in an oil bath at 60 °C for 14 days. The solvent was then changed to DMF, and DCC (1.6 g, 7.75 mmol) was added to the solution. The mixture was allowed to stir at room temperature for 24 h. The mixture was applied to column chromatography (silica gel, 3.5 × 25 cm, 70–230 mesh; solvent, chloroform/methanol (gradient from 95/5 to 80/20)). The desired portion ($R_f$ = 0.31, solvent system, chloroform:methanol:water = 8:2:0.2) was collected and treated with methanolic ammonia (10 mL) for 2 days. The solvent was then removed in vacuo and the oily residue was added to a mixture of methanol and ether to obtain 0.1 g (4%) of **6h**: mp 215 °C dec.; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.45 (d, 6 H, $2CH_3$), 3.44–3.53 (m, 2 H, 5′-$CH_2$), 3.91 (d, 1 H, 4′-CH), 4.08 (t, 1 H, 3′-CH), 4.54–4.59 (m, 2 H, 2′-CH + CH), 5.09 (d, 1 H, 3′-OH), 5.34 (d, 1 H, 2′-OH), 5.59 (d, 1 H, 1′-CH), 5.82 (m, 1 H, 5′-OH), 7.86 (s, 1 H, 8-CH), 8.04 (s, 2 H, $NH_2$). Anal. Calcd for $C_{13}H_{19}N_5O_5$ (325.325): C, 47.99; H, 5.89; N, 21.53. Found: C, 47.76; H, 5.88; N, 21.30.

**1-Allylxanthosine (12).** Compound **6b** was dissolved in 0.2 N sodium hydroxide solution (30 mL). The solution was heated at 80 °C in an oil bath for 40 h. The pH of the mixture was adjusted to pH 5 with acetic acid, and the mixture was allowed to stand at room temperature. The crude product was collected by filtration and purified from a mixture of DMF and water to give 0.34 g (68%) of **12**: mp 250 °C dec; IR (KBr) 3516, 3126, 2864, 1712 (C=O), 1661 (C=O), 1617, 1573, 1450, 1312, 1123, 1082, 904, 869 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.64 (s, 2 H, 5′-$CH_2$), 3.99 (s, 1 H, 4′-CH), 4.05 (s, 1 H, 3′-CH), 4.23 (m, 1 H, 2′-CH), 4.42 (d, 2 H, $CH_2$, $J$ = 4.86 Hz), 5.00–5.07 (m, 2 H, 5′-OH + CH), 5.28 (d, 1 H, 3′-OH, $J$ = 3.81 Hz), 5.48 (d, 1 H, 2′-OH, $J$ = 6.12 Hz), 5.77 (d, 1 H, 1′-CH, $J$ = 6.87 Hz), 5.79–5.87 (m, 1 H, CH), 6.05 (br s, 1 H, NH), 7.90 (s, 1 H, 8-CH), 12.04 (br s, 1 H, NH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 41.82, 61.25, 70.82, 74.05, 86.11, 88.69, 115.67, 115.97, 133.13, 135.71, 137.96, 149.94, 156.94. Anal. Calcd for $C_{13}H_{16}N_4O_6 \cdot {}^1/_2\ H_2O$ (333.301): C, 46.85; H, 5.14; N, 16.81. Found: C, 47.06; H, 5.05; N, 17.06.

**3-(β-D-Ribofuranosyl)-6,7-dihydrothiazolo[3,2-*a*]purin-9-one (14).** A mixture of AICA-riboside (**1**; 1.0 g, 3.87 mmol) and 2-chloroethyl isothiocyanate (**2c**; 4.7 g, 38.7 mmol) in pyridine (40 mL) was heated at 50 °C for 3 days. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (silica gel, 60 g; solvent system, chloroform/methanol/water = 8/2/0.2; column diameter, 2.0 cm). The right fraction ($R_f$ = 0.33, solvent system, chloroform:methanol:water = 8:2:0.2) was collected and recrystallized from water to give 0.28 g (22%) of **14**: mp 221–225 °C (lit.[24] mp 220–221 °C); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.51–3.62 (m, 4 H, 5′-$CH_2$ + $CH_2$), 3.91 (d, 1 H, 4′-CH), 4.09 (d, 1 H, 3′-CH), 4.41 (m, 3 H, 2′-CH + $CH_2$), 5.03 (br s, 1 H, 3′-OH), 5.20 (br s, 1 H, 2′-OH), 5.46 (br s, 1 H, 5′-OH), 5.76 (d, 1 H, 1′-CH), 8.22 (s, 1 H, CH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 27.37, 48.66, 61.25, 70.28, 74.03, 85.62, 87.17, 120.83, 138.24, 148.70, 155.27, 161.28. Anal. Calcd for $C_{12}H_{14}N_4O_5S \cdot {}^1/_4H_2O$ (330.83): C, 43.56; H, 4.42; N, 16.93. Found: C, 43.26; H, 4.38; N, 16.80.

**Acknowledgment.** This investigation was supported by research grants from the National Science Council of the Republic of China (No. NSC78-0420-B016-98 and NSC79-0420-B016-136).

# Heterocyclic Aromatic Anions with 4*n* + 2 π-Electrons

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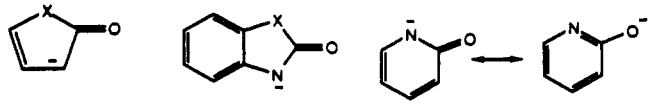
*Received October 25, 1990 (Revised Manuscript Received March 22, 1991)*

Equilibrium acidities in DMSO for several cyclic carboxamides, thiocarboxamides, esters, and sulfones that form anions possessing 4*n* + 2 electrons have been measured. Aromatic stabilization energies (ASEs) for these anions have been estimated by comparing their p$K_{HA}$ values with those of open-chain analogues. The ASEs (kcal/mol) are 8.3 for *N*-methylindolin-2-one, 15.5 for *N*-methylindoline-2-thione, 7.1 for 2-oxo-2,3-dihydrobenzo[*b*]furan, 8.5 for 2-oxo-2,3-dihydrobenzo[*b*]thiophene, 11.4 for 3-phenyl-2*H*-thiopyran 1,1-dioxide, and 23 for cyclopentadiene. These values need to be corrected, however, for the effects of cyclization on p$K_{HA}$ values, which are about 3 kcal/mol for carboxamides and 5 kcal/mol for esters.

