Nonbenzenoid Aromatic Systems. VI.[1a] pK_a Values of Azuloic Acids

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The thermodynamic pK_a values of 1-, 2-, 5-, and 6-azuloic acids, 1-, 4-, and 6-azulylacetic acids, and azulene-1,2-dicarboxylic acid were determined in 50% aqueous ethanol (v/v) at 25°. The relative acidities of the azuloic acids ($1 < 2 < 5 < 6$) were consistent with decreasing π-electron density at these positions in the order of $1 > 2 > 5 > 6$.

While experimental and theoretical results agree that the 1 position of azulene is the site of largest π-electron density and the site of ready electrophilic substitution, there is disagreement in both types of results as to whether the 2 or 5 position is the second most electron-rich ring site. Experimentally, Vilsmier formylation of 1,3-dimethylazulene reportedly gave the 2-carboxaldehyde while 1,3-di-*tert*-butylazulene produced only the corresponding 5-carboxaldehyde probably due to steric control in the substitution.[2] However, acylation and halogenation of 1,3-dihaloazulenes (X = Cl, Br) and 1,3-dibenzoyloxyazulene produced only the products of 5 substitution.[3] The molecular orbital π-electron density calculations commonly referred to in this chemistry[4-6] likewise disagree in the ordering of these two positions.

The above experimental results involve 1,3-disubstituted azulenes which offer electronic perturbations and steric effects in the reactions examined. Further, these electrophilic substitution reactions would not necessarily reflect the ground state of the unperturbed azulene molecule.

Our approach to this question was to determine the thermodynamic pK_a's of the azuloic acids where steric factors should not be important and the electronic perturbation caused by the carboxylic acid and its conjugate base should be reduced compared to electrophilic substitution and be more constant at each of the nonequivalent ring positions. The pK_a's for four of the possible five azuloic acids are given in Table I. The previous nonthermodynamic pK_a value for 1-azuloic acid is in good agreement with the present result, but reported values for 5- and 6-azuloic acids are shown to be incorrect.[7]

Of significance is the increasing acidity order of these four acids, 1- < 2- < 5- < 6-azuloic acid. While it is recognized that the carboxylic acid and carboxylate anion groups surely perturb the electron densities at these nonequivalent azulene ring positions, we suggest that such perturbations are not sufficient to cause reversal of the relative electron densities at these positions ($1 > 2 > 5 > 6$) and that the above acidity order gives a truer reflection of these relative electron densities than previous experimental results.[7a]

TABLE I

pK_a's OF AZULOIC ACIDS IN 50% AQUEOUS ETHANOL (v/v) AT 25.0°

Acid	pK_a	Lit. pK_a[a]
1-Azuloic	6.992 ± 0.004[b]	7.01
2-Azuloic	5.855 ± 0.016	
5-Azuloic	5.682 ± 0.017	6.25
6-Azuloic	5.206 ± 0.013	6.09

[a] These literature values are corrected by adjusting the pK_a given for benzoic acid to 5.80; lit. pK_a +0.34.[7] [b] Standard deviations.

It is interesting that plotting these pK_a's *vs.* the charge densities of azulene listed by Streitwieser,[4] the results of the HMO, with or without ω technique, and the VESCF methods give reasonably linear correlations while the correlations from the nonempirical SCF and Pariser–Parr values are poorer. The VESCF correlation predicts that 4-azuloic acid would have a pK_a of about 4.8 in this medium. The acidity of 4-azuloic acid may decrease somewhat if hydrogen bonding to the electron-rich 3 position occurs in the acid which we believe accounts for the observed order of the pK_a's of 1- (pK_a = 5.987 ± 0.006), 4- (pK_a = 5.596 ± 0.010), and 6-azulylacetic acid (pK_a = 5.508 ± 0.032), the latter two being inverted from the order expected. It is our hope that these pK_a results will be helpful to those applying these and more advanced MO methods to azulene.

We have also determined the pK_a's of azulene-1,2-dicarboxylic acid (**1**); p$K_a{}^1$ = 3.352 ± 0.015, p$K_a{}^2$ = 10.459 ± 0.008. The K_1/K_2 ratio of $10^{7.1}$ is very large compared to that of phthalic acid in water, K_1/K_2 = 288.[8a] This shows that there is a larger distance separating the carboxylic acid groups on the five-membered ring of **1** approaching an optimum distance for hydrogen bonding in the half-neutralized **1** compared to the acid groups in phthalic acid (six-membered ring attachments).[8b,9] We were unable to determine the pK_a's of azulene-5,6-dicarboxylic acid (**2**)[10] because of

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[1] (a) For paper V see R. N. McDonald, D. L. Morris, H. E. Petty, and T. L. Hoskins, *Chem. Commun.*, 743 (1971). (b) NDEA Fellow, 1968–1970; NSF Trainee, 1970–1971.

