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CORRESPONDENCE BETWEEN THEORETICALLY PREDICTED AND EXPERIMENTALLY OBSERVED SITES OF ELECTROPHILIC SUBSTITUTION ON A FUSED-TRICYCLIC HETEROAROMATIC (AZULENE) SYSTEM

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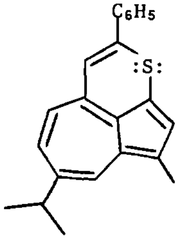
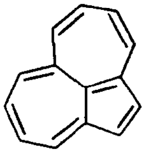
In this paper we report on simple Hückel Molecular Orbital[1] calculations (with modern adaptations[2]) that appear to describe properly the aromaticity of the tricyclic, (sulfur-containing) nucleus of 2-phenyl-8-methyl-7-isopropylazuleno[1,8-*bc*]thiapyran, 1. In addition, similar HMO calculations on all reasonable electrophilic substitution intermediates indicate that only three sites are energetically accessible for such substitution. Subjection of substrate 1 to typical electrophilic substitution conditions demonstrates that there is a single favorable site of attack which is one of those predicted by our HMO calculations.[2,3] Steric factors and charge density (the latter from our HMO calculations) considerations allow one to rationalize why the position of actual substitution might be expected from theoretical principles.

The preparation of this substituted azuleno[1,8-*bc*]thiapyran, 1, has been reported earlier;[4] the proton magnetic resonance and ultraviolet spectra and the thermal stability of 1 imply that its fused, tricyclic nucleus (a π-equivalent analog of hydrocarbon 2) is indeed aromatic.



1



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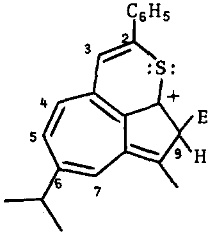
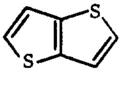


3

Although the limits of use of simple HMO calculations are well documented,[3] it has been recently shown[2] that judicious development of the reference (localized) structure related to such calculations allows very successful classification of the aromatic character of various π-conjugated cyclic compounds, including sulfur-heterocycles.[2a] Application of this procedure to the tricyclic nucleus of compound 1 gives rise to a calculated resonance energy of 0.212 β (total π-binding energy = 16.332 β; π-additive energy for localized 1 = 16.120 β)[2] and thus, for this 14 π-electron system, a resonance energy per π-electron (REPE) of 0.015 β. This REPE value implies aromaticity for 1 since, *e.g.*, thieno[3,2-*b*]thiophene, 4, has the same REPE, is stable, and undergoes electrophilic substitution.[5]



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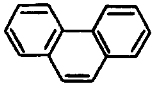


8

In order to characterize more fully the aromatic character of 1, we attempted predictions of the position of electrophilic substitution on 1 by calculating the π-electron energy of intermediates ("Wheland" Intermediates[6]) such as 3. These energies (for intermediates) are then used to determine the ΔE values for Table I; so-determined ΔE values are estimates of the relative ease of substitution of 1 (*i.e.*, the data can be viewed as the contribution to the activation energy due to π-electron reorganization, if we assume that the intermediates energetically "resemble"[7] the corresponding transition states). A number of modifications were implemented via the HMO calculations; *i.e.*, inclusion of the phenyl group (at C-2) as part of the delocalized system, neglect of the phenyl group, and variations of the Coulomb and resonance integrals for the sulfur atom and the carbon-sulfur bond, respectively, according to established procedures.[8] None of these many variations affected the break-point indicated by the broken line in Table I; *i.e.*, positions 4, 3, and 9 are more energetically accessible than the remaining position by at least 0.1 β (*ca.* 1.6 kcal/mole, assuming β = 16 kcal/mole[9]). Despite the approximate nature[3] of these calculations, one can clearly remove positions 5 and 7 from further consideration.