Five- and six-membered ring heterocycles with 4*n* + 2 π-electrons, such as furan, thiophene, pyrrole, and pyridine, are known to display aromatic properties and to have aromatic stabilization (resonance) energies estimated to range from about 15 to 32 kcal/mol.[1] Cyclic carbanions bearing a 4*n* + 2 π-electron system, such as those formed on deprotonating 1,3-cyclopentadiene or indene, are also believed to possess aromatic stabilization energies (ASEs), and this concept has been extended to comparable heterocyclic anions of the type **1**–**3**. Two criteria have been



**1** **2** **3a** **3b**

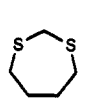
used to detect aromaticity in anionic systems: (1) the existence of aromatic ring currents and (2) the demonstration of exceptional stability. The former, frequently probed using $^1$H NMR spectroscopy, has been branded as unreliable because of the complexity of the factors affecting chemical shifts (diamagnetic ring current, charge distribution, anisotropy, and geometry of the heteroatom).[2] Alternatively, acidity measurements have been used to detect exceptional stability in cyclic anions with 4*n* + 2 π-electrons formed by deprotonation. Comparison with a suitable model (Δp$K_{HA}$) may then afford an estimate of the ASE for the ion. In practice, the acidity method has been difficult to apply since thermodynamic techniques capable of determining the p$K_{HA}$ values of weak carbon acids have not been available until recently. Consequently, kinetic methods, which may not reflect true thermodynamic acidities, have been employed. For example, since 1,3-dithia-4,6-cycloheptadiene (**4a**) was found to undergo H/D exchange in *t*-BuOD/*t*-BuOK at 83 °C at least 150 times faster than the saturated analogue (**4b**), a minimum

(1) Cook, M. J.; Katritzky, A. R.; Linda, P. In *Advances in Heterocyclic Chemistry* **1974**, *17*, 255–356. For recent discussion of the role of π- and σ-electrons in aromaticity, see: Shaik, S. S.; Hiberty, P. C.; Lefour, J. M.; Ohanessian, G. *J. Am. Chem. Soc.* **1987**, *109*, 363–374. Jug, K.; Köster, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 6772–6777.

(2) Semmelhack, C. L.; Chin, I.-C.; Grohmann, K. G. *J. Am. Chem. Soc.* **1976**, *98*, 2005–2006.

0022-3263/91/1956-4218$02.50/0 


4a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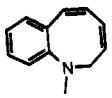
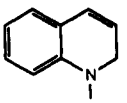
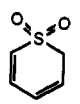

5a


5b

ASE of 3 kcal/mol was estimated for its conjugate base.[2] Similarly, an 83-fold faster rate of deuterium exchange for **5a** than for **5b** with *t*-BuOK–*t*-BuOD in DMSO-$d_6$ was interpreted as indicating the presence of ASE in the 14 π-electron anion.[3] Also, benzo derivatives of 2*H*-thiopyran 1,1-dioxide (**6**) undergo base-catalyzed deuterium exchange in [$^2H_5$]pyridine–$D_2O$ at rates $10^3$–$10^5$ times faster than acyclic models.[4] As a final example, proton abstraction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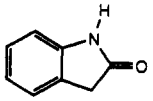
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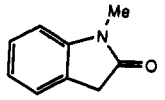

8

from indolin-2-one (oxindole; **7**) has been found to be extraordinarily facile when compared with lactams in which the anions are not uniquely stabilized.[5] Thus, Hino[6] found the *N*-methylindolin-2-one (**8**) undergoes 90% dideuterio exchange of the C–H protons in $D_2O$ in 1.5 h when catalyzed by $K_2CO_3$, and Challis and Rzepa found that **7** undergoes base-catalyzed iodinization at a rate at least $10^6$ times that of acetamide.[7]

In the present study we have made equilibrium acidity measurements in a dimethyl sulfoxide (DMSO) solution in order to obtain estimates of the ASEs of anions derived from the indolin-2-one and related systems.

## Results and Discussion

**Acidity Measurements in DMSO.** The $pK_{HA}$ measurements in DMSO were made on 23 compounds by the overlapping indicator method described in earlier publications (Table I).[8] Addition of an aliquot of unknown acid, HA, to a solution of the conjugate base of an indicator acid, HIn, of known $pK_{HIn}$ led to rapid establishment of an equilibrium (1) from which the $pK_{HA}$ could be calculated by eq 2. The compounds in Table I were well behaved

$$HA + In^- \rightleftarrows HIn + A^- \quad (1)$$

$$pK_{HA} = pK_{HIn} + \log [In^-]/[HIn] + \log [HA]/[A^-] \quad (2)$$

in $pK_{HA}$ determinations except for phenyl phenylacetate and phenyl phenylthiolacetate (**21** and **22**, and the butenolides **25** and **26**). Two two-point titrations of **21** with 4-chloro-2-nitroaniline ($pK_{HIn}$ = 18.9) and a one-point titration with 9-phenylfluorene ($pK_{HIn}$ = 17.9) gave a reliable $pK_{HA}$ = 18.7 ± 0.05, and two one-point titrations for **22** against 9-(isopropylthio)fluorene ($pK_{HIn}$ = 16.9) gave an estimated $pK_{HA}$ of 16.9 ± 0.1. The instability of the anions derived from **21** and **22** is no doubt due to the elimination of $PhO^-$ and $PhS^-$ ions, respectively, with the consequent formation of phenylketene.[9]

Addition of either **25** or **26** to an indicator solution gave a rapid drop in absorbance which briefly leveled off and then rose. The $pK_{HA}$ values calculated from the leveling off period were 18.8 and 18.0, respectively, and are reproducible, but are probably not reliable.