[2] K. Hafner and K. L. Moritz, *Justus Liebigs Ann. Chem.*, **656**, 40 (1962).

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[4] A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 456–457.

[5] See footnotes 7–9 in ref 3.

[6] K. Kuroda, T. Ohta, and T. L. Kunii in "Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity," E. D. Bergmann and B. Pullman, Ed., Academic Press, New York, N. Y., 1971.

[7] P. A. Leermakers and W. A. Bowman, *J. Org. Chem.*, **29**, 3708 (1964). The 5- and 6-azuloic acids were obtained as oils, possibly containing various benzenoid carboxylic acid impurities.

[7a] NOTE ADDED IN PROOF.—Using ^{13}C chemical shifts for azulene, the relative π-electron densities would be $1 > 5 > 2 > 6$: P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1838 (1961).

[8] (a) H. C. Brown, D. H. McDaniel, and O. Hafliger in "Determination of Organic Structures by Physical Methods," Vol. 1, E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, Chapter 14. (b) J. A. Richards and T. J. Curphey, *Chem. Ind. (London)*, 1456 (1956), reported p$K_a{}^1$ = 3.64 and p$K_a{}^2$ ≥ 12 for ferrocene-1,2-dicarboxylic acid in 2:1 ethanol–water.

[9] L. L. McCoy, *J. Amer. Chem. Soc.*, **89**, 1673 (1967).

[10] (a) We wish to thank Professor K. Hafner for a generous sample of the dimethyl ester of **2**. (b) The pK_a's of azulene-1,3-dicarboxylic acid could not be measured in 50% ethanol due to insolubility of this diacid.

ready anhydride formation; this requires the acid functions to be quite close, probably closer than those in phthalic acid. These findings agree with the expectation that groups on adjacent carbons of the five-membered ring of azulene are more distant from one another than those on the seven-membered ring.

Experimental Section

1-Azuloic Acid.—Methyl 1-azuloate[11] (110 mg, 0.68 mmol) [mp 59–60°; λ_{max} (c-C_6H_{12}) 544 nm (lit.[12] mp 56–57°); λ_{max} 544 nm)] was hydrolyzed with 0.3 g of potassium hydroxide in 50% methanol. Chromatography of the acid product on silica gel and recrystallization from ether–hexane gave 60 mg of lavender crystals of 1-azuloic acid, mp 183–184° (lit.[13] mp 181–182°).

2-Azuloic Acid.—Methyl 2-azuloate[11] (90 mg, 0.56 mmol) [mp 109–110°; λ_{max} (c-C_6H_{12}) 654 nm (lit.[14] mp 110–111°; λ_{max} 656 nm)] was hydrolyzed and purified as above giving 50 mg of green crystals of 2-azuloic acid, mp 205–210° dec [lit.[14,15] mp 200–203° dec; 218–220° dec].

5- and 6-Azuloic Acids.—A slightly modified procedure described by Plattner, *et al.*,[16] for the ethyl diazoacetate ring enlargement of indan was employed.[11a] After dehydrogenation with chloranil in refluxing benzene, the resulting blue oil was dissolved in a small quantity of hexane and extracted with 70% sulfuric acid which was again washed with hexane. Careful dilution of the acid layer with water and extraction with hexane gave a mixture (460 mg) of ethyl 5- and 6-azuloates in a 3:1 ratio (nmr), respectively, contaminated with only trace amounts of benzenoids. Separation of these isomers was achieved by saponifying this mixture in 100 ml of 1% methanolic potassium hydroxide. After standing for 48 hr, water was added and the mixture was extracted with ether. The aqueous layer was acidified with 5% hydrochloric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to give a green residue which when sublimed at 75° (0.25 mm) yielded a dark gray-black sublimate. When the temperature was raised to 125°, a green solid sublimed.

Each of these sublimates was treated with ethereal diazomethane and chromatographed on basic, activity I alumina. The first sublimate, after recrystallization from hexane at −25°, yielded 70 mg of green needles of methyl 6-azuloate, mp 112–113°, λ_{max} (c-C_6H_{12}) 634 nm (lit.[16] mp 112.5–113°, λ_{max} 635 nm). The second sublimate, after similar recrystallization, gave 270 mg of deep blue plates of methyl 5-azuloate, mp 38–40°, λ_{max} (c-C_6H_{12}) 567 nm (lit.[16] mp 40–41°, λ_{max} 565 nm).

