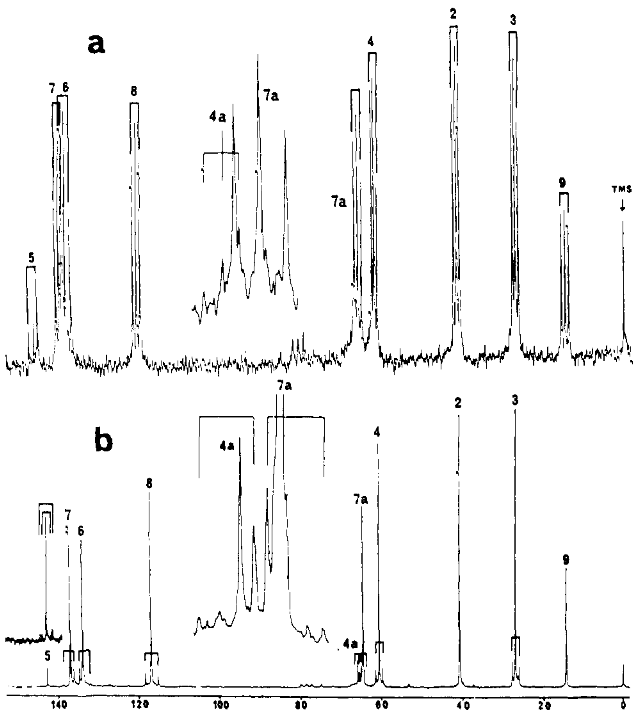

Figure 2. Proton noise-decoupled Fourier transform cmr spectrum of dihydrolatumcidin in $CDCl_3$. (a) From $^{13}CH_3{}^{13}CO_2Na$ (90% enriched), 55 mg. The precursor, diluted with unlabeled CH_3CO_2Na by 2.5 times in order to avoid excess labeling which would result in a complicated spectrum, was added to the fermentation broth of *S. reticuli* var. *latumcidicus* 14, 19, and 24 hr after inoculation. A 100-mg portion of the acetate was added to each 500-ml flask containing 100 ml of medium. The labeled dihydrolatumcidin was isolated by solvent extraction 63 hr after inoculation; pulse width, 25 μsec; acquisition time, 0.8 sec; 11,735 transients. (b) From a 1:1 mixture of $^{13}CH_3CO_2Na$ and $CH_3{}^{13}CO_2Na$ (both 90% enriched). A 100-mg portion of the precursor was added to each flask 14 hr after inoculation. A yield of 63 mg/five flasks was obtained; 62,325 transients.

Table I. Chemical Shift and Coupling Constant of Dihydrolatumcidin

Carbon	Chemical shift	Multiplicity on off-resonance decoupling	$J_{^{13}C-^{13}C}$, Hz: Doubly labeled	$J_{^{13}C-^{13}C}$, Hz: Mixed labeled
2	39.6[a]	t[b]	35.4	
3	25.9	t	35.4	43.4
4	59.2	d	30.7	43.4
4a	64.1	s	30.7	46.0, 57[c,d]
5	140.0	s	53.4	78.7, 57.9
6	131.7	d	53.0	68.1[c]
7	133.8	d	43.4	68.3
7a	63.1	d	43.8	46.1
8	114.9	d	44.8	78.7
9	14.0	q	44.8	

[a] Downfield from internal TMS. [b] s, singlet; d, doublet; t, triplet; q, quartet. [c] Small splittings or line broadening caused by long-range coupling were observed. [d] Due to the overlapping of the 7a signal, this value was obtained with the single labeled sample.[8]

$C_{(4a)}Y<$, $=C_{(5)}C_{(6)}H=$, $=C_{(7)}HC_{(7a)}HZ$, and $=C_{(8)}H-C_{(9)}H_3$, where X, Y, and Z represent oxygen or nitrogen. Although another combination between C_5 and C_6 is possible, namely $>C_{(5)}=C_{(6)}H$, the magnitude of the coupling constant ($J_{5,6}$ = 53.4 Hz) indicates clearly the latter possibility to be unlikely (*cf.* ethylene,[10] $J_{1,2}$ = 67.2 Hz; 1,3-butadiene,[11] $J_{1,2}$ = 68.8 Hz and $J_{2,3}$ = 53.7 Hz).

