methylpropane), *m/e* 202 ($M^+ + H$); HRMS, *m/e* 201.0781 ($C_{12}H_{11}NO_2$ requires 201.0790).

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Reexamination of the Notion of π-Electron Delocalization Energy as a Theoretical Index to the Empirical Resonance Energy

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As early as in 1959, using the modified Hückel MO (HMO) method in which the effect of the σ-bond compression is taken into account, Longuet-Higgins and Salem[2] pointed out that in [4n + 2] annulenes the total bond energy of π electrons decreases along the bond-alternation mode. However, this important result has, until recently, escaped the attention it deserves. Recently, Epiotis[3] reaffirmed the above result, and Shaik and Hiberty[4] raised the question whether it is really the π system that drives benzene to be a symmetric hexagonal species. Very recently, Hiberty et al.[5] presented computational evidence that the symmetrical hexagonal structure of benzene is driven by the σ framework alone, the π system being found to favor a distorted and localized structure (see also ref 6 and 7). In these circumstances, the traditional view that the π-electron delocalization energy (DE) is useful as a theoretical index to the empirical resonance energy (RE) turns out to be erroneous and meaningless. Note that DE is the quantity defined in the framework of the constant-β HMO approximation, and it favors energetically the symmetric hexagonal benzene and a delocalized symmetric species in general. Nevertheless, it is well-known that in alternant hydrocarbons, the π-electron DE value has an excellent correlation with the empirical RE.[8] The aim of this paper is to understand the physical basis behind the above apparent correlation and to rationalize the π-electron DE value as an index to be used in predicting the stabilities and geometries of conjugated hydrocarbons.

The RE of a conjugated hydrocarbon is defined as

$$\mathrm{RE} = E_{\mathrm{tot}}(\mathrm{M}) - E_{\mathrm{tot}}(\mathrm{K}) \qquad (1)$$

where $E_{\mathrm{tot}}(\mathrm{M})$ and $E_{\mathrm{tot}}(\mathrm{K})$ are the total energies of a delocalized symmetric structure and a Kekulé-type one in which isolated double bonds are linked by single bonds, respectively. According to Longuet-Higgins and Salem,[2] the total bond energy associated with a CC bond taken to be the sum of the σ-bond energy (f) and the π-electron energy is given by

$$E_{ij} = f_{ij} + 2P_{ij}\beta_{ij} = -(2/b)(\mathrm{d}P_{ij}/\mathrm{d}r_{ij})\beta_{ij} + \mathrm{const} \qquad (2)$$

where P_{ij} is the π-bond order of the i–j bond and the resonance integral, $\beta_{ij}(r_{ij})$, has been assumed to be an exponential function of the form

$$\beta_{ij}(r_{ij}) = \beta_{\mathrm{b}} \exp[b(r_{\mathrm{b}} - r_{ij})] \qquad (3)$$

where β_{b} and r_{b} are the values in benzene. Now, the equilibrium bond length, r_{ij}, is assumed to be related to P_{ij} by

$$r_{ij}/\text{Å} = r_0 - aP_{ij} \qquad (4)$$

Differentiating this equation with respect to r_{ij} and substituting for $(\mathrm{d}P_{ij}/\mathrm{d}r_{ij})$ in eq 2, we obtain

$$E_{ij} = (2/ab)\beta_{ij} + \mathrm{const}$$

Summing E_{ij} over all the CC bonds, we obtain the total energy of an alternant hydrocarbon as

$$E_{\mathrm{tot}} = \frac{2}{ab}\sum_{i<j}^{\text{all bonds}} \beta_{ij} + N\alpha + E_{\mathrm{core}}{}^{\sigma} + \mathrm{const} \qquad (5)$$

where α is the Coulomb integral of the C atom, N the number of π electrons, and $E_{\mathrm{core}}{}^{\sigma}$ the σ core energy. Further, substituting for r_{ij} in eq 3 from eq 4, we obtain

$$\beta_{ij} = B \exp(abP_{ij}) \qquad (6)$$

where

$$B = \beta_{\mathrm{b}} \exp[b(r_{\mathrm{b}} - r_0)] \qquad (7)$$

It should be noted that in order for benzene to keep D_{6h} symmetry, the condition $ab < 1$ must be fulfilled.[9]

Since $abP_{ij} < 1$ ($abP_{ij} \simeq 0.5$ in benzene), we now expand $\exp(abp_{ij})$ in power series of abP_{ij} and neglect the terms higher than the first power, thus obtaining

$$\beta_{ij} = B(1 + abP_{ij}) \qquad (8)$$

Substituting eq 8 into eq 5, we then have

$$E_{\mathrm{tot}} = \sum_{i<j}^{\text{all bonds}} \left(2P_{ij}B + \frac{2}{ab}B\right) + N\alpha + E_{\mathrm{core}}{}^{\sigma} + \mathrm{const} \qquad (9)$$

