ground states must experience severe energetic penalties (loss of stability and possibly aromaticity). Instead, the aromatic and π electron moieties remain independent and highly localized. Similarly, the conjugated alkenes, unsaturated carbonyl compounds, enamines, esters and enols remain highly localized in their ground states.

The data for the heterocyclic molecules reveal that the fusion of a hetero-aromatic nucleus to a benzenoid nucleus reduces the degree of aromaticity in the heterocyclic moiety, because of the reluctance of the benzenoid nucleus to permit global delocalization which involves (and quite possibly disrupts) its stable π electron density distribution. The chemical consequences of the loss of aromaticity in the heterocyclic parts of benzo-fused hetero-aromatic molecules have been widely observed.[3]

The reluctance of the benzenoid ring to participate in delocalization involving entities attached to the ring can also be appreciated by considering the efficiency of delocalization in radicals and carbocations, common reactive intermediates. For example, homolytic bond dissociation energies[18a] indicate that a carbon radical is stabilized just as much by one flanking π bond (as in the allylic radical) as by a flanking phenyl group (as in the benzylic radical), even though the benzylic radical could possibly provide greater overall delocalization.

However, as the internal energy of the reactive intermediate increases, so

too will the energetic advantages of extensive delocalization because of the stability to be gained. Thus, we should expect delocalization to be a feature of very high energied intermediates, as indeed is suggested by the experimental data. For example, heterolytic bond dissociation energies[18b] indicate that the carbocation center of a benzylic carbocation is more highly stabilized than that of an allylic carbocation.

When free rotation is possible, the conformations adopted by localized conjugated π systems are not determined by resonance or delocalization effects, but by through-space π-π, n-π, π-π* and n-π* interactions,[19] and steric and dipole-dipole interactions.[2]

Truly aromatic heterocyclic molecules in their ground states will also demonstrate a reluctance to participate in external delocalization processes, similar to benzene, and this fact must guide our discussions on the chemistry and structural features of all the polycyclic hetero-aromatic molecules.

The Chemical Reactivity of Conjugated π Systems

The data above leads us to conclude that molecular orbital theory has unwittingly been inappropriately applied to the rationalization of the structural/electronic features of some conjugated π electron systems, whose ground states had incorrectly been assumed to be delocalized. However, these molecular orbital theoretical studies have been used successfully in the rationalization of the free radical and ionic chemistry of conjugated π systems, and in the rationalization of their electrocyclic, sigmatropic and cycloadditive reactions.[20] This paradoxical situation suggests that these π systems do achieve true delocalization at an early stage in their reactions and so become systems to which molecular orbital theory can then be rigorously and properly applied.

The bond order and bond length data for simple enamines and enol ethers have indicated that these molecules are not delocalized in their ground states.[5] These non-delocalized, conjugated π systems examined above must therefore react either in discrete steps (by a totally non-concerted

reaction), or initially in a non-concerted fashion followed by a concerted process (a partly concerted reaction).

Partly Concerted Reactions

The reaction of a conjugated, but localized, π system could be initiated by an "event" which perturbed the π systems (and hence the geometry) of the reacting molecule, so leading to the establishment of true delocalization. Then, the molecular orbital theoretical analyses, developed on the assumption that these π systems were delocalized in their ground states, would become completely valid for the subsequent steps in the reaction. This reaction type could validly be described as a "partly concerted reaction".

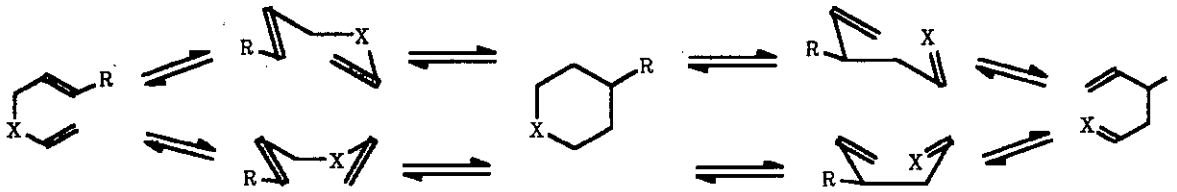
The nature of this critical "event" will differ from one reaction to another (it might be a rehybridization, or an energy or electron transfer process), but the "event" undoubtedly requires much less energy than the overall activation energy of the reaction since these "events" have eluded detection to date. The wide range of experimental conditions over which the electrocyclic, cycloaddition and the other "concerted" reactions of simple conjugated π systems are known to occur is probably indicative of the energy requirements of these "events".