These carbon sequences can be further extended by utilizing the following sequences obtained with I labeled by mixed labeled acetate: $C_{(3)}H_2C_{(4)}HX$, $C_{(7a)}HZ-C_{(4a)}YC_{(5)}=C_{(8)}H$ and $C_{(6)}H=C_{(7)}H$. The very small coupling constant between C_4 and C_{4a} ($J_{4,4a}$ = 30.7 Hz), which is not in agreement with the expectation of rather large coupling constant due to the binding of these carbons to electronegative substituent,[4] can only be explained in terms of the epoxide structure. The presence of the epoxide is also supported by the large $^{13}C-H_4$ coupling constant ($J_{^{13}C-H}$ = 178 Hz). Therefore, the remaining unexplained bonds of the heteroatom on C_{7a} (which must be nitrogen) and the nitrogen bonding to C_2 must be connected to each other.

Thus, the complete structure of I has been established as shown in Figure 1. It should be emphasized that by the aid of the "alternate double labeling method" we have arrived at the correct structure without using any other information usually available by conventional methods such as ir, uv, and proton nmr spectroscopy.

Acknowledgment. Support of this work by the Mitsubishi Foundation is acknowledged. We thank Dr. M. Tanabe of Stanford Research Institute for taking cmr spectra.

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[10] D. M. Graham and C. E. Holloway, *Can. J. Chem.*, **41**, 2114 (1963).

[11] G. Becker, W. Lüttke, and G. Schrumpf, *Angew. Chem., Int. Ed. Engl.*, **12**, 339 (1973).

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Gas-Phase Acidity of Monosubstituted Phenols

Sir:

Recent studies of the acidity of molecules in the gas phase have elucidated a number of glaring discrepancies between gas-phase and solution behavior. For example, in the gas phase toluene is a stronger acid than water, and the acidity order of the aliphatic alcohols is *reversed* from that observed in solution.[1,2] In this communication we report the relative gas-phase acidity of a number of monosubstituted phenols and examine the correlation with the corresponding ionization constants in water.

Using pulsed ion cyclotron resonance spectroscopy,[3] equilibrium constants can be measured for reactions such as

$$AH + B^- = BH + A^- \qquad (1)$$

where AH and BH are Brønsted acids, and A^- and B^- are the corresponding conjugate bases.[4] Since acidity

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[1] (a) J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **93**, 4315 (1971); (b) J. I. Brauman and L. K. Blair, *ibid.*, **92**, 5986 (1970); (c) J. I. Brauman and L. K. Blair, *ibid.*, **90**, 6561 (1968).

[2] (a) D. K. Bohme, E. Lee-Ruff, and L. B. Young, *ibid.*, **94**, 5153 (1972); (b) D. K. Bohme, E. Lee-Ruff, and L. B. Young, *ibid.*, **93**, 4608 (1971).

[3] (a) R. T. McIver, Jr., *Rev. Sci. Instrum.*, **41**, 555 (1970); (b) J. D. Baldeschwieler and S. S. Woodgate, *Accounts Chem. Res.*, **4**, 114 (1971); (c) R. T. McIver, Jr., and R. C. Dunbar, *Int. J. Mass Spectrom. Ion Phys.*, 7, 471 (1971).

[4] (a) M. T. Bowers, D. H. Aue, H. M. Webb, and R. T. McIver, Jr., *J. Amer. Chem. Soc.*, **93**, 4314 (1971); (b) R. T. McIver, Jr., and J. R. Eyler, *ibid.*, **93**, 6334 (1971); (c) R. T. McIver, Jr., J. A. Scott, and J. M. Riveros, *ibid.*, **95**, 2706 (1973).

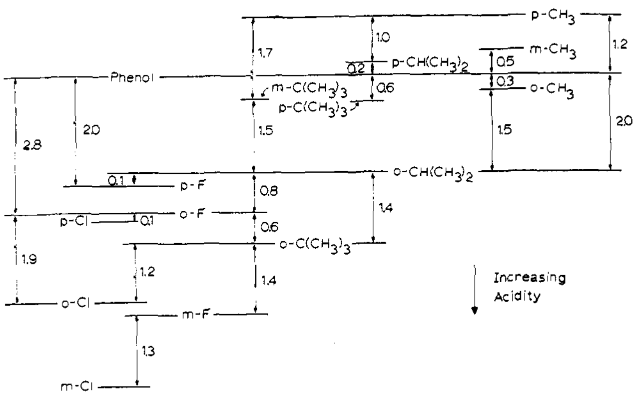

Figure 1. Relative acidity of monosubstituted phenols in the gas phase as a function of substituent and ring position. The numbers are experimental values of $\Delta G°_{298}$ (kcal/mol) for proton-transfer reactions of the type shown in eq 1. The more acidic species are at the bottom of the figure.

