

## Antiaromaticity

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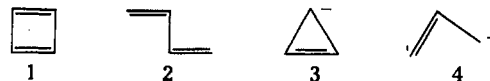
"Aromaticity" is a word with many meanings;<sup>1</sup> it shares this property with most other words in the English language. Such regrettable imprecision is thus cause for caution (although it is hardly a reason to discard the word, as some have suggested<sup>2</sup>). For our present purpose we adopt the common energetic definition that a compound is aromatic if cyclic delocalization of ( $\pi$ ) electrons stabilizes it relative to an analogous model compound without cyclic delocalization.

It has been understood for many years that among simple monocyclic systems only compounds with  $4n + 2$   $\pi$  electrons, such as benzene or cyclopentadienyl anion, would actually be aromatic. Cyclic conjugated systems with  $4n$   $\pi$  electrons, which did not fit Hückel's  $4n + 2$  rule for aromaticity, were generally<sup>3</sup> classed as "pseudoaromatic." However, both theory and experiment suggest that for at least some members of the  $4n$  series cyclic delocalization of  $\pi$  electrons leads to strong destabilization of the compound, in contrast to the stabilization characteristic of aromaticity. For this reason, we proposed<sup>4</sup> the term "antiaromatic" to describe such systems.

A cyclic conjugated system is considered to be antiaromatic if its  $\pi$  electron energy is higher than that of a suitable reference compound which is not cyclically delocalized. Thus antiaromaticity is a particular aspect of antibonding, just as aromaticity is a particular aspect of bonding. In both cases, the definition assumes that there are ways of assigning the total energy of a given molecule to various compartments, one of which reflects the result of cyclic delocalization of its  $\pi$  electrons.

The choice of suitable reference compounds is a problem, just as it is for aromaticity. We have generally preferred<sup>5</sup> to refer the cyclic compound, *e.g.*, cyclobutadiene (1), to its linear analog, in this case 1,3-butadiene (2). An alternative would refer cyclobutadiene to two isolated ethylene molecules. The experimental difference in this case is slight, since 1,3-butadiene has little extra resonance energy of its own, but in the case of organic ions the choice of ref-

erence compounds is more significant. Thus, antiaromatic cyclopropenyl anion (3) can be referred either to allyl anion (4) or to an isolated double bond and an isolated carbanion. Since the allyl anion system has significant resonance stabilization, it should furnish a bigger contrast with the instability of the cyclopropenyl anion than would an isolated carbanion and double bond system. As we will describe, experimental evidence is available which is relevant to both types of comparisons.



Antiaromaticity is predicted by quantum mechanical calculations at various levels of sophistication. Thus, a simple Hückel calculation predicts that cyclobutadiene, with delocalization energy of  $4.0\beta$ , will be equivalent in  $\pi$ -electron energy to two isolated double bonds and less stable than 1,3-butadiene, whose  $\pi$ -electron energy is calculated to be  $4.47\beta$ .

Although with this simple Hückel calculation cyclobutadiene is predicted to be nonaromatic if two isolated double bonds are the reference system, the inclusion of overlap in the calculation<sup>6</sup> leads to a prediction of antiaromaticity even relative to two isolated double bonds. Our PPP-SCF-CI calculations<sup>7</sup> on cyclopropenyl anion *vs.* allyl anion similarly predict that cyclopropenyl anion should be destabilized relative to the open-chain analog. A number of other calculations also are consistent with these concepts. Thus, Dewar<sup>8</sup> has used a semiempirical SCF-MO procedure to calculate that cyclobutadiene is conjugatively destabilized by 18 kcal/mol, relative

(1) For a good recent review of this subject, *cf.* P. J. Garratt, "Aromaticity," McGraw-Hill, London, 1971.

(2) *E.g.*, some of the discussions in "Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity," E. D. Bergmann and B. Pullman, Ed., Israel Academy of Sciences and Humanities, Jerusalem, 1971.

(3) *Cf.* A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley, New York, N. Y., 1961.

(4) R. Breslow, *Chem. Eng. News*, 43, 90 (June 28, 1965). Although some confusion on this point has been introduced into the literature, this seems to be the first use of this term. *Cf.* also M. J. S. Dewar, *Advan. Chem. Phys.*, 8, 65 (1965).

(5) R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.*, 85, 431 (1963).

(6) Although neglect of overlap is usually justified on the basis that "it works," in this instance HMO theory would work better with its inclusion.