Delocalization in Heterocyclic Transition States

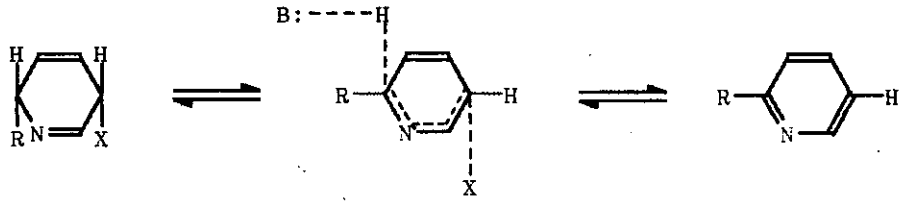
The concept of delocalization has also been invoked, and abused, in discussions of transition states of reactions. Some transition states have been referred to as "aromatic" because they are suggested to be cyclic and involve the simultaneous reorganization of 4N+2 electrons. Often however, this terminology cannot be justified when a comparison is made between these transition states and the important stereo-electronic features of aromatic molecules.

For example, the heterocyclic transition state invoked in the mechanism for the Claisen rearrangement reaction is not planar and is usually described as being either chair-like, or boat-like.[21] Further, the new σ bond is being established between the ends of the π bonds, C1 and C6, by a linear

overlapping of two "p type" orbitals (not to be confused with the edgewise overlapping of two "p type" orbitals which normally would lead to a π bond), scheme 1. Thus, regardless of the possibility that 6 (or any other 4N+2 number of) electrons might simultaneously (if we ignore the Uncertainty Principle[1]) be involved in the transition state, this type of transition state does not show the stereo-electronic features required of aromatic molecules (either by the new criteria, or by Huckel's rules).



Scheme 1



Scheme 2

On the other hand, the transition state in the transformation of a dihydropyridine to the aromatic product, scheme 2, must show the features typically found in aromatic systems and can thus be cautiously described as an aromatic transition state. Thus, the term "aromatic transition state" should properly be reserved for the transition states of reactions which create, disrupt, or rearrange truly aromatic systems since these transition states do have the features of truly aromatic entities.

The Chemistry and Physical Properties of Some Conjugated Heterocyclic Molecules. Hetero-aromaticity and the Tertiary Structures of DNA

The discussions above will be meaningful in understanding the chemistry and physical properties of some heterocyclic systems which satisfy Huckel's Rules but which are not truly aromatic in their ground states. Some of

these heterocycles sporadically show aromatic character in their chemistry and this inconsistent chemistry, particularly when not properly interpreted mechanistically, has led to great uncertainty as to the aromatic status of these molecules. A discussion of two examples of heterocyclic molecules that show varying degrees of aromaticity, depending on their environments, will help to clarify this topic.

a) Furan

Furan's chemistry occasionally seems to be similar to that of a truly aromatic molecule, particularly when very high energied intermediates are involved or when the reactions require high activation energies. However, the chemistry of furan[3] is clearly consistent with that of a non-aromatic molecule, since it very frequently undergoes addition reactions instead of substitution reactions. Further, the structural criteria stated above show that furan (13) is non-aromatic in its ground state.

This ambiguity in the chemistry of furan reminds us that there are several molecules whose features almost, but not totally, satisfy the criteria for aromatic systems. During their reactions, these molecules can gain enough energy, or undergo subtle structural modification, to enable them to form highly delocalized intermediates, but this does not mean that the parent molecules were aromatic in their ground states.