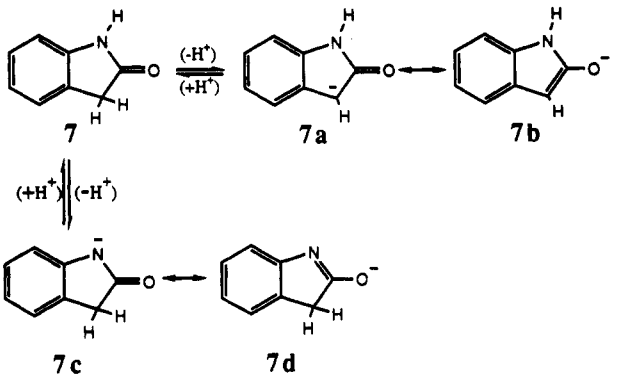
**Anion Stabilization Energies from Acidities of Carboxamides.** Nitrogen acids are usually about 17 kcal/mol stronger in DMSO than analogous carbon acids, but carboxamides are exceptional in this regard, being only 1 or 2 kcal/mol more acidic than their ketone analogues.[10] Deprotonation of **7** could give either a carbanion–enolate ion (**7a** ↔ **7b**), which has a 10 π-electron system, or a

**Table I. Equilibrium Acidities of Heterocycles and Related Open-Chain Molecules in DMSO Solution**

| compound | $pK_a$[a] |
|---|---|
| indolin-2-one (oxindole; **7**) | 18.2 |
| *N*-methylindolin-2-one (**8**) | 18.5 |
| 3,3-dimethylindolin-2-one (**9**) | 18.5 |
| 3,3-dibenzylindolin-2-one (**10**) | 18.7 |
| $C_6H_5CH_2CON(Me)Ph$ (**11**) | 24.6 |
| $C_6H_5CH_2CONHPh$ | 20.6 |
| indoline-2-thione (**12**) | 10.0 |
| *N*-methylindoline-2-thione (**13**) | 10.0 |
| $C_6H_5CH_2CONMe_2$ (**14**) | 26.6 |
| $C_6H_5CH_2C(=S)NMe_2$ (**15**) | 21.3 |
| $CH_3C(=S)NMe_2$ (**16**) | 25.7 |
| *N*-acetylindolin-2-one (**17**) | 13.7 |
| $CH_3COCH_2CONMe_2$ (**18**) | 18.2 |
| 2-oxo-2,3-dihydrobenzo[*b*]furan (**19**) | 13.5 |
| 2-oxo-2,3-dihydrobenzo[*b*]thiophene (**20**) | 10.7 |
| $C_6H_5CH_2CO_2C_6H_5$ (**21**) | 18.7[b] |
| $C_6H_5CH_2COSPh$ (**22**) | 16.9[b] |
| 2-indanone (**23**) | 16.9 |
| $(C_6H_5CH_2)_2C=O$ (**24**) | 18.7 |
|  (**25**) | c |
|  (**26**) | c |
| 3-phenyl-2*H*-thiopyran 1,1-dioxide (**27**) | 11.85 |
| 6-methyl-3-phenyl-2*H*-thiopyran 1,1-dioxide (**28**) | 13.7 |
| benzo[*b*]-2*H*-thiopyran 1,1-dioxide (**29**) | 16.0 |

[a] Measured by an overlapping indicator method using two three-point titrations against two or more indicators unless otherwise noted. The $pK_{HA}$ selected was obtained from an average of all the runs or an average of runs made with the indicator closest to that of the acid measured. Further details are recorded in the Ph.D. Dissertation of H. E. Fried, Northwestern University, 1978. [b] One-point titrations in which the change in absorbance was extrapolated back to zero time. [c] One-point titrations suggested $pK_{HA}$ values near 18, but these are believed to be erroneous (see text).

**Scheme I**



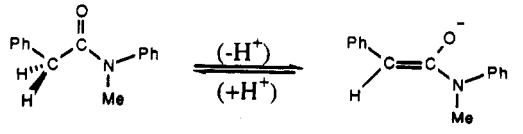

(3) Coates, R. M.; Johnson, E. F. *J. Am. Chem. Soc.* **1971**, *93*, 4016–4027.
(4) (a) Bradamante, S.; Maiorana, S.; Mangia, A.; Pagani, G. *J. Chem. Soc. B* **1971**, 74–78. (b) Gaviraghi, G.; Pagani, G. *J. Chem. Soc., Perkin Trans. 2* **1973**, 50–51.
(5) Sunberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; p 341.
(6) Hino, T. J.; Nakagawa, M.; Tsuneoka, K.; Misawa, S.; Kaboshi, S. A. *Chem. Pharm. Bull.* **1969**, *17*, 1651.
(7) Challis, B. C.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1822–1826.
(8) (a) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, A.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014. (b) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424–1427.
(9) Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956–5964.
(10) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330–3336.

nitranion (7c–d) (Scheme I).