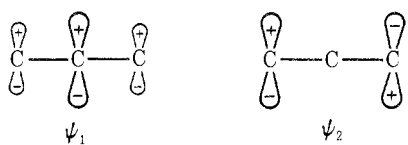
(7) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, 7, 565 (1968). PPP-SCF-CI are Pariser-Parr-Pople self-consistent field calculations with configuration interaction.

(8) N. C. Baird and M. J. S. Dewar, *J. Amer. Chem. Soc.*, 91, 352 (1969).

Dr. Ronald Breslow was born in Rahway, N. J., on March 14, 1931. He received an A.B. in Chemistry, an A.M. in Biochemistry, and a Ph.D. in Organic Chemistry, all at Harvard. He spent 1955-1956 at Cambridge University as a National Research Fellow with Sir Alexander Todd, and then joined the staff of Columbia University where he is now S. L. Mitchill Professor of Chemistry. His research interests in recent years have centered on aromaticity and antiaromaticity, biochemical model systems, and small-ring systems.

to linear butadiene as the reference system. Schaad and Hess<sup>9</sup> set the antiaromaticity of cyclobutadiene at 33 kcal/mol using a modified HMO method.

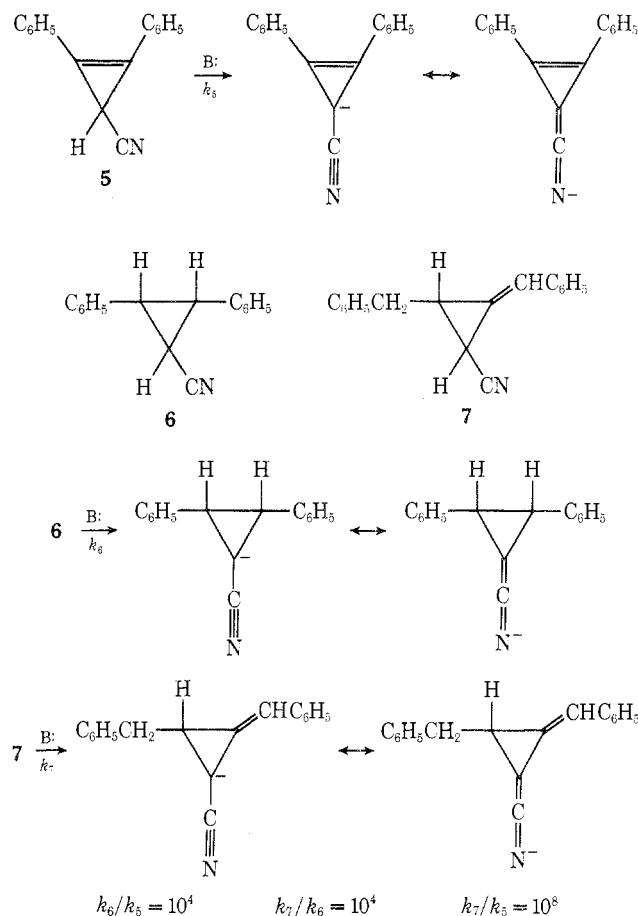
The antiaromaticity of the cyclopropenyl anion can also be understood by considering it as a perturbed allyl anion, with an extra 1,3 interaction. The result of such 1,3 interaction is to introduce extra bonding for the two electrons in  $\psi_1$  and antibonding for the two electrons in  $\psi_2$ . The coefficients of carbons 1 and 3 are larger in the latter case, so the antibonding interaction is larger than the bonding one, and this leads to net destabilization. This approach, involving orbital symmetries, is completely equivalent to the one utilizing a full calculation of energies. In fact, as Dewar has pointed out,<sup>10</sup> consideration of the aromaticity and antiaromaticity of transition states is fully equivalent to consideration of orbital symmetry in predicting allowed chemical reactions.



The experimental evidence for antiaromaticity in cyclic conjugated compounds with  $4n$   $\pi$  electrons is of two types. One kind of evidence is simply strongly suggestive, *e.g.*, the extremely high chemical reactivity of cyclobutadiene whenever it is generated.<sup>11-13</sup> The rate of a reaction depends on the difference in energy between starting materials and transition state, and it would in principle be possible that cyclobutadiene be enormously reactive not so much because its starting energy was abnormally high but instead simply because the energy of the transition state for any of its reactions is abnormally low. However, this kind of formal possibility seems quite unlikely: the high reactivity of cyclobutadiene undoubtedly reflects a high energy content in the compound itself. The second kind of evidence is thermodynamic, not kinetic, and involves the actual measurement of the energy of a  $4n$   $\pi$ -electron system in some way. The energy must then be corrected for all the other factors which contribute to it so as to extract that part of it which can be attributed to  $\pi$ -electron delocalization. This is much more difficult, and has been successful so far in only a few cases.