Using eq 9, we can write the total energy of a Kekulé-type structure with $P = 1$ for double bonds and $P = 0$ for single bonds as

$$E_{\mathrm{tot}}(\mathrm{K}) = 2nB + \sum_{i<j}^{\text{all bonds}} \frac{2}{ab}B + N\alpha + E_{\mathrm{core}}{}^{\sigma} + \mathrm{const} \qquad (10)$$

where n is the number of double bonds. The RE can thus be written in the following form:

$$\mathrm{RE} = E_{\mathrm{tot}}(\mathrm{M}) - E_{\mathrm{tot}}(\mathrm{K}) = \left[\sum_{i<j}^{\text{all bonds}} 2P_{ij} - 2n\right]B \qquad (11)$$

The last expression of eq 11, if B is replaced by β_{b}, is nothing but the expression of the DE defined in the constant-β HMO approximation. It is thus revealed that there does exist a proportionality between the RE and DE values. It should be remarked that the value of β that

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[2] (a) Longuet-Higgins, H. C.; Salem, L. *Proc. R. Soc. London A* **1959**, *A251*, 172. (b) Salem, L.; Longuet-Higgins, H. C. *Proc. R. Soc. London A* **1960**, *A255*, 435. (c) Salem, L. *The Molecular Orbital Theory of Conjugated Systems*; Benjamin: New York, 1966; pp 495–505.

[3] Epiotis, N. D. *Nouv. J. Chim.* **1984**, *8*, 11.

[4] Shaik, S. S.; Hiberty, P. C. *J. Am. Chem. Soc.* **1985**, *107*, 3089.

[5] Hiberty, P. C.; Shaik, S. S.; Lefour, J.-M.; Ohanessian, G. *J. Org. Chem.* **1985**, *50*, 4657.

[6] Baird, N. C. *J. Org. Chem.* **1986**, *51*, 3907.

[7] Hiberty, P. C.; Shaik, S. S.; Ohanessian, G.; Lefour, J.-M. *J. Org. Chem.* **1986**, *51*, 3908.

[8] Streitwieser, A., Jr. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961; pp 237–255.

[9] Nakajima, T. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 83.

0022-3263/87/1952-2323$01.50/0

reproduces the empirical RE values ($\beta \simeq -16$ kcal mol^{-1}) is far smaller than the values derived by other correlations such as ionization potentials versus energies of the highest occupied MOs.[8] The reason for this is given by the fact that, as is shown in eq 11, the proportionality constant is not β_b but B given by eq 7: using $b = 4.5$ Å^{-1} and $r_0 = 1.520$ Å,[9] we have $B = 0.57\beta_b$.

Schaad and Hess[10] have given a rationalization for the use of the simple HMO method that takes into account only the π-bonding energy in calculating RE by demonstrating that for each bond both the σ-compression energy and the π-bonding energy are approximately linear functions of π-bond order. They have actually shown that the constant-β HMO method can reproduce well Dewar's RE[11,12] if, following Dewar, one uses a polyene reference structure. However, their results show erroneously that the σ-compression energy favors a distorted and localized structure.

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[10] Schaad, L. J.; Hess, A., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3068.

[11] Dewar, M. J. S.; Gleicher, G. J. *J. Am. Chem. Soc.* **1965**, *87*, 685, 692.

[12] Dewar, M. J. S.; de Llano, C. *J. Am. Chem. Soc.* **1969**, *91*, 789.

Synthetic Approaches to 4-Spiro-2-hydroxytetronic Acids[1]

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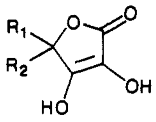
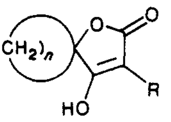
Tetronic acids are components of numerous natural products,[2] including chlorothricin,[3,4] (−)-vertinolide,[5] ircinianin,[6] hippospongin,[7] and ionophore M 139603,[8] of contemporary interest. The aci-reductone 2-hydroxytetronic acid system 1 found in chlorothricin[3,4] and ascorbic acid[2] has received considerably less attention. Discovery of the antiaggregatory and antilipidemic properties of the 4-(4-chlorophenyl) analogue 2[9] provided the impetus for us to investigate mechanism-based,[10] structure–activity relationships. The early work of Dahn et al.[11] on the synthesis of aci-reductones employing a benzoin condensation is only applicable for the preparation of 4-aryl-2-hydroxytetronic acids. We investigated synthesis of spiro targets 4 and 5 with a view toward development of a general approach to the preparation of 4,4-disubstituted analogues.