Examination of Table I shows that *N*-methylindolin-2-one (8), which must be a C–H acid giving a $4n + 2$ $\pi$-electron anion, has a $pK_{HA}$ value of 18.5, only 0.3 unit higher than that of indolin-2-one (7), which could be either a carbanion or a nitranion. The similarity of these two $pK_{HA}$'s provides circumstantial evidence for ionization of 7 as a C–H acid. We sought to check this observation by comparing the $^{13}C$ NMR chemical shift for the carbonyl group of the anion derived from 7, relative to that of the parent carboxamide [$\Delta\delta$(C=O)]. The shift of −12.97 ppm observed was found to be in the same range as for typical carboxamides (N–H) acids, such as 1,2,3,4-tetrahydroquinolin-2-one (34) [$\Delta\delta$(C=O)] = −10.75. Conversely, $\Delta\delta$(C=O) values are positive for carboxamides acting as C–H acids (+9.71) for *N*-methylindolin-2-one and +5.11 for *N*-methyl-$\alpha$-phenylacetanilide). But the oxidation potential in DMSO for the conjugate base of 7 is 0.030 V,[11] which is close to that for *N*-methylindolin-2-one anion, a carbanion (0.030[11]), and much more negative than that for 34 (0.684[11]), a nitranion. Evidently, ionization of 7 in DMSO gives *both* $N^-$ and $C^-$ ions. Since 3,3-dimethylindolin-2-one (9), an N–H acid, and *N*-methylindolin-2-one (8), a C–H acid, have identical $pK_{HA}$ values (Table I), it would appear that the $pK_{HA}$ values for the N–H and C–H acidic sites in 7 are about equal.

This near identity of the acidities of N–H and $\alpha$-C–H bonds in a carboxamide is most unusual. The acidic C–H bond in *N*-methyl-*N*-phenylphenylacetamide (11) has a $pK_{HA}$ of 24.6, which is 4 $pK_{HA}$ units (5.5 kcal/mol) higher than that of the N–H bond in $C_6H_5CH_2CONHPh$ (Table I). The N–H bond in acetamide has a $pK_{HA}$ in DMSO of 25.5, whereas the acidic C–H bond in *N,N*-dimethylacetamide is too weak to be measured in DMSO. Its $pK_{HA}$ is estimated to be about 36 from the $\Delta pK_{HA}$ between $C_6H_5CH_2CONMe_2$ (14) and $C_6H_5CH_2C(=S)NMe_2$ of 5.3 units, plus the $\Delta pK_{HA}$ between $CH_3C(=S)NMe_2$ (15) and $C_6H_5CH_2C(=S)NMe_2$ of 4.4 units. The difference of 14.4 kcal/mol in acidities of the C–H and N–H bonds in acetamide is nearly that expected for the element effect caused by the difference in electronegativities of carbon and nitrogen.[10] The relatively high acidity of the C–H bond in 7 clearly must have its origin in the stabilizing effect of the 10 $\pi$-electron system in the anion.

**Open-Chain Analogues as Models for Aromatic Carboxamide Anions.** *N*-Phenyl-*N*-methylphenylacetamide (11), an open-chain model of 8, is 6.1 units (8.3 kcal/mol) less acidic. Of course, 11 is not an ideal model in that its enolate ion (11a) probably adopts a *Z* geometry as shown, whereas the enolates from 7 and 8 (e.g., 7b) are

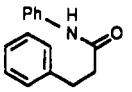
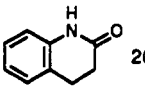
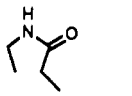
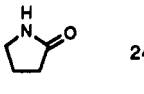
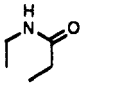
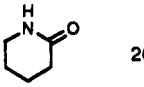
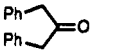
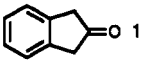
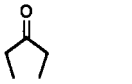
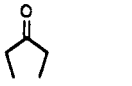
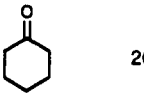
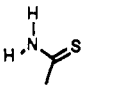
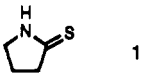
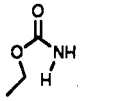
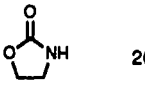



11 11a

held in an enforced *E* geometry. The data given in Table II show that incorporation of carboxamide or ketone functions into a five-membered ring leads to increases in acidity amounting to 1.3–2.3 $pK_{HA}$ units. Correction of the $\Delta pK_a$ of 11 by 3.1 kcal/mol for the ring structure would leave 5.2 kcal/mol as an estimate of the ASE for 8 (or 7). Table III summarizes the ASEs for representative carboxamides, esters, sulfones, and hydrocarbons (without ring corrections).

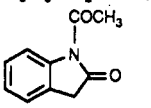
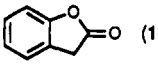
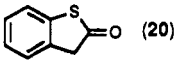
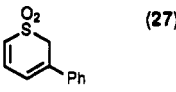
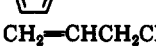
(11) Harrelson, J. A., Jr.; Zhang, X., unpublished results. This does not exclude the presence of nitranions, however, because carbanions have been found to be oxidized much more readily than nitranions of the same basicity.

**Table II. Comparison of Acidities of Cyclic Functions and Their Open-Chain Analogues in DMSO**

| $pK_{HA}$ (acyclic model)[a] | $pK_{HA}$ (cyclic compound)[a] | $\Delta pK_{HA}$ (kcal/mol) |
|---|---|---|
|  20.6 |  20.7 | −0.1 |
|  26.5 |  24.2 | +2.3 (3.1) |
|  26.5 |  26.6 | −0.1 |
|  18.65 |  16.95 | +1.7 |
|  27.1 |  25.8 | +1.3 |
|  27.1 |  26.4 | +0.7 |
|  18.5 |  18.1 | +0.4 (0.55) |
|  24.2[b] |  20.8[c] | +3.4 (4.7) |

[a] Measured in DMSO against two indicators as reported in Table I or by Fried, H. E. Ph.D. Dissertation, Northwestern University, 1978. [b] Measured by John A. Harrelson, Jr. [c] Measured by Xianman Zhang.