For the cyclopropenyl anion, both kinetic and thermodynamic evidence is available. Thus, we have studied<sup>14</sup> base-catalyzed deuterium exchange in cyanodiphenylcyclopropene (5) and various related compounds and have found that these compounds are kinetically much less acidic than are the corresponding saturated cyclopropane derivatives, such as

6. Since for related compounds a good correlation is known<sup>15</sup> to exist in general between kinetic acidity and equilibrium acidity, these data indicate that the cyclopropenyl anion derivatives produced by basic removal of a proton are destabilized relative to the cyclopropane anion derivatives. By contrast, the kinetic acidity of a methylenecyclopropane derivative (7) is greatly increased<sup>16</sup> over that of the saturated compound.



These studies involve the two kinds of reference compounds we have discussed. In the comparison of the cyclopropene acidity with the cyclopropane acidity one is asking the question "How is a cyclopropenyl anion destabilized relative to an isolated carbanion not interacting in any way with a double bond?" In the comparison with the methylenecyclopropane derivative one is asking "How is a cyclopropene anion destabilized relative to an open-chain allyl anion analog?" In both cases the use of a cyclopropane ring as part of the system is designed to correct for various effects of angle strain on these acidities, and thus to separate the  $\pi$ -electron interactions from all the other effects in the cyclopropenyl anion.

We have detailed the argument elsewhere<sup>17</sup> that this is successful, and that the low acidity of these cyclopropene hydrogens does reflect chiefly an electronic conjugative destabilization, *i.e.*, antiaromaticity, in the cyclopropenyl anion. The argument is twofold. First of all, the decreased acidity of a cyclopropene derivative relative to the cyclopropane ana-

(9) L. J. Schaad and B. A. Hess, Jr., *J. Amer. Chem. Soc.*, **93**, 305 (1971); **94**, 3068 (1972).

(10) M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).

(11) M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967.

(12) L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 3253 (1965).

(13) C. Y. Lin and A. Krantz, *J. Chem. Soc., Chem. Commun.*, 1111 (1972); O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Amer. Chem. Soc.*, **95**, 614 (1973); S. Masamune, M. Suda, H. Ona, and L. M. Leichter, *J. Chem. Soc., Chem. Commun.*, 1268 (1972); G. Maier and B. Hoppe, *Tetrahedron Lett.*, 861 (1973).

(14) R. Breslow, J. Brown, and J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967); R. Breslow and M. Douek, *ibid.*, **90**, 2698 (1968).

(15) This is, of course, essentially the Brønsted catalysis law.

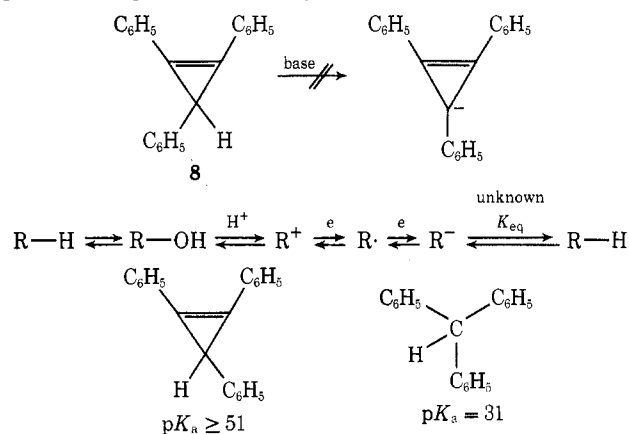
(16) Unpublished work of E. Nathan. See A. T. Bottini and A. J. Davidson, *J. Org. Chem.*, **30**, 3302 (1965), for a related observation.

(17) R. Breslow, *Pure Appl. Chem.*, **28**, 111 (1971).

log is seen with a variety of activating groups: cyano, ketone, sulfone, carbalkoxy. Anions next to some of these groups are sensitive to angle strain, but for some of the activating groups angle strain is known not to destabilize the anions. The decreased acidity of cyclopropenes is completely uncorrelated with the known sensitivity or lack of sensitivity to angle strain effects; it is thus not caused by such strain. The second argument involves the study<sup>18</sup> of an optically active cyclopropene derivative and the rate at which it loses optical activity during base-catalyzed deuterium exchange. The results are uniquely consistent with electronic, not steric, destabilization of cyclopropenyl anions.