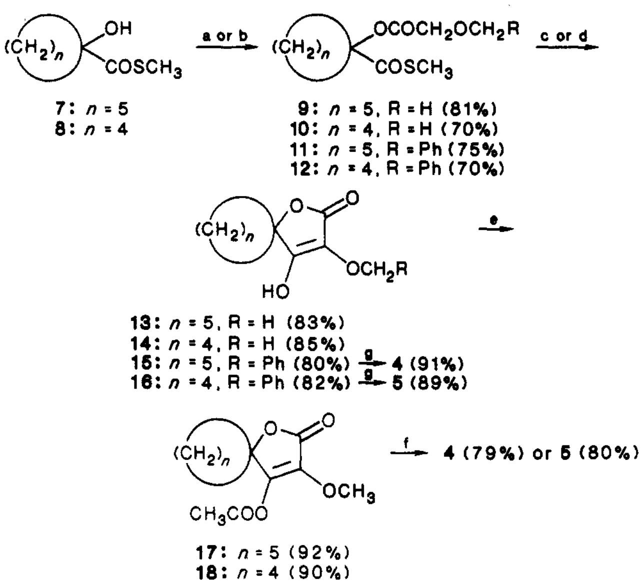


1: R$_1$ = R$_2$ = H
2: R$_1$ = H, R$_2$ = p-ClC$_6$H$_4$
3: R$_1$ = R$_2$ = Me



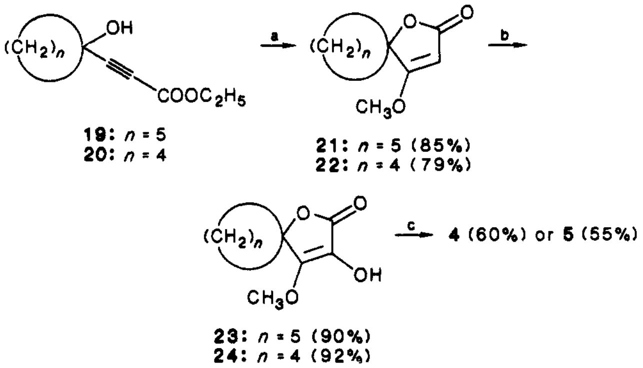
4: n = 5, R = OH
5: n = 4, R = OH
6: n = 5, R = H

Scheme I[a]



[a] Reagents and conditions: (a) n-BuLi, CH$_3$OCH$_2$COCl, reflux, 1 h; (b) n-BuLi, PhCH$_2$OCH$_2$COCl, reflux, 1 h; (c) LDA, −78 °C to room temperature, 2 h; (d) lithium hexamethyldisilazide (LiHMDA), −78 °C to room temperature, 2 h; (e) Ac$_2$O, Py; (f) BBr$_3$, CH$_2$Cl$_2$, −78 °C to room temperature, 2 h; (g) Pd/C (10%), cyclohexene, reflux, 15 min.

Scheme II[a]



[a] Reagents and conditions: (a) NaOMe, MeOH, room temperature, 6 h: (b) LDA, −78 °C (0.5 h), B(OMe)$_3$ (0.5 h), AcOH, H$_2$O$_2$ (30%); (c) HBr (48%), 45 °C.

2-Hydroxy derivative 4 previously had been prepared by Schank and Blattner[12] from the corresponding spiro-

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[2] (a) Haynes, L. J.; Plimmer, J. R. *Q. Rev. Chem. Soc.* **1960**, 292–315. (b) Rao, Y. S. *Chem. Revs.* **1976**, *76*, 625–694. (c) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133–198.

[3] Berdy, J. In *Handbook of Antibiotic Compounds*; CRC: Boca Raton, FL, 1980; Vol. II, p 415.

[4] (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041–3052. (b) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635–648.

[5] (a) Trifonov, L. S.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Helv. Chim. Acta* **1981**, *64*, 1843–1846. (b) Trifonov, L.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Rast D. M.; Hoesch, L. *Tetrahedron* **1982**, *38*, 397–403. (c) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761–3764.

[6] (a) Hofheinz, W.; Schönholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367–1370. (b) Gregson, R. P.; Ouvrier, D. *J. Nat. Prod.* **1982**, *45*, 412–414. (c) Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903–3906.

[7] Kobayashi, J.; Ohizumi, Y.; Nakamura, H. *Tetrahedron Lett.* **1986**, *27*, 2113–2116.

[8] Doherty, A. M.; Ley, S. V. *Tetrahedron Lett.* **1986**, *27*, 105–108.

[9] Witiak, D. T.; Kokrady, S. S.; Patel, S. T.; Huzoor-Akbar; Feller, D. R.; Newman, H. A. I. *J. Med. Chem.* **1982**, *25*, 90–93.

[10] Witiak, D. T.; Kim, S. K.; Romstedt, K.; Newman, H. A. I.; Feller, D. R. *J. Med. Chem.* **1986**, *29*, 2170–2174.

[11] (a) Dahn, H.; Lawendel, J. S.; Hoegger, E. F.; Schenker, E. *Helv. Chim. Acta* **1954**, *37*, 1309–1318. (b) Dahn, H.; Lawendel, J. S. *Helv. Chim. Acta* **1954**, *37*, 1318–1327. (c) Dahn, H.; Hauth, H. *Helv. Chim. Acta* **1956**, *39*, 1366–1370.

[12] Schank, K.; Blattner, R. *Chem. Ber.* **1981**, *114*, 1958–1962.

0022-3263/87/1952-2324$01.50/0