may be defined as the free energy change $\Delta G°_{298}$ for the process

$$AH = A^- + H^+ \qquad (2)$$

it is apparent that the free energy change for reaction 1 is a quantitative measure of the *relative* acidity of AH and BH. The pulsed icr apparatus is essentially a mass spectrometer in which the equilibrium abundance of A^- and B^- can be determined. Since the partial pressures of AH and BH in the system can be determined by an ionization gauge calibrated by a capacitance manometer, the equilibrium constant for reaction 1 can be readily calculated. The pulsed icr experiments are performed at very low pressures in the range from 10^{-6} to 10^{-4} Torr. Under these conditions the species A^- and B^- exist as free gaseous ions, completely separated from a solvent medium.

Our data for the relative acidity of monosubstituted phenols in the gas phase are shown in Figure 1.[5] Multiple overlaps are used to check the data for internal consistency and to confirm that equilibrium is being attained. For example, direct measurements for the equilibrium between phenol and *o*-fluorophenol give $\Delta G°_{298} = +2.8$ kcal/mol. Separate measurements between phenol and *o*-isopropylphenol and between *o*-isopropylphenol and *o*-fluorophenol give $\Delta G°_{298} = 2.0 + 0.8 = +2.8$ kcal/mol. Comparisons of this type establish an internal consistency of ±0.3 kcal/mol for the precision of the relative acidities measured by this method. The data in Figure 1 are summarized in Table I where positive values of $\Delta G°_{298}$ indicate a species *more acidic* than phenol itself.[6] The magnitude of the substituent effects is surprisingly large; *p*-methylphenol is 1.2 kcal/mol less acidic than phenol, whereas *m*-chlorophenol is 6.1 kcal/mol more acidic than phenol.

Table I. $\Delta G°_{298}$ (kcal/mol) for the Gas-Phase Reaction $C_6H_5OH + XC_6H_4O^- = XC_6H_4OH + C_6H_5O^-$

Substituent	Ring position Ortho	 Meta	 Para
Methyl	0.3	−0.5	−1.2
Isopropyl	2.0		−0.2
tert-Butyl	3.4	0.5	0.6
Fluoro	2.8	4.8	2.1
Chloro	4.6	6.1	2.9

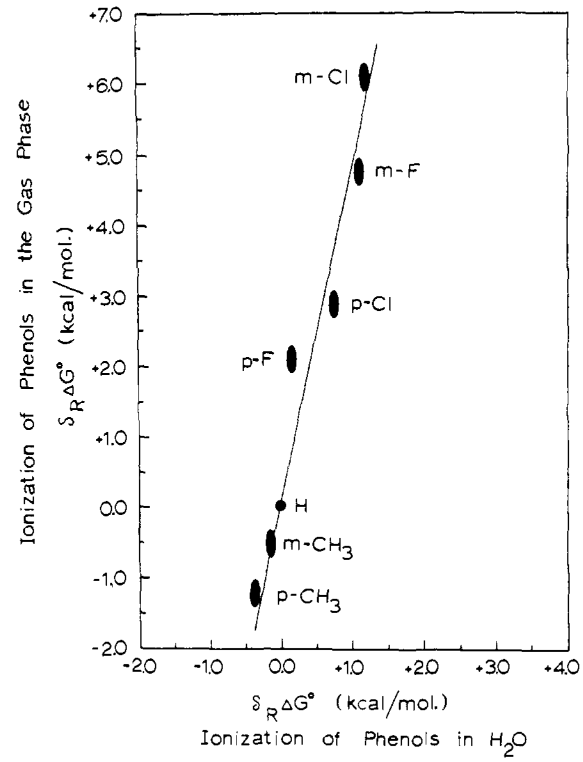

Figure 2. Linear free-energy relationship between gas- and aqueous-phase acidities of substituted phenols.

Figure 2 compares the gas-phase acidity data for the monosubstituted phenols with the corresponding ionization constants in water at 298°K.[7] There is a reasonably good correlation for meta and para substituents, indicating that aqueous pK_a values for the monosubstituted phenols parallel the intrinsic gas-phase values. The slope of the line, 4.7, reveals that the intrinsic effect of the substituent is attenuated greatly by the solvent medium. Results quite similar to this have been reported by Taagepera, *et al.*, for the gas-phase basicity of 4-substituted pyridines.[8] The data for ortho substituted phenols are not shown in Figure 2, and there is no apparent correlation between gas-phase and solution acidity. In fact, *o-tert*-butylphenol is 1.8 kcal/mol less acidic than phenol in aqueous solution,[9] but in the gas phase it is 3.4 kcal/mol *more acidic* than phenol.