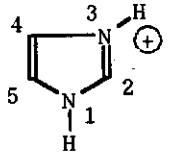
b) Imidazoles

The structural data for imidazole (16) and benzimidazole (17) have been presented and show that these heterocycles are highly localized in their unsolvated ground states and so must be, at best, only very weakly aromatic. Remarkably, the protonation of these molecules (to produce the symmetrical imidazolium (16A) and benzimidazolium (17A) ions) causes quite dramatic structural and π electron density changes which convert the resulting ions into more strongly aromatic species. This observation helps us to rationalize the basicities of these molecules, particularly imidazole, by revealing that there are two important factors involved, namely:

a) the stability gained by the increased aromaticity in the ion, and

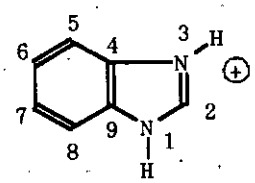
b) the strength of the new N-H bond.

imidazolium (16A)



bond	bond length (pm)[5c]	bond order[5c]
1 - 2	(133.7)	1.673
2 - 3	(133.7)	1.673
3 - 4	(136.9)	1.524
4 - 5	(137.9)	1.783
5 - 1	(136.8)	1.524

benzimidazolium (17A)



bond	bond length (pm)[5c]	bond order[5c]
2 - 3	(133.8)	1.679
3 - 4	(136.7)	1.514
4 - 5	(141.3)	1.548
5 - 6	(139.0)	1.741
6 - 7	(142.3)	1.571
9 - 4	(142.0)	1.524

Imidazole (16) and benzimidazole (17) thus introduce us to the fact that the hetero-aromaticity of suitable molecules can be manipulated by simple processes. We have recognized that hydrogen bonding, dipole-dipole, ion-dipole and ion-ion interactions are structural and stereo-electronic factors that influence the chemistry, reactivity and structural features of organic molecules. Now we must add to that list the manipulation of the hetero-aromaticity of suitable heterocycles, which as we see above, can be "switched on" and "switched off" in a predetermined fashion by simple processes.

The Tertiary Structures of DNA. The Aromaticities of Hydrogen Bonded Purines and Pyrimidines

Purines and pyrimidines occur naturally (as their glycosides) in the polynucleotides DNA and RNA. The DNA polymers adopt helical and other tertiary structures which are stabilized by the interactions between the bases in the polynucleotide chains. In RNA, the polynucleotide chain often folds back onto itself so bringing bases of non-adjacent nucleotidic units close enough for them to interact and stabilize the folded structure. The stabilities of these three dimensional polymeric structures undoubtedly play vital roles in their abilities to act as biologically important molecules.[22] Understanding the origins of the stability of the tertiary

structures of DNA and RNA is clearly very important and three main factors[22] are now thought to be significant:

a) Watson-Crick type[23] hydrogen bonding between the base pairs,

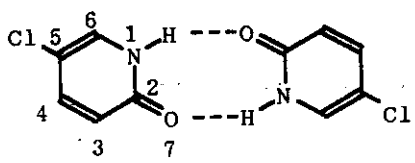
b) π orbital interactions between the "stacked" base pairs, and

c) repulsions among the charged phosphate residues of the nucleotide backbone.

The observation that imidazole and benzimidazole gain substantial increases in their aromaticities upon becoming protonated suggests that a similar effect might be displayed by the nucleotidic bases after they have become involved in Watson-Crick type hydrogen bonding.

Indeed, the stimulation of aromaticity in heterocyclic systems by Watson-Crick type hydrogen bonding is probably quite common in suitable molecules. For example, the 2-pyridones are non-aromatic in their unsolvated ground states,[5] but become aromatic on dimerization (by mutual hydrogen bonding of their amide groups in a "Watson-Crick type pattern"). This is quite clearly shown comparing the X-ray crystallographic data[24] for 5-chloro-2-pyridone (19) with the calculated bond lengths for its unsolvated ground state (given in brackets).

5-Chloro-2-pyridone (19)



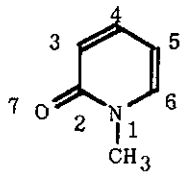
bond	bond length (pm)[24,5c]	
1 - 2	136.6	(137.1)
2 - 3	142.7	(145.9)
3 - 4	134.3	(136.7)
4 - 5	140.5	(144.0)
5 - 6	134.2	(137.4)
6 - 1	135.6	(137.4)
7 - 2	125.0	(123.3)

The "push-pull" nature of the hydrogen bonds in these dimers are clearly apparent. The hydrogen bond to the carbonyl oxygen polarizes the electron densities in the C=O (double) and the N-H bonds, and these polarizations facilitate the delocalization of the lone pairs of electrons of the amidic nitrogen (the pull). The developing positive charge on the amidic nitrogen of one entity is then simultaneously stabilized by the developing negative charge on the carbonyl oxygen of the other molecule (the push). These

effects are undoubtedly synergistic and mutually maximize both the strength of the hydrogen bond and the polarization of the amidic group.