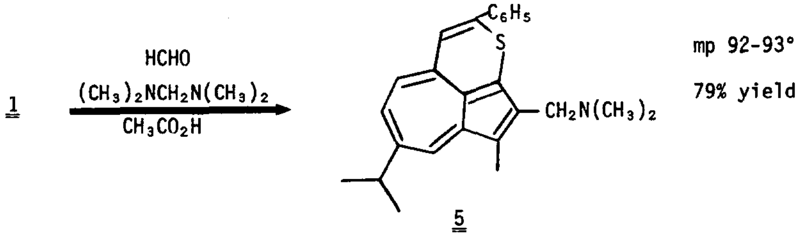
TABLE I: DIFFERENCE IN ENERGY (ΔE)[a] BETWEEN ELECTROPHILIC SUBSTITUTION INTERMEDIATES AND REACTANT (1) DETERMINED BY HMO CALCULATIONS

Position of Substitution[b]	$\alpha_S = \alpha_C + \beta$[c] $\beta_{C-S} = 0.68\beta$		$\alpha_S = \alpha_C$[d] $\beta_{C-S} = 0.8\beta_{C-C}$		$\alpha_S = \alpha_C$[d] $\beta_{C-S} = 1.0\beta_{C-C}$	
	R[e] = C_6H_5	R = H	R = C_6H_5	R = H	R = C_6H_5	R = H
4	1.920	1.926	1.705	1.704	1.682	1.680
3	1.953	2.074	1.709	1.795	1.676	1.750
9	2.008	2.009	1.759[a]	1.754	1.719	1.715
7	2.230	2.238	1.877	1.783	1.873	1.869
5	2.449	2.445	2.015	2.008	2.015	2.009

[a] *e.g.*, ΔE = E_2-E_1 = 1.759, where E_2 = π-binding energy for 3 and E_1 = π-binding energy for 1.[2]
[b] Similar calculations on the phenyl ring positions indicated that substitution at these positions resulted in such high energy intermediates that further consideration of these positions was unnecessary. *Ipso* substitution [C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 93, 3389 (1971)] was not considered since it was unclear as to how to calculate the effect of the displayed alkyl groups and since *ipso* substitution is apparently unknown in these systems. [c] Values from ref. 2c. [d] Values suggested by Streitwieser, ref. 8. [e] R = nature of substituent at C-2 of 1 and 3.

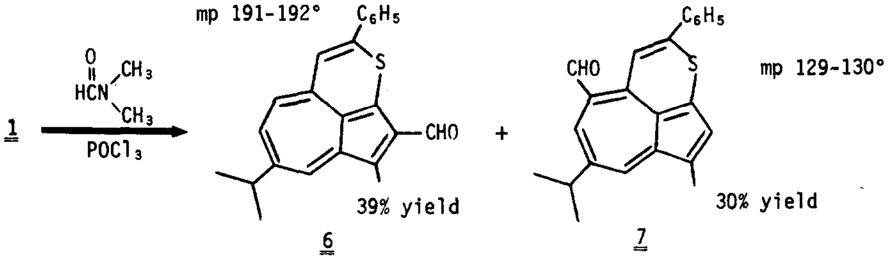
Experimental results are gratifyingly in accord with the above predictions. Subjection of 1 to Mannich reaction conditions[10] gave a high yield of substitution at C-9 (Scheme I). The product of this reaction (5) is confirmed by its proton magnetic resonance (pmr)

SCHEME I



spectrum: (CDCl$_3$; H$_3$, τ 3.78, s; H$_4$, τ 4.27, d, J=11 Hz; H$_5$, τ 3.63, d of d, J=11 Hz, 2 Hz; H$_7$, τ 2.90, d, J=2 Hz; 8-C*H*$_3$, τ 7.60, s; -C*H*$_2$-, τ 6.50, s; -N(C*H*$_3$)$_2$, τ 7.82, s; C$_6$*H*$_5$-, τ 2.63, m), elemental analysis: (% C, H, N, Calc.: 80.38, 7.29, 3.75; Found: 80.70, 7.44, 4.02), ultraviolet spectrum: [cyclohexane, λ_{MAX} in nm, (log ε_{MAX}): 262 (4.40), 300 (4.57), 358 (4.03), 420 (3.45), 451 (3.44), 481 (3.34)] and its visible spectrum: [cyclohexane, λ_{MAX} (ε_{MAX}): 808 (430), 900 (502), 1010 (275)]. Formylation of 1 using Vilsmeier[11] conditions (Scheme II)