**Table III. Estimates of Aromatic Stabilization Energies for Various Anions Derived from $\Delta pK_{HA}$ Values**

| compounds and models | $pK_{HA}$[a] | $\Delta pK_{HA}$[b] | ASE[c] |
|---|---|---|---|
| *N*-methylindolin-2-one (8) | 18.5 | | |
| $C_6H_5CH_2CON(Me)(Ph)$ (11) | 24.6 | 6.1 | 8.3[d] |
|  | 13.5 | | |
| *N*-methylindoline-2-thione (13) | 10.0 | | |
| $C_6H_5CH_2C(=S)NMe_2$ (15) | 21.3 | 11.3 | 15.5 |
|  (19) | 13.5 | | |
| $C_6H_5CH_2CO_2C_6H_5$ (21) | 18.7 | 5.2 | 7.1 |
|  (20) | 10.7 | | |
| $C_6H_5CH_2COSPh$ (22) | 16.9 | 6.2 | 8.5 |
|  (27) | 11.85 | | |
| (*E*)-$PhSO_2CH_2CH{=}CHPh$ | 20.2 | 8.3 | 11.4 |
|  | 18.0 | | |
| $CH_2{=}CHCH_2CH{=}CH_2$ | ~35 | 17 | ~23[e] |

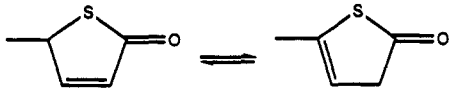
[a] See Table I and the text for details. [b] $pK_{HA}$ (model) − $pK_{HA}$, uncorrected for cyclization effects. [c] Aromatic stabilization energy in kcal/mol uncorrected for cyclization effects. [d] Decreased to ~5.2 when corrected for cyclization effects (see text). [e] See: Bordwell, F. G.; Drucker, G. D.; Fried, H. E. *J. Org. Chem.* **1984**, *46*, 632–635 for a discussion.

Replacement of the carbonyl group in 7 by a thiocarbonyl group to give indoline-2-thione (12) increases the acidity by 8.2 $pK_{HA}$ units (11.2 kcal/mol). A similar effect was observed for *N*-methylindoline-2-thione (13), relative to its carbonyl derivative ($\Delta pK_{HA}$ = 8.5 or 11.6 kcal/mol; both are C–H acids). These effects are about 2 kcal/mol larger than those observed for a comparable structural change on the N–H acidities of $CH_3C(=O)NH_2$ vs $CH_3C(=S)NH_2$.[12] They are also appreciably larger than the effects observed on the C–H acidities of open-chain analogues $C_6H_5CH_2C(=O)NMe_2$ (14) versus $C_6H_5CH_2C(=S)NMe_2$ (15) (5.3 units or 9.0 kcal/mol). The 15.5 kcal/mol greater acidity for indoline-2-thione and its *N*-methyl derivative than for the open-chain model 15 points to a large increase in ASE. If we correct this $\Delta pK_{HA}$ by 3.1 kcal/mol (assuming the same effect on cyclization as observed for pyrrolidin-2-one) the estimated ASE is 12.4 kcal/mol. Comparison of the acidity of 15 with that of $CH_3(=S)NMe_2$ (16) reveals a $\Delta pK_{HA}$ of 4.4 units. This is a relatively small phenyl-acidifying effect compared to that for $PhCH_2CN$ vs $CH_3CN$ ($\Delta pK_{HA}$ = 9.4), pointing to an appreciable steric effect in 15, which may cause the $pK_{HA}$ for 15 to be abnormally high. This would tend to enhance the estimated ASE. On the other hand, the correction for cyclization may be smaller (Table II).

The origins of the large effects on $pK_{HA}$ caused by the change from C=O to C=S are not entirely clear. In earlier papers we have suggested that the superior ability of sulfur than oxygen to bear a negative charge and the greatly increased ground-state energies of the thio compounds may be causative factors.[12] To these we can now add, in the case of 12 and 13, an appreciable enhanced aromaticity for the anions.

**Anion Stabilization Energies from Acidities of Esters.** 2-Oxo-2,3-dihydrobenzo[*b*]furan (19) and 2-oxo-2,3-dihydrobenzo[*b*]thiophene (20) are 4.7 and 7.5 $pK_{HA}$ units more acidic than their open-chain carboxamide counterpart (8). The open-chain ester analogues phenyl phenylacetate (21) and phenyl phenylthiolacetate (22) are 7.9 and 9.7 $pK_{HA}$ units less acidic than 19 and 20, respectively. The ASEs for these esters estimated from the $\Delta pK_{HA}$ values in Table III are 7.1 and 8.5 kcal/mol, respectively. The correction for cyclization in these esters is about 4.7 kcal/mol, as judged by the difference in acidities of ethyl carbamate and 2-oxazolidone (Table II). (This relatively large correction is due to the dipolar effect of the C–O bond brought about by the conformational restraint imposed by the ring structure.[13])

Attempts to measure the acidities of the butenolides 25 and 26 were unsuccessful due to anion decomposition. A tautomeric mixture of a thio analogue (30a ⇄ 30b) has



30a 30b

been found to have a $pK_a$ = 10.18 in aqueous solution, however, and the $pK_a$ of 30b has been calculated to be 8.75.[14a] It is difficult to compare the latter value with that of 10.7 for the benzo analogue 20 in DMSO since they were determined in different solvents. The $pK_a$ of the benzo oxygen analogue (19) has been found to be about 12–12.5 in water,[14b] however, which is 1–1.5 units lower than our value in DMSO (Table I). The estimated $pK_a$ in DMSO for 30b is then about 9.5 in DMSO (assuming a similar solvent effect). This low value is consistent with the $pK_a$ data for 19 and 20 and suggestive of an appreciable aromatic stabilization energy for the anion derived from 30b.

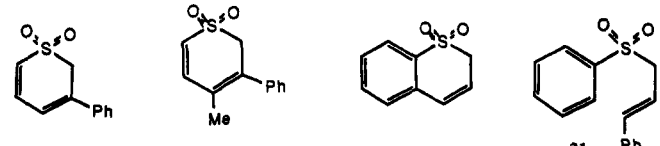
Table IV. Acidities of Pyrrole, Cyclopentadiene, and Their Benzo Derivatives

| compound | $pK_{HA}$[a] | compound | $pK_{HA}$[a] |
|---|---|---|---|
| pyrrole | 23.05 | cyclopentadiene | 18.0 |
| indole | 20.95 | indene | 20.1 |
| carbazole | 19.9 | fluorene | 22.6 |

[a] Bordwell, F. G. *Acc. Chem. Res.* 1988, *21*, 456–463.