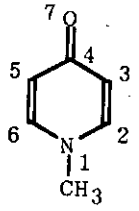
The hydrogen bonds linking the nucleotidic bases in Watson-Crick patterns are very similar to those in the 5-chloro-2-pyridone dimer (19) and could have a equally dramatic effects on the structural and electronic features of the hydrogen bonded nucleotidic bases.

N-Methyl-2-pyridone (20)



bond	bond length (pm)[5c]	bond order[5c]
1 - 2	(138.3)	1.449
2 - 3	(146.1)	1.369
3 - 4	(136.5)	1.850
4 - 5	(143.6)	1.450
5 - 6	(137.2)	1.821
6 - 1	(138.1)	1.451
7 - 2	(123.5)	1.780

N-Methyl-4-pyridone (21)

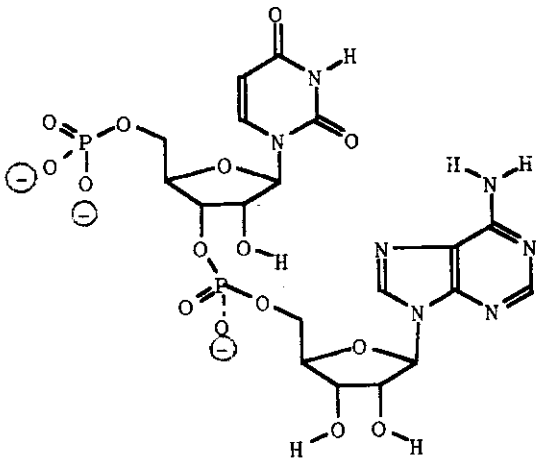


bond	bond length (pm)[5c]	bond order[5c]
1 - 2	(138.2)	1.444
2 - 3	(137.0)	1.835
3 - 4	(145.7)	1.374
4 - 7	(122.9)	1.821

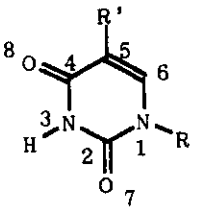
The non-aromaticity of the unsolvated ground states of *N*-methyl-2-pyridone (20) and *N*-methyl-4-pyridone (21) has been discussed.[5] Their data are presented for comparison with those of compound (19) and the pyrimidones. The unsolvated structures of the purines and pyrimidines, *N*-methylated at positions 9 or 3, were modelled in order to generate simple analogues of the nucleotidic bases, whose bond lengths and orders might allow us to better understand their electronic features.

The calculated bond length and bond order data for the homologous molecules *N*-methylthymine (22) and *N*-methyluracil (23) reveal that they have nearly identical structural parameters and that both are non-aromatic in their unsolvated ground states (see Table 2).

The calculated bond length and bond order data for 4-aminopyrimidine (24) suggest that, like pyrimidine (9), this molecule is aromatic. However, the

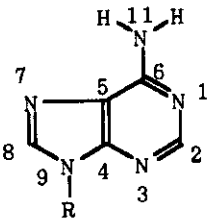


ApU (28)