Finally, it should be noted that the  $10^4$  (5.6 kcal/mol) or  $10^8$  (11.2 kcal/mol) destabilizations indicated by the kinetic data on compounds 5, 6, and 7 are only a fraction of the antiaromaticity of the unsubstituted cyclopropenyl anion—much of the charge in the anion of 5 is removed into the substituents.

Thermodynamic studies on the cyclopropenyl anion are difficult. Simple cyclopropenes have no detectable acidity of the ring hydrogen, and even an activated derivative such as triphenylcyclopropene (8) does not furnish the corresponding cyclopropenyl anion on treatment with very strong base.<sup>19</sup> Thus the equilibrium  $pK_a$  of these cyclopropenes cannot be directly determined. For this reason we have devised an electrochemical method<sup>20</sup> for determining the thermodynamic acidity of compounds such as triphenylcyclopropene. The method (which correctly reproduces known  $pK_a$ 's) involves a thermodynamic cycle by which a cyclopropenyl anion can be related to a covalent cyclopropene derivative. The experimental connection is to a cyclopropenol, which can be equilibrated with a cyclopropenyl cation. It is then possible to determine the energy required to add two electrons to this cation to generate triphenylcyclopropenyl anion, and in this way to get a measure of the energy of the triphenylcyclopropenyl anion relative to triphenylcyclopropenol. By the use of various reference compounds we can translate these data into a thermodynamic  $pK_a$  for triphenylcyclopropene; the result is that triphenylcyclopropene has a  $pK_a$  of 51 or higher.

Table I<sup>21</sup>Oxidation Potentials for Hydroquinone Dianions<sup>a</sup>

Compd	$E_1, V$	$E_2, V^b$
11	-1.50	-0.68
9	-0.90	-0.25
13	-1.22	-0.45
15	-1.17	-0.36

<sup>a</sup> 20° in dimethylformamide with 0.5 M tetrabutylammonium perchlorate. <sup>b</sup> Vs. Ag-AgCl, at Pt electrode.

The uncertainty comes from the fact that both triphenylcyclopropenyl radical and triphenylcyclopropenyl anion are extremely reactive. Even using very fast electrochemical methods, it is not quite possible to determine a reversible potential for these reductions, so the  $pK_a$  may be a few units higher than 51. Triphenylcyclopropene is thus at least  $10^{20}$  less acidic than triphenylmethane, a related compound in which the negative charge is also stabilized by three phenyl groups but in which the negative charge does not suffer a destabilizing interaction with a double bond as in the antiaromatic cyclopropenyl nucleus. Actually, the phenyls in the triphenylmethyl anion are somewhat more twisted than they are in triphenylcyclopropenyl anion, so the phenyl conjugation should have been even more effective in stabilizing the cyclopropenyl derivative.

Of course in this comparison there is no cyclopropane reference compound to correct for the effect of angle strain on such acidities. Accordingly, of the  $10^{20}$   $pK$  units (28 kcal/mol) by which the cyclopropene is less acidic, much of it is probably due to antiaromaticity in the cyclopropenyl anion, but an undetermined fraction is the result of angle strain effects. Using these same electrochemical techniques we have been able<sup>20</sup> to estimate the  $pK_a$ 's of some simple trialkylcyclopropenes, such as trimethylcyclopropene, as 65 or higher. These are the highest  $pK_a$ 's for which there is direct experimental evidence, higher than the most reliable estimates for the  $pK_a$  of methane or other saturated hydrocarbons.

In the case of cyclobutadiene there is a considerable amount of evidence from various laboratories that this molecule is extremely reactive.<sup>11-13</sup> We have done two studies which relate to the thermodynamic conjugation energy in a cyclobutadiene system. The first of them<sup>21</sup> involves the electrochemical oxidation of a series of hydroquinone anions. As Table I shows, it is much more difficult to oxidize compound 9 than to oxidize compound 11. In the case of 9 the starting structure has been written to indicate that the four-membered ring is not a cyclobutadiene. Of course this is only one of the structures of the resonance hybrid, and in reality there is a certain amount of double bond order in the four-membered ring. Thus 9 has some cyclobutadiene character.