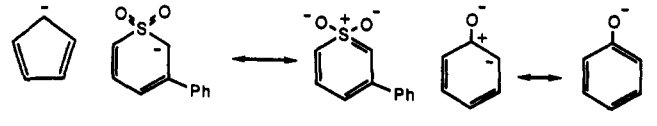
**Acidities of Pyrrole, Cyclopentadiene, and Their Benzo Derivatives.** The acidities in DMSO for pyrrole, indole, and carbazole increase along this series whereas those for cyclopentadiene, indene, and fluorene go in the opposite direction (Table IV). This order for the carbon acids was first observed over fifty years ago (in benzene)[15] and was explained for many years by assuming progressively higher ASEs as the anions decrease in size. Measurements of gas-phase acidities revealed, however, that the intrinsic order was the reverse of that observed in solution, indicating that the solution order was dictated by solvation effects.[16]

**Anions Derived from Thiopyran 1,1-Dioxides.** 3-Phenyl-2*H*-thiopyran 1,1-dioxide (27), its 6-methyl derivative (28), and benzo[*b*]-2*H*-thiopyran 1,1-dioxide (29) are 4.2–8.4 $pK_{HA}$ units more acidic than the acyclic model (*E*)-1-phenylalkyl phenyl sulfone (31), $pK_{HA}$ = 20.2 (Table III). This is consistent with Pagani's suggestion, based



27 28 29 31

on kinetic acidities, that the anions derived from these sulfones may possess considerable aromatic stabilization.[4] This is not unreasonable when one considers that the anion derived from 27 has some of the characteristics of the cyclopentadienide ion (32) and the phenoxide ion (33). All three are 6 π-electron systems. Insertion of $SO_2$ into $Cp^-$



32 27a 27b 33a 33b

disrupts the conjugation, but not entirely. Although most of the π-electron density remains in the ring for the sulfone 27a, some is on oxygen, wherein it resembles the phenoxide ion 33a.

## Experimental Section

Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected unless otherwise indicated.

Elemental analyses were performed by Micro-Tech Laboratories of Skokie, IL.

Mass spectra (M) were determined by Dr. Doris Hung.

(12) (a) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* 1988, *110*, 5903–5904. (b) Bordwell, F. G.; Harrelson, J. A., Jr.; Lynch, T.-Y. *J. Org. Chem.* 1990, *55*, 3337–3341.

(13) (a) Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* 1987, *109*, 809–812. (b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* 1988, *110*, 1870–1872. (c) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* 1988, *110*, 1872–1874.

(14) (a) Hornfeldt, A.-B. *Ark. Kemi* 1968, *29*, 247–252. (b) Tobias, P. S. Ph.D. Dissertation, University of Chicago, 1971.

(15) McEwen, W. K. *J. Am. Chem. Soc.* 1936, *58*, 1123–1129.

(16) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* 1988, *21*, 463–469.

**Materials and Syntheses. General.** All reagents were commercially available reagent-grade chemicals unless otherwise noted. Purity of p*K* samples was ascertained by VPC, thin-layer chromatography (TLC) (on Eastman Chromagram sheets No. 13181, silica gel with fluorescent indicator), HPLC, NMR, IR, mp, and bp, whenever applicable. Thick-layer chromatography was performed on Quantum Industries Quanta/Gram PQ6F or PQ5F plates. Sulfones **27**, **28**, and **29** were gifts from G. Pagani.[4]

**Indolin-2-one (7).** A commercial sample (Parish Chemical Co.) was repeatedly recrystallized from ethanol/water solution affording long white needles, mp 126–7 °C.

***N*-Methylindolin-2-one (8).** A mechanically stirred mixture of sodium hydride (2.5 g, 0.05 mol; 50% dispersion in oil) in 100 mL of dry xylene, under a nitrogen atmosphere, was heated to near reflux for 0.5 h. Oxindole (6.65 g, 0.05 mol) was then slowly added via an addition funnel and stirred at reflux for 1.5 h. Dimethyl sulfate (7.0 g, 0.05 mol) was then added all at once, whereupon the resulting homogeneous solution was refluxed for an additional 2 h. After cooling to room temperature, the reaction solution was washed several times with water, dried ($Na_2SO_4$), and concentrated under reduced pressure to afford a tan oil. Crystallization from hexane gave 5.2 g (68%) of tan needles melting at 85–87 °C. Treatment of the solid with activated carbon followed by multiple recrystallization yielded pure white needles: mp 86–7.5 °C (lit.[17] mp 89 °C); NMR δ 3.09 (s, 3 H), 3.38 (s, 2 H), 6.5–7.4 (m, 4 H).

**3,3-Dimethylindolin-2-one (9).** A sample kindly provided by Dr. Yoshiki Ohshiro was recrystallized from ethyl acetate giving clear prisms, mp 148–150 °C.

**3,3-Dibenzylindolin-2-one (10).** To oxindole (1.16 g, 0.009 mol) in 50 mL of absolute ethanol, cooled to 0 °C in an ice–water bath, was added (under nitrogen) 0.2 g 0.009 mol) of sodium metal. The mixture was stirred until a homogeneous yellow solution was obtained, whereupon 1.1 mL of benzyl chloride was added rapidly via syringe. Stirring at room temperature was continued for 24 h. The precipitate that formed (NaCl?) in the resulting orange reaction mixture was filtered, and the resulting filtrate was added to 5 equiv of water. Following two extractions with chloroform, the organic portions were combined, dried ($Na_2SO_4$), and concentrated on a rotary evaporator, giving 2.3 g of red oil. A NMR spectrum of this oil indicated the presence of more than one product. The reaction oil was then crystallized from an ethanol/water solution, affording 450 mg of a high melting solid (~200 °C). Subsequent recrystallizations from benzene gave pure white needles: mp 199–200 °C; NMR δ 3.25 (q, 4 H), 6.3–7.3 (m, 4 H), 7.55–7.75 (broad, H); M (313).