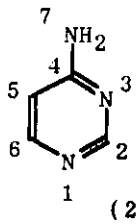


(22) R = R' = CH_3

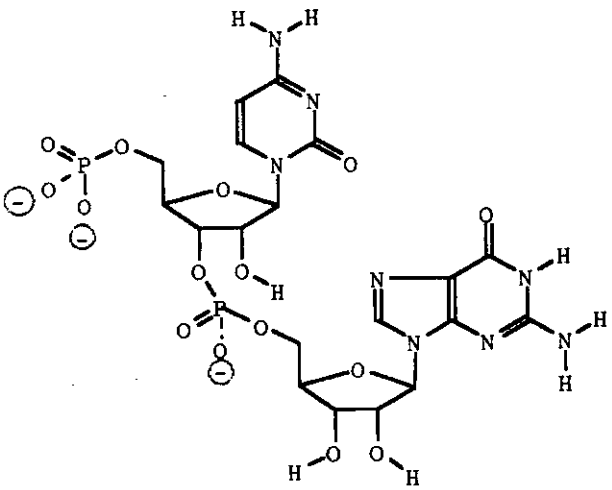
(23) R = CH_3, R' = H



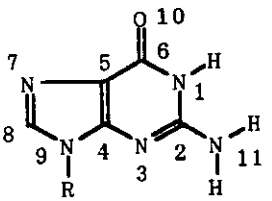
(25) R = CH_3



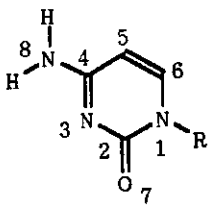
(24)



GpC (29)



(27) R = CH_3



(26) R = CH_3

calculated bond length and bond order data for 9-methyladenine (25) is ambiguous and suggests that this molecule might only be weakly aromatic in its unsolvated ground state. It seems likely that the bicyclic structure of this molecule has resulted in the attenuation in the aromaticity of each ring, as was demonstrated above for the benzo-fused heterocycles.

The calculated bond length and order data for methylcytosine (26) show that it cannot be aromatic in its unsolvated ground state, and similar data for 9-methylguanine (27) indicate that the "pyrimidone" ring, like cytosine, also cannot possibly be aromatic in the unsolvated ground state of molecule (27). The "imidazole" ring of the molecule (27) could however be very weakly aromatic.

The X-ray crystallographic structural data of sodium adenylyl-3',5'-uridine hexahydrate[25] (ApU) (28) and sodium guanylyl-3',5'-cytidine nonahydrate[26] (GpC) (29) have been obtained. Each of these molecules crystallized as a highly hydrated dimer held together by Watson-Crick type hydrogen bonding (as well as ion-dipole interactions) and so these molecules are acceptable models for the nucleotidic fragments of the double-helical structures of DNA.

Notwithstanding the similarities between the compounds (28), (29) and fragments of the DNA polymers, the Watson-Crick hydrogen bonded nucleotidic pairs of the DNA polymers will be located in a much less hydrated, more hydrophobic, environment[22] than the hydrated dimers of the compounds (28) and (29) are in their solid phases. The hydrophobic core of the DNA polymers will stimulate the formation of stronger hydrogen bonds between the nucleotidic bases than would exist in a more hydrated, environment. Thus, the stereo-electronic effects observed in the solid phase studies of the compounds (28) and (29) will be attenuated in comparison to those which exist in the hydrophobic core of the DNA polymers.

A comparison of the bond length data for the bases in the structures (28) and (29) with those data for the compounds (22), (23), (25), (26) and (27) (Tables 2) show that adenine, in compound (28), is the only base that