A sample of methyl 5-azuloate was hydrolyzed as above for the other acids. Silica gel chromatography and recrystallization from ether–hexane gave the bluish-gray solid acid, mp 203–205° (lit.[16] mp 206–207°).

Similar hydrolysis of methyl 6-azuloate and purification of the resulting acid gave 6-azuloic acid as green crystals, mp 208–212° dec (lit.[16] mp 225–227° dec). While we presently do not understand this discrepancy in melting points, we hasten to add that we have obtained 6-azuloic acid from a completely different route and find its decomposition point to again be as we have recorded it.

4- and 6-Azulylacetic Acids.—Both acids were prepared by the procedure of Hafner, *et al.*,[17] for the synthesis of 6-azulylacetic acid. Chromatography on silica gel and recrystallization from ether–hexane gave blue crystals of 4-azulylacetic acid: mp 123–125° dec; ir (KBr) 3000–2820 (OH) and 1690 cm^{-1} (C═O); nmr (DMSO-d_6, internal TMS) τ −2–0 (s, OH, 1), 1.2–3.0 (m, Az H's, 7), and 5.74 (s, CH_2, 2); visible–uv (CH_2Cl_2) 677 nm (log ϵ 2.08), 617 (2.52), 575 (2.60), 356 (3.14), 343 (3.68), 329 (3.54), 286 (4.67), and 280 (4.68); mass spectrum (70 eV, direct insertion) m/e (rel intensity) 186 (M^+, 100) and 142 (19).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.15; H, 5.33.

Similarly, 6-methylazulene gave blue-green crystals of 6-azulylacetic acid, mp 130–131° dec (lit.[17] mp 126–127° dec).

1-Azulylacetic Acid.—This was prepared according to the procedure of Anderson, *et al.*[18] Chromatography on silica gel and recrystallization from ether–hexane gave blue needles of 1-azulylacetic acid, mp 91–92° (lit.[18] mp 92–93°).

Azulene-1,2-dicarboxylic Acid.—Dimethyl azulene-1,2-dicarboxylate [mp 46.5–47.5°, λ_{max} (c-C_6H_{12}) 578 nm][11,19,20] was hydrolyzed as above to give the diacid which was recrystallized from aqueous ethanol: mp 205–215° dec; λ_{max} (95% EtOH) 573 nm (log ϵ 2.87), 368 (3.86), 346 (3.98), 308 (4.72), and 298 (4.71).

Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.95; H, 3.91.

Determination of Dissociation Constants.—A 25-ml, jacketed, round-bottomed titration cell was maintained at 25.00 ± 0.01°. The cell stopper was fitted with glass (half of a Metrohm EA 147X combination electrode) and calomel (Radiometer K 100) electrodes, and the tip of a microburet. Solutions of the acids (0.003 M) were stirred magnetically using a micromagnetic stirring bar encased in Teflon and were titrated with 0.03 N NaOH in 50% aqueous ethanol (v/v).

The microburet (Koch type) was constructed from a three-way Teflon stopcock, a 1-ml pipet calibrated in 0.01-ml divisions, and a 25-ml reservoir. The buret was connected to the cell by means of Teflon microtubing fitted at the end with a capillary glass tube constricted halfway closed at its tip. The tip was placed 0.5 cm below the surface of the solution during titrations.[21]

The pH of the cell was determined with a Metrohm Herisau E 436 recording potentiograph. Scale expansion in this instrument allowed pH readings to ±0.001.

Standardization of the pH scale was based on the thermodynamic pK_a of benzoic acid, 5.80 ± 0.01, in 50% ethanol.[22] A 0.003 M solution of zone-refined benzoic acid (Fisher Certified Reagent Zone Refined) in 50% ethanol was titrated to half-neutralization with 0.03 N NaOH in 50% ethanol. The pH of the cell was adjusted to read 5.750, which is the theoretical, "apparent" pH of benzoic acid at half-neutralization under these concentration and solvent conditions.[22] The calculated pK_a of benzoic acid was then found to be 5.799 ± 0.009. The pH of 0.02 M potassium hydrogen phthalate in 50% ethanol was then 5.415 and was used as a secondary reference buffer. Before and after each titration the pH of the secondary reference was determined; any run that gave readings differing by 0.005 pH units was rejected.

The solution of acid was transferred to the cell by means of a 10-ml pipet. The stopper holding the electrodes, which were rinsed with 50% ethanol, was set in place in the cell. The titrant inlet glass capillary tube was inserted through a hole in the stopper and placed with its tip below the solution's surface. The pH values were recorded on the chart paper at 9–10 stages between 25 and 75% neutralization of the acid. After each addition of a volume of base titrant, magnetic stirring was continued for *ca.* 1 min and then the stirrer was shut off to record the pH. Complete neutralization was assumed at pH *ca.* 10 in this solvent system and was used to verify the original acid concentration.