***N*-Methyl-α-phenylacetanilide (11).** This compound was prepared by careful addition of phenylacetyl chloride to freshly distilled *N*-methylaniline. After approximately 2 h of stirring at room temperature, a solution of 10% HCl was carefully added. The resulting solution was washed twice with ether, and the organic fractions were combined and then washed once with a 10% NaOH solution. The ethereal solution was dried over $Na_2SO_4$ and concentrated under reduced pressure giving a yellow liquid. Distillation of the liquid under reduced pressure [bp 127–28 °C (0.3 mm)] [lit.[18] bp 163 °C (2 mm)] gave the product pure by VPC: NMR δ 3.24 (s, 3 H), 3.45 (s, 2 H), 7.0–7.6 (m, 10 H).

**1,2,3,4-Tetrahydroquinolin-2-one (34).** *o*-Nitrocinnamic acid (Aldrich Chemical Co.) (2.1 g, 0.0011 mol) dissolved in 300 mL of 95% ethanol was hydrogenated over a 10% palladium on carbon catalyst for 3 h at 35 psi on a Parr hydrogenator. The resulting solution was filtered through Celite and concentrated under reduced pressure, affording 1.7 g (~100%) of an off-white solid melting at 159–62 °C. Activated carbon treatment and multiple recrystallization (EtOH/$H_2O$) of this solid gave white needles: mp 163–4 °C (lit.[19] mp 163 °C); NMR δ 2.4–3.2 (m, 4 H), 6.7–7.3 (m, 4 H), 8.8–9.3 (broad, 1 H).

**1-Acetylindolin-2-one (17).** This compound was prepared by heating 1.2 g (0.009 mol) of oxindole in 30 mL of acetic anhydride for 15 h on a steam bath. The resulting solution was poured into 200 mL of cold water and extracted with diethyl ether. The combined ethereal layers were washed twice with a 10% NaOH solution and twice with water, dried ($MgSO_4$), and concentrated in vacuo to give 1.6 g (~100%) of an off-white solid. Repeated recrystallization from absolute ethanol yielded pure white needles: mp 127–8 °C (lit.[20] mp 127 °C); NMR δ 2.68 (s, 3 H), 3.61 (s, 2 H), 6.9–7.5 and 8.0–8.3 (m, 4 H).

**2-Oxo-2,3-dihydrobenzo[*b*]furan (2-Coumaranone, 19).** A commercial sample (Aldrich Chemical Co.) was treated with activated carbon and repeatedly recrystallized from ethanol/water, giving small white needles.

**2-Oxo-2,3-dihydrobenzo[*b*]thiophene (20).** This compound was prepared similarly to the literature procedure.[21] To 5.25 g (0.040 mol) of benzo[*b*]thiophene in 80 mL of dry ether at 0 °C was added 18 mL (0.040 mol) of 22% *n*-butyllithium in hexane over a 10-min period. The yellow solution was allowed to stir at room temperature for 1 h when 10.4 g (0.045 mol) of *n*-butyl borate in 15 mL of ether was added dropwise at 0 °C over a 20-min period. After the reaction mixture was stirred for an additional 45 min, ethanol and then 100 mL of a 10% HCl solution were added. The organic layer was separated, and the aqueous portion was extracted twice with ether. The ethereal and organic fractions were then combined and extracted three times with a 10% KOH solution. The combined alkaline extracts were treated with concentrated HCl solution until acidic to litmus paper. Final extraction with ether (twice), drying of the organic portion, and concentration under reduced pressure gave 13.6 g (71%) of an oil. Upon addition of hexane to this oil, 7.2 g of a white precipitate was formed (mp >270 °C).

This solid cyclotriboroxane (1.0 g, 0.0021 mol) was dissolved in 10 mL of absolute ethanol and cooled to 0 °C. A 30% hydrogen peroxide solution (1.8 mL, 0.016 mol) was added, and the resulting reaction mixture was stirred at room temperature overnight. After the addition of water the product was extracted with chloroform. Combination of the organic portions, drying ($Na_2SO_4$), and removing the solvent left 1.0 g of an oil. Purification by chromatography on silica gel with benzene as eluent gave 0.8 g (85%) of a slightly yellow solid. Recrystallization from hexane gave slightly yellow prisms, which were sublimed (50 °C, 5 mm) to give the pure white product: mp 43.5–4.0 °C (lit.[22] mp 43–4 °C); NMR δ 3.91 (s, 2 H), 7.15–7.45 (m, 4 H).

**Phenyl Phenylacetate (21).** This compound was prepared by allowing equal portions of phenylacetyl chloride and phenol to stir in ether for 2 days at room temperature. The workup was analogous to that employed in the isolation of the thiol ester **22**. Recrystallization of the product from ethanol/water solution gave the pure white solid: mp 40–1.5 °C (lit.[23] mp 42 °C); NMR δ 3.82 (s, 2 H), 6.9–7.6 (m, 10 H).

**Phenyl Phenylthiolacetate (22).** To phenylacetyl chloride (10.9 g, 0.071 mol) in 125 mL of dry benzene at 0 °C was added a solution of 10 mL (0.078 mol) of thiophenol and 12 mL of triethylamine (0.164 mol). The solution, under a nitrogen atmosphere, was stirred overnight at room temperature. The product was isolated by pouring the reaction mixture in a 10% KOH solution, separating the organic portion and washing twice more with the KOH solution. After one wash with water, the organic fraction was dried ($Na_2SO_4$) and the solvent was removed on a rotary evaporator, giving 12.0 g (74%) of crude liquid. This material was distilled under vacuum (158–160.5 °C, 1.4 mm) to give a slightly yellow liquid. Purification by column chromatography using silica gel and a 50% hexane/benzene solution as eluent gave the pure (by VPC) clear liquid: NMR δ 3.76 (s, 2 H), 7.1–7.5 (m, 10 H).