Table 2

Bond	Crystallographic Bond Lengths (pm)		Calculated[5c]	
	N-methylthymine[27]	2-deoxythymidine[27]	*N*-methylthymine (22)	
1 - 2	137.9	138.5	(138.2)	1.445
2 - 3	137.9	138.1	(137.1)	1.429
3 - 4	137.5	137.8	(136.9)	1.443
4 - 5	143.2	145.3	(146.7)	1.329
5 - 6	134.6	134.3	(136.5)	1.874
6 - 1	138.3	137.4	(139.0)	1.387
7 - 2	121.4	120.6	(123.7)	1.760
8 - 4	123.7	123.0	(123.0)	1.810
	ApU (28)	2-deoxyuridine[28]	*N*-methyluracil (23)	
1 - 2	137.8	138.3	(138.5)	1.433
2 - 3	137.5	137.9	(137.1)	1.434
3 - 4	138.8	138.1	(136.9)	1.438
4 - 5	142.1	144.0	(146.5)	1.324
5 - 6	134.2	133.4	(136.4)	1.870
6 - 1	136.0	138.0	(138.7)	1.409
7 - 2	121.7	121.9	(123.6)	1.767
8 - 4	126.2	123.1	(122.9)	1.817
	ApU (28)	Adenosine[29]	9-methyladenine (25)	
1 - 2	134.6	134.0	(136.3)	1.580
2 - 3	134.6	133.0	(132.7)	1.748
3 - 4	135.0	134.9	(137.5)	1.467
4 - 5	136.4	138.1	(139.9)	1.643
5 - 6	142.9	141.5	(143.0)	1.457
6 - 1	134.0	135.1	(135.0)	1.629
5 - 7	136.4	138.5	(137.7)	1.471
7 - 8	132.6	130.8	(132.2)	1.775
8 - 9	136.4	136.2	(137.2)	1.523
9 - 4	136.7	137.4	(137.3)	1.458
10 - 6	136.1	133.2	(135.4)	1.536
	GpC (29)	2-deoxycytidine(HCl)[30]	*N*-methylcytosine (26)	
1 - 2	139.4	138.2	(138.8)	1.419
2 - 3	134.5	138.6	(135.3)	1.414
3 - 4	131.8	135.7	(133.0)	1.703
4 - 5	144.5	141.2	(144.4)	1.400
5 - 6	134.1	133.8	(137.1)	1.824
6 - 1	135.7	136.9	(137.8)	1.472
7 - 2	123.6	121.4	(123.9)	1.780
8 - 4	132.7	130.8	(135.7)	1.532
	GpC (29)	guanosine	9-methylguanine (27)	
1 - 2	138.2	136.5	(138.2)	1.429
2 - 3	136.2	133.1	(133.3)	1.716
3 - 4	135.0	136.2	(139.5)	1.366
4 - 5	135.8	138.0	(139.3)	1.683
5 - 6	145.2	141.9	(146.3)	1.340
6 - 1	139.0	139.0	(137.6)	1.435
5 - 7	139.7	138.4	(136.8)	1.521
7 - 8	132.0	131.1	(132.5)	1.761
8 - 9	136.1	136.5	(137.0)	1.528
9 - 4	137.9	137.1	(137.1)	1.474
10 - 6	120.6	123.4	(123.1)	1.799
11 - 2	133.1	133.3	(136.4)	1.489

becomes truly aromatic on hydrogen bonding in the Watson-Crick pattern. This result must be viewed cautiously however, because while we can conclude that adenine will be aromatic in environments in which it is engaged in Watson-Crick hydrogen bonding (and so in the DNA polymers), we cannot conclude that the other bases will not become aromatic in the DNA polymers, whose environments are quite different from the crystals of compounds (28) and (29).

Unfortunately, we must await the atomic resolution X-ray crystallographic studies of nucleotidic oligomers (structurally more similar to DNA) in order to determine the roles of the other nucleotidic bases in the tertiary structures of DNA, but the data from the crystallographic structures of the compound (28) have clearly revealed a special role for adenine in the tertiary structure of DNA.

There are several other features of the Watson-Crick hydrogen bonded nucleotidic bases of the compounds (28) and (29) which should be noted.

a) Notwithstanding the data for the molecule (27), whose imidazoloid ring seemed to be weakly aromatic, the guanyl group in compound (29) has structural features which indicate that it is non-aromatic.

b) The lone pairs of the primary amino-groups of cytosine, guanine and adenine, are delocalized into the flanking C=N bonds, in all of their compounds.

c) The lengths of the C5-C6 bonds of the pyrimidinoid compounds (22), (23), (26), uracyl of (28), and cytosyl of (29) are all quite close to that of an isolated C=C double bond and hence these bonds are highly localized.

Any system whose structural components are induced into aromaticity, by hydrogen bonding (like adenine) or protonation (like imidazole), during its assembly, or reactions, will gain both the stability due to the new bond and the newly-established/strengthened aromatic character. Thus, while we can deduce that the stability of the tertiary structures of DNA will increase as the proportion of adenine in the polymer increases, future studies will be required to reveal the true roles of the other nucleotidic

bases.

CONCLUSION

The elegantly subtle manipulation of hetero-aromaticity by nature has not been previously recognized because of the absence of rigorous criteria for defining aromaticity. The new criteria for establishing the presence of delocalization in molecules containing conjugated π systems have revealed many aspects of organic chemistry which were previously unrecognized, and have assisted in the resolution of some difficult issues.

Since the delocalization phenomena can now be unequivocally identified, and since we are now aware of the simple methods by which the aromaticity of suitable heterocyclic molecules can be manipulated, we should be able to use this information in the rational design of molecules for specific uses. Further, solutions to some of the old mechanistic puzzles from the rich legacy of experimental organic chemistry will now become apparent.

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