However, when 9 is oxidized to the quinone 10 then the four-membered ring is essentially a full cyclobutadiene ring. This oxidation thus increases the amount of cyclobutadiene character in that ring. If cyclobutadiene were resonance stabilized this would

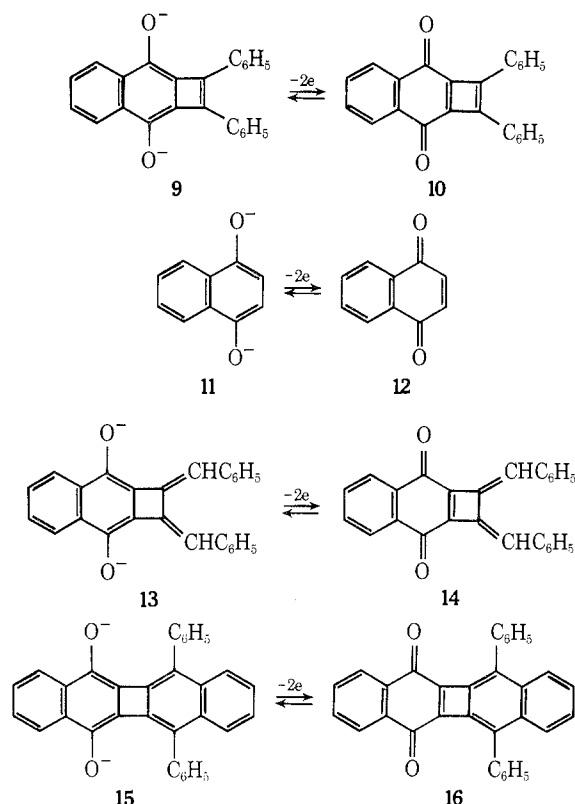
(18) R. Breslow and M. Douek, *J. Amer. Chem. Soc.*, **90**, 2698 (1968).

(19) For the interesting reactions which it does undergo with base, cf. R. Breslow and P. Dowd, *J. Amer. Chem. Soc.*, **85**, 2729 (1963).

(20) R. Breslow and K. Balasubramanian, *J. Amer. Chem. Soc.*, **91**, 5182 (1969); R. Breslow and W. Chu, *ibid.*, **92**, 2165 (1970); **95**, 411 (1973).

(21) R. Breslow, R. Grubbs, and S. Murahashi, *J. Amer. Chem. Soc.*, **92**, 4139 (1970); and unpublished work of D. Murayama.

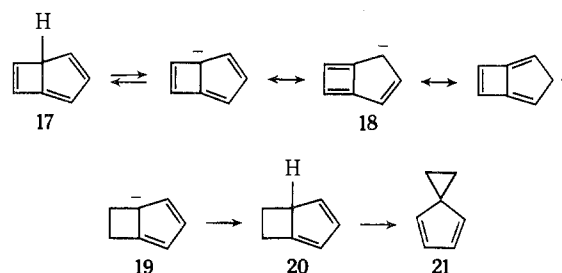
make the oxidation easier; the observed oxidation potentials of 9 compared with 11 indicate that the cyclobutadiene ring is destabilizing in 10. Potentials for related compounds are also listed in Table I, including compound 13 which is an almost perfect model for the various inductive and steric effects which operate on the oxidation potential of 9. Compound 15 produces 16, which has partial cyclobutadiene character. Thus 15 is intermediate in oxidation potential between 9 which develops a full cyclobutadiene ring, and 11 and 13 which do not.



These data indicate that cyclobutadiene conjugation is in fact thermodynamically destabilizing; the magnitude of the destabilization is of the order of at least 12 kcal/mol. Since some of this cyclobutadiene destabilization is probably being felt even in compound 9 before oxidation, the true cyclobutadiene antiaromatic destabilization energy is probably of the order of 15-20 kcal/mol. This compares with the calculation<sup>8</sup> by Dewar of 18 kcal/mol using a sophisticated MO method and the calculation by Schaad and Hess<sup>9</sup> of 33 kcal/mol using a modified HMO method.

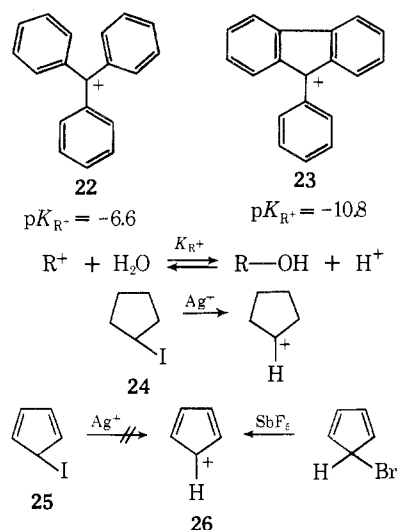
The second piece of experimental evidence on this number is a study<sup>22</sup> on the  $pK_a$  of a compound, 17, a cyclopentadiene system fused to a four-membered unsaturated ring. We find that this compound is approximately 11  $pK_a$  units less acidic than is cyclopentadiene itself. One description of the anion 18 is that it is a cyclopentadienyl anion which is destabilized by fusion to a cyclobutadiene ring, so that some of the resonance forms of 18 have a formal cyclobutadiene structure. Another way of describing this general situation is that in the change between 17