SCHEME II



resulted in two monosubstitution products in a high (combined) yield (69%); the major product (6) again corresponds to C-9 substitution. The structures assigned to 6 and 7 are spectrally supported: 6, anal. (% C, H: Calc.: 80.21, 5.85; Found: 79.79, 5.87), infrared (CHCl$_3$, C=O, 6.13 μm), pmr (CDCl$_3$, H$_3$, τ 3.44, s; H$_4$, τ 4.22, d, J=12 Hz; H$_5$, τ 3.70, d of d, J=12, 2 Hz; H$_7$, τ 3.08, d, J=2 Hz; -C*H*O, τ -0.37, s; 8-C*H*$_3$, τ 7.45, s; -CH(C*H*$_3$), τ 8.90, d, J=7 Hz; C$_6$H$_5$, τ 2.52, m), ultraviolet [cyclohexane, λ_{MAX} (log ε_{MAX}), 300 (4.56), 367 (3.80), 388 (3.83), 450 (3.28), 480 (3.25)], and visible [cyclohexane, λ_{MAX}, (ε_{MAX}), 821 (324), 911 (400), 1043 (262)], and 7, anal. (% C, H: Found: 79.92, 5.97), infrared (CHCl$_3$, C=O, 6.02 μm), pmr (CDCl$_3$, H$_3$, τ 1.91, s; H$_5$, τ 2.90, d, J=2 Hz; H$_7$, τ 3.10, d, J=2 Hz; H$_9$, τ 3.00, s; C*H*O, τ 0.50, s; 8-CH$_3$, τ 7.60, s; CH(C*H*$_3$)$_2$, τ 8.80, d, J=7 Hz; C$_6$*H*$_5$, τ 2.57, m), ultraviolet [cyclohexane, λ_{MAX} (log ε_{MAX}), 318 (4.34), 367 (4.11), 406 (3.82), 429 (3.92), 479 (4.03), 508 (4.13)], and visible [cyclohexane, λ_{MAX} (log ε_{MAX}), 780 (440), 870 (492), and 970 (276)]. Subjecting 1 to mild Friedel-Crafts acetylation conditions (heated pyridine, acetyl chloride) resulted in a product, which, albeit only a partially characterized mixture, is almost certainly composed of both C-9-

monosubstitution and a C-4,9-disubstitution product. Thus we have implied a 9>4>>3 substitution preference for substrate 1.

Steric and electrostatic considerations allow rationalization of the substitution priority sequence; positions 4 and 3 seem less likely to be substituted for the succeeding reasons: Although charge densities alone would be insufficient for predicting the position of electrophilic substitution, it does seem reasonable that simple electrostatic interaction between the π-system and the electrophile would have some bearing on the position of substitution;[12] Table II implies that position 9 would be most favored by such charge density considerations. If one considers Dreiding molecular models of 1, coplanarity of the phenyl group with the central π-system strongly suggests that position 3 is sterically hindered; the combined effect of the phenyl orthohydrogens and *peri*-planar interaction of the C-4 hydrogen would likely produce a steric barrier sufficient to block substitution at C-3. The steric effect at C-3 of 1 appears to be analogous to the steric requirements of substitution at C-4 of phenanthrene (8); nitration at C-4 of phenanthrene proceeds at a much slower rate than predicted by molecular orbital considerations,[13] presumably due to inhibition by the hydrogen at C-5. A reasonable argument is that electrophiles that are even smaller than those in the Villsmeier reaction (*e.g.*, those in protonation) could effect substitution in the order 4>9.

TABLE II. CHARGE DENSITIES FOR COMPOUND 1 DETERMINED FROM SIMPLE HMO CALCULATIONS[a]

Position	Charge Density[b]
9	-0.209
3	-0.155
4	-0.064

[a] Charge density defined as 1.00 less the electron density (see p. 52 of Streitwieser, ref. 81) at that position. [b] Note that disagreement of the order of substitution preference implied by Table II (see text), compared to Table I, constitutes a violation of Streitwieser's "non-crossing" rule (ref. 1, p. 347). Correlations are difficult in such cases.

In summary, detailed consideration of a combination of intermediate stability (HMO) calculations, charge density results and steric constraints allows reasonably accurate predictions of the position of electrophilic substitution on aromatic substrate 1.

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