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(11) The esters used to obtain the acids in this investigation resulted from the studies of (a) H. E. Petty and (b) N. L. Wolfe. Their contribution to the present results is gratefully acknowledged.

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(19) This is one of the products obtained from carbonation of the adduct formed from reaction of lithium dicyclohexylamide and azulene followed by acidification and reaction with diazomethane. The results of this reaction will be given elsewhere: R. N. McDonald, H. E. Petty, and N. L. Wolfe, unpublished results.

(20) W. v. E. Doering and D. W. Wilye, *Tetrahedron*, **11**, 183 (1960), reported the preparation of what appears to be impure dimethyl azulene-1,2-dicarboxylate.

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The pK_a values for these monocarboxylic acids were calculated using the computer program of Leung.[21,23,24]

The water used was distilled water which was passed slowly through a Barnstead Mixed Bed Demineralizer Cartridge (#8902) and redistilled. The ethanol was twice distilled 95% ethanol.

Registry No.—4-Azulylacetic acid, 26157-13-1; azulene-1,2-dicarboxylic acid, 34906-10-0.

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Intermolecular Aromatic Substitution by Aryl Nitrenes

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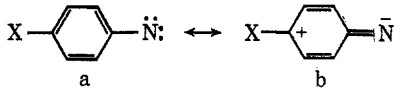
Thermally generated aryl nitrenes have been shown to undergo intermolecular aromatic substitutions provided that the nitrene is made sufficiently electrophilic by the introduction of an electron-withdrawing substituent in the aromatic nucleus and the aromatic substrate is sufficiently nucleophilic. The nitrenes were generated both by the thermolysis of aryl azides and from monomeric nitrosobenzenes and triethyl phosphite. The rate of first-order decomposition of *p*-cyanophenyl azide was found to be independent of the presence of *N*,*N*-dimethylaniline or of its concentration. The formation of a number of by-products is discussed.

The intermediacy of nitrenes in the thermolysis and photolysis of aryl azides is well documented.[1-3] Evidence for the involvement of nitrenes in deoxygenation reactions of nitro and nitroso compounds[4] is good in some cases but more tenuous in others, and depends largely upon analogy of the products of these reactions with those of the corresponding azide reactions. In particular, aryl nitrenes (or their rearrangement products) generated by thermolysis or photolysis of aryl azides or by deoxygenation of nitroso compounds have been trapped by nucleophiles, such as aniline,[5] diethylamine,[6] and carbon monoxide.[7]

Singlet aryl nitrenes generated thermally drop readily to the triplet ground state, so that these species can exhibit reactions typical of both singlet (intramolecular substitution[1] and rearrangement[2]) and triplet states (C–H insertion and hydrogen abstraction[8]). Intramolecular electrophilic aromatic substitution has been extensively studied; the thermal[1] and photolytic[2,9] conversion of *o*-azidobiphenyls to carbazoles involves free nitrenes except in those cases where there is a phenylazo, nitro, acetyl, or benzoyl group ortho to the azido function. Kinetic studies have indicated that there is a concerted loss of nitrogen and cyclization in these cases.[10] Cadogan and Todd[11] have cyclized a number of substituted *o*-nitrobiphenyls to carbazoles with phosphorus reagents. Nitrenes appeared to be involved, but the possibility of a concerted loss of phosphate could not be ruled out, though easy cyclization onto both electron-rich and electron-poor rings make this last rather unlikely. Products of intramolecular aromatic substitution have also been observed from the thermolysis of *o*-azidodiphenyl sulfides,[12] and the deoxygenation of *o*-nitro-*N*-acetyldiphenylamines.[13]

In contrast to the ready intramolecular aromatic substitutions by aryl nitrenes, the corresponding intermolecular reactions are relatively unknown. The decomposition of phenyl azide in aromatic solvents did not yield any diphenylamines. In benzene, only azobenzene and aniline were formed[14] even when 1000-fold excess of benzene was present.[15] On the other hand, intermolecular attack of an aromatic nucleus by ethoxycarbonyl-,[16] cyano-,[17] and sulfonylnitrenes[18] is well known. The absence of intermolecular aromatic substitution by aryl nitrenes could be attributed to rapid decay of the thermally generated singlet nitrene to the triplet[8] before substitution could take place, but could also be due to the possibility that, unlike the above nitrenes, phenylnitrene was insufficiently electrophilic to substitute into benzene. If the latter is true, then it should be possible to increase the electrophilic character of the aryl nitrene by the introduction of electron-withdrawing substituents into the aromatic ring, which would have the effect of decreasing the contribution of **1b** to the structure of the singlet



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