and 18 some partial double bond character is introduced into the four-membered ring in addition to the double bond which is already there, so that some partial cyclobutadiene character is now found in anion 18. In the comparison there is no correction for any strain energy changes which may be involved in the  $pK_a$ . The  $pK_a$  of 20 would have assisted in such a correction, but unfortunately protonation of anion 19 to afford 20 is followed<sup>23</sup> by very rapid irreversible rearrangement to 21. The observed destabilization of



18 by 11  $pK_a$  units (15 kcal/mol) is quite large; the antiaromatic component again represents only part of the cyclobutadiene destabilizing resonance energy, since anion 18 has only partial cyclobutadiene character.

In the case of cyclopentadienyl cation there are also several kinds of evidence. One is the  $pK_R^+$ 's found<sup>24,25</sup> for compounds 22 and 23. Even though in 23 the system is more planar and better conjugated, the inclusion of the positive charge in a cyclopentadienyl cation system is the apparent cause of a net destabilization of cation 23 compared with 22. Recent work has focused on unsubstituted cyclopentadienyl cation itself. Thus, we have compared<sup>26</sup> the silver-assisted solvolysis of saturated cyclopentyl iodide (24) with that of cyclopentadienyl iodide (25). The transition states for such solvolyses strongly resemble the solvated carbonium ions, and rates of such processes in general correlate well with carbonium ion stabilities. We find that there is no detectable solvolysis of 25 to the cyclopentadienyl cation;



(23) M. Oda and R. Breslow, *Tetrahedron Lett.*, 2537 (1973).

(24) N. Deno, J. Jaruzelski, and A. Schriesheim, *J. Amer. Chem. Soc.*, 77, 3044 (1955).

(25) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, 83, 3727 (1961).

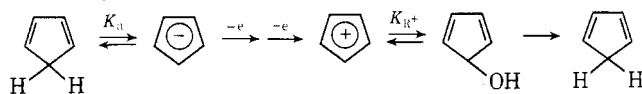
(26) R. Breslow and J. Hoffman, Jr., *J. Amer. Chem. Soc.*, 94, 2110, 2111 (1972).

(22) R. Breslow, W. Washburn, and R. Bergman, *J. Amer. Chem. Soc.*, 91, 196 (1969); R. Breslow and W. Washburn, *ibid.*, 92, 427 (1970).

this undetectable process is at least  $10^5$  slower than the normal silver-assisted solvolysis of **24**. Thus on this basis we can conclude that cyclopentadienyl cation is destabilized not simply relative to its open-chain analog linear pentadienyl cation but also relative to an isolated carbonium ion.

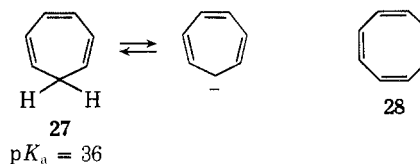
Although the iodocyclopentadiene would not undergo solvolysis *via* cyclopentadienyl cation, unsubstituted cyclopentadienyl cation (**26**) can indeed be prepared<sup>27</sup> by reaction of 5-bromocyclopentadiene with  $\text{SbF}_5$ , an extremely powerful Lewis acid.  $\text{C}_5\text{H}_5^+$  is in fact<sup>27</sup> a ground-state triplet, with two unpaired electrons, just as had been observed<sup>28</sup> for  $\text{C}_5\text{Cl}_5^+$ . However, it should be emphasized that the extreme thermodynamic instability of such compounds is not the result of their existing as triplets. The electrons unpair in a compound such as  $\text{C}_5\text{H}_5^+$  because a half-occupied pair of degenerate orbitals is available and the molecule can stabilize itself by such electron unpairing. Thus, the singlet state of  $\text{C}_5\text{H}_5^+$  would be of even higher energy, although the amount of energy involved in this singlet-triplet splitting is not large.