**2-Indanone.** A commercial sample (Aldrich Chemical Co.) was repeatedly recrystallized from 95% ethanol and then sublimed (~25 °C, 2 mm).

**1,3-Diphenylpropan-2-one.** A commercial sample (Eastman Chemical Co.) was Kugelrohr distilled (120–140 °C 0.5 mm); however, two spots were still present on TLC. Purification was

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achieved by column chromatography on silica gel with benzene as eluent.

**Indoline-2-thione (12).** This compound was synthesized by following the literature procedure.[18] Oxindole (1.33 g, 0.01 mol) and phosphorus pentasulfide (0.45 g, 0.002 mol) were heated to reflux in 50 mL of benzene for 2 h. Filtration of the hot solution followed by the addition of hexane to the filtrate yielded 0.5 g of yellow solid. An additional 0.75 g of solid was obtained by concentrating the filtrate under reduced pressure. Multiple recrystallization of the first 0.5 g of solid gave 300 mg of yellow needles: mp 142-43.5 °C (lit.[24] mp 147-9 °C); NMR δ 4.02 (s, 2 H), 6.7-7.3 (m, 4 H), 10.5-10.8 (broad, 1 H).

***N*-Methylindoline-2-thione (13).** 1-Methylindolin-2-one (1.0 g, 0.0068 mol) and phosphorus pentasulfide (0.3 g, 0.0013 mol) were heated over a steam bath for 4 h in 50 mL) of toluene. Upon cooling, the reaction mixture was decanted and concentrated under reduced pressure to give a gummy yellow solid (1.0 g). Multiple recrystallization from hexane gave yellow needles: mp 106.5-8.0 °C (lit.[24] mp 109-10 °C); NMR δ 3.60 (s, 3 H), 4.08 (s, 2 H), 7.24 (s, 4 H).

***N,N*-Dimethylphenylthioacetamide (15).** Phosphorus pentasulfide (0.35 g, 0.0015 mol) was added to *N,N*-dimethylphenylacetamide (1.2 g, 0.0074 mol) in 20 mL of toluene. This solution was heated on a steam bath for 3 h, decanted, and concentrated in vacuo, leaving 1.0 g (75%) of a yellow solid. Repeated recrystallization from benzene/hexane solution followed by sublimation (40 °C, 0.5-1.0 mm) afforded the pure white product: mp 74.0-5.5 °C (lit.[25] mp 79 °C); NMR δ 3.20 (s, 3 H), 3.50 (s, 3 H), 4.31 (s, 2 H), 7.31 (s, 5 H).

***N,N*-Dimethylthioacetamide (16).** Phosphorus pentasulfide (6.6 g, 0.30 mol) was added to a solution of *N,N*-dimethylacetamide (12.9 g, 0.148 mol) in 10 mL of toluene whereupon a highly exothermic reaction ensued causing the solution to reflux. This solution was maintained at reflux for 4 h and then concentrated under reduced pressure leaving a yellow solid (8.6 g, 56%). Multiple recrystallization from hexane gave long spiny white needles melting at 72-3 °C (lit.[26] mp 74.5 °C): NMR δ 2.61 (s, 3 H), δ 3.30 (s, 3 H), δ 3.48 (s, 3 H).

**γ-Crotonolactone (25).** This compound was prepared according to the Organic Synthesis procedure.[27] γ-Butyrolactone was brominated by reaction with bromine and phosphorus. The α-bromo lactone was then dehydrohalogenated using trimethylamine to afford the desired product: bp 61-3 °C (1.8 mm); NMR δ 4.99 (m, 2 H), 6.16 (m, 1 H), 7.77 (m, 1 H).

**$\Delta^{\beta,\gamma}$-5-Methylbutenolide (26).** A p*K* pure sample was graciously provided by Dr. G. Kraus.

**Acknowledgment.** This research was supported by the National Science Foundation.

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# Heterocyclic Betaines. Aza Analogues of Sesquifulvalene. 1. Structural Studies of 1-Alkyl-4-azolylidene-1,4-dihydropyridines and Azolium Azolate Inner Salts

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*Received July 20, 1990*

The aza analogs of sesquifulvalene may adopt various structures, and of these several 1-alkyl-4-azolylidene-1,4-dihydropyridines **8A** ↔ **8B** have been prepared by deprotonation of their corresponding 1-alkyl-4-azolylpyridinium salts. These novel structures **8** could show a spectrum of properties ranging from those of ethylenes to betaines. Semiempirical (MNDO//MNDO), experimental dipole moment values (ca. 9.05 D), $^1$H and $^{13}$C NMR data, and single-crystal X-ray diffraction analysis of compound **16** are consistent with the betaine character of these compounds. The electronic and molecular structure of azolium azolate inner salts **10** has been investigated. Theoretical calculations (MNDO//MNDO), experimental dipole moments (9.18 to 11.33 D), $^1$H and $^{13}$C NMR spectra, EIMS, and single-crystal X-ray diffraction analysis of compound **35** are consistent with the highly dipolar structure of this type of mesomeric betaines.

A general principle of heterocyclic chemistry is to relate heterocyclic compounds to aromatic ones. This is obvious when the aromatic compound is a classical one, but when the reference compound is an unusual structure, such as sesquifulvalene (**1**),[2] the possibilities are richer. Sesquifulvalene (**1**) can be described in a first approximation by covalent resonance structure **1A** and a dipolar one, **1B**.

At least three reasonable possibilities exist (i → iii) and Figure 1 shows structures **2-5** represented in their dipolar resonance form B. The first possibility has been carefully explored, and the term hetero analogues of sesquifulvalene is usually used for compounds that are formally derived from **1** by replacement of the seven-membered carbocyclic ring by a quaternary heteroaromatic ring.[3] To the best

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