Electrochemistry can also be used<sup>29</sup> to get an estimate of the stability of  $\text{C}_5\text{H}_5^+$ . Thus, the thermodynamic cycle we described earlier can be run in the oxidation direction, and unstable cations can be obtained by oxidation of accessible anions. Starting with the known  $\text{p}K_a$  of cyclopentadiene, we can estimate the  $\text{p}K_R^+$  of cyclopentadienol by the use of the oxidation potentials for successive removal of two electrons from cyclopentadienyl anion and other thermodynamic information which is available. We have shown<sup>29</sup> that this technique successfully reproduces the known  $\text{p}K_R^+$ 's of a number of other carbonium ions with high accuracy. Applied to  $\text{C}_5\text{H}_5^+$ , this electrochemical technique indicates that its  $\text{p}K_R^+$  is  $-40$  or lower. Since the  $\text{p}K_R^+$  of allyl cation is approximately  $-20$ , this indicates that the extra double bond in the cyclopentadienyl cation adds considerable instability, not stability, to the allylic cation system.



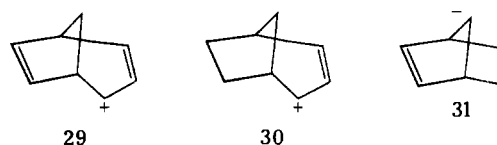
For larger systems, the evidence is less substantial. Thus, cycloheptatriene (**27**) forms  $\text{C}_7\text{H}_7^-$  with a  $\text{p}K_a^{20,30}$  of  $+36$ . While cycloheptatriene is thus certainly less acidic than cyclopentadiene, with a  $\text{p}K_a$  of  $+18$ , it is much more acidic than is methane. In this system the conjugation acts to stabilize the anion overall, although it may not stabilize it as much as would be the case for a linear analog with three double bonds and a charge. Cyclooctatetraene (**28**) exists as a puckered molecule, and possibly some of the barrier for ring inversion involves a destabilizing<sup>31</sup> interaction of the four double bonds in the planar conjugated cyclooctatetraene system. For

larger annulenes it is clear<sup>32</sup> that the  $4n$  systems are less stable than are the  $4n + 2$  systems, but there is no strong evidence yet for conjugative destabilization in the  $4n$  systems relative to normal compounds.



It has, however, been found<sup>32</sup> that  $4n$  annulenes have a paramagnetic ring current detectable in the nmr compared to the diamagnetic ring current for the  $4n + 2$  systems. An nmr criterion can thus be advanced<sup>33</sup> according to which diamagnetic ring currents indicate aromaticity while paramagnetic ring currents indicate antiaromaticity. However, this magnetic definition is not equivalent to the energetic definition of aromaticity and antiaromaticity we have been using up until now; it is not at all clear that compounds with paramagnetic ring currents also have strong conjugative destabilization.

Although "conjugation" involves, by definition, interaction of neighboring unsaturated atoms, it is also possible to get appreciable interaction of unsaturated atoms separated by a saturated atom or otherwise held near each other. Such through-space interaction in spite of the formal interruption of conjugation is termed<sup>34</sup> homoconjugation. The evidence for homoconjugation has led to a suggestion<sup>35</sup> that some systems can be homoaromatic and to the possibility that homoantiaromaticity would also be detectable. Although there is some evidence<sup>36</sup> that **29**, a bishomocyclopentadienyl cation, is less stabilized than is **30**, without the extra double bond, no significant evidence for destabilization was detected<sup>37</sup> in a derivative of 7-norbornenyl anion (**31**), which can be considered a bishomocyclopropenyl anion. Effective homoconjugation frequently requires a geometric distortion to increase overlap, and compounds would not undergo such a distortion if the result were to be a destabilizing interaction.



Finally, heterocyclic systems should be mentioned. Compounds such as acetylene oxides (**32**)<sup>38</sup> or azirenes (**33**) exist only as very unstable intermediates. They are analogs of the  $4\pi$ -electron cyclopropenyl anion and thus may be antiaromatic. However, to date there is no direct evidence on the sign and magnitude of their conjugation energy.

(32) F. Sondheimer, *Accounts Chem. Res.*, **5**, 81 (1972); J. A. Pople and K. G. Untch, *J. Amer. Chem. Soc.*, **88**, 4811 (1966).

(33) R. C. Haddon, V. R. Haddon, and L. M. Jackman, *Top. Current Chem.*, **16**, 103 (1971).

(34) M. Simonetta and S. Winstein, *J. Amer. Chem. Soc.*, **76**, 18 (1954).

(35) For a review, cf. S. Winstein, *Quart. Rev., Chem. Soc.*, **23**, 141 (1969).

(36) A. F. Diaz, M. Sakai, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 7480 (1970).

(37) R. Breslow, R. Pagni, and W. Washburn, *Tetrahedron Lett.*, 547 (1970); however, see J. K. Stille and K. N. Sannes, *J. Amer. Chem. Soc.*, **94**, 8489 (1972), for evidence consistent with some destabilization.

(38) J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Amer. Chem. Soc.*, **95**, 124 (1973).

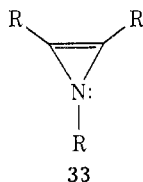
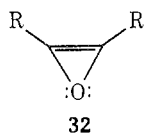
(27) M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Neill, R. Breslow, J. M. Hoffman, Jr., C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuch, *J. Amer. Chem. Soc.*, **95**, 3017 (1973).

(28) R. Breslow, H. W. Chang, R. Hill, and E. Wasserman, *J. Amer. Chem. Soc.*, **89**, 1112 (1967).

(29) R. Breslow and S. Mazur, *J. Amer. Chem. Soc.*, **95**, 584 (1973).

(30) H. Dauben and M. Rifi, *J. Amer. Chem. Soc.*, **85**, 3041 (1963).

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Major antiaromatic effects have been detected so far principally in the normal  $4\pi$  conjugated systems:

cyclopropenyl anion, cyclobutadiene, and cyclopentadienyl cation. Within these systems, however, the effects are quite substantial, comparable in magnitude of energy to the aromaticity in benzene.

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## Hydrodynamic Analysis of Human Low Density Lipoproteins<sup>†</sup>

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Anyone who has faced a clogged kitchen drain will agree that lipids have a very limited solubility in water. Moreover, the consequences of accidental stoppage can be disastrous.

This household problem has a counterpart in the transport of lipids through the blood and lymph of the human body. These fatty substances must be kept in aqueous suspension while they are distributed to the organs and tissues. After a meal very high in lipid, the serum may become a milky white due to light scattered from opalescent particles of fat, which are kept from coalescing by a thin coat of protein, phospholipid, and cholesterol. The particles are large enough to be seen in the dark field microscope, and they are called chylomicra.

Chylomicra are produced by the gut after a meal containing fat.<sup>1</sup> Other lipoproteins are primarily produced by the liver. In fact, on a high carbohydrate diet, lipoprotein levels may rise higher than ever in some people.<sup>2</sup> Fatty acids are synthesized from carbohydrates in the liver or obtained from adipose tissue. In turn, fats and phospholipids are synthesized from the fatty acids. Finally, the newly synthesized fats and phospholipids, together with protein, are packaged and excreted directly into the blood.<sup>3</sup> These particles are usually a little smaller than the chylomicra, but still very large. They are called very low density lipoproteins (conveniently abbreviated VLDL).

Unlike amino acids and carbohydrates, and perhaps unique to lipids, the first step in the metabolism of lipoproteins takes place directly within the blood capillaries. The enzyme, lipoprotein lipase, is attached to sites within the capillary walls, and it can hydrolyze either chylomicra or VLDL, flooding

the adjacent tissue with fatty acids. The presence or absence of this lipase is under hormonal control; thus, the fatty acids released from chylomicra may be directed to adipose tissue for storage during feeding, or the VLDL fatty acids, to heart and skeletal muscle for utilization during starvation.<sup>4</sup>

Low density lipoproteins (LDL) are a third class of lipoproteins which are smaller molecules than either the chylomicra or the VLDL. In fact, there is considerable evidence that the LDL constitute the molecular residue left after the hydrolysis of most of the triglyceride from the chylomicra and VLDL by lipoprotein lipase.<sup>5</sup> In addition, some LDL may be produced by the gut or liver.<sup>6</sup> The low density lipoproteins are present in gram quantities in normal human serum, and the average levels depend upon age and sex.<sup>7</sup> The hydrodynamic properties of the low density lipoproteins are the special subject of this Account.

For completeness, we must mention the high density lipoprotein class (HDL). This class is composed of several types of molecules of 200,000 to 400,000 molecular weight, composed of about 50% protein and 50% lipid, mostly phospholipids.<sup>8</sup> All of their functions are not understood, but there is considerable evidence that the HDL plays roles in enzyme activation of lipoprotein lipase and lecithin-cholesterol acyltransferase (LCAT). In Tangier disease, a congenital lack of HDL, massive deposits of cholesteryl ester occur throughout the lymphatic tissues.

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