The effect of the substituent on the acidity of the phenol substrate can be examined by considering the following thermodynamic cycle.

$$C_6H_5O\cdot + XC_6H_4OH = XC_6H_4O\cdot + C_6H_5OH \qquad (3)$$

$$C_6H_5O^- + XC_6H_4O\cdot = XC_6H_4O^- + C_6H_5O\cdot \qquad (4)$$

$$C_6H_5O^- + XC_6H_4OH = XC_6H_4O^- + C_6H_5OH \qquad (5)$$

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[5] For this study the monosubstituted phenoxide ions were generated by reaction of CH_3O^- with the corresponding neutral phenol. Methyl nitrite captures low energy electrons efficiently to generate CH_3O^- in the gas phase; see K. Jagar and A. Henglein, *Z. Naturforsch. A*, **22**, 700 (1967).

[6] $\Delta G°_{298}$ values are calculated using $\Delta G° = -RT \ln K$, where $T = 298°K$.

[7] Aqueous pK_a values were obtained from the following references: (a) A. I. Biggs and R. A. Robinson, *J. Chem. Soc., London*, 388 (1961); (b) P. D. Bolton, F. M. Hall, and I. H. Reece, *Spectrochim. Acta*, **22**, 1149 (1966); (c) P. D. Bolton, F. M. Hall, and I. H. Reece, *ibid.*, **22**, 1825 (1966).

[8] M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Amer. Chem. Soc.*, **94**, 1369 (1972).

[9] C. H. Rochester, *J. Chem. Soc., London*, 4603 (1965).

Insufficient data are available for evaluating the energetics of reactions 3 and 4, but it is quite reasonable to assume that the free energy change for reaction 3 is determined primarily by the difference in the O–H bond dissociation energy for phenol and the substituted phenol. Similarly, the main contribution to $\Delta G°$ for reaction 4 is expected to be the difference in the electron affinity of $C_6H_5O\cdot$ and $XC_6H_4O\cdot$. Enhanced gas-phase acidity will result, therefore, when the substituent decreases the O–H bond dissociation energy and increases the electron affinity of the substituted phenoxy radical.

In general the substituent would be expected to cause only small changes in the phenolic O–H bond dissociation energy. But considering the large magnitude of the intramolecular ion dipole and ion-induced dipole interactions,[1b] one would expect larger differences in the electron affinity of the substituted phenoxy radicals. Within this degree of approximation, the data in Table I can be analyzed in terms of the effect of the substituent on the electron affinity of the substituted phenoxy radicals. The enhanced acidity produced by halogen substituents is best explained by a large electron withdrawing inductive effect which provides internal stabilization for the halophenoxide ions. This effect is decreased somewhat the ortho and para positions due most probably to electron-donating resonance forms involving the p orbitals of the halogens. Alkyl substituents can stabilize the phenoxide substrate by an ion-induced dipole polarization interaction which increases with the size of the alkyl group and its proximity to the negative charge on oxygen. Brauman and Blair have shown this to be the predominant effect determining the intrinsic acidity of aliphatic alcohols.[1] Several members of the phenol series show, however, that alkyl groups can also *destabilize* negative charge. Hybridization effects of this type have also been observed in the acidity of alkynes and carboxylic acids.[1,10]

A more complete discussion of these substituent effects within the context of gas-phase acidity data for a broader set of substituted phenols is planned. In particular, the influence of ortho substituents and the distinction between hyperconjugation and hybridization effects will be considered.

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[11] Alfred P. Sloan Fellow, 1973–1975.

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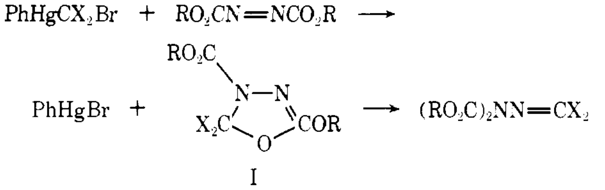
Synthesis of Heterocyclic Systems *via* 1,4-Addition Reactions of Phenyl(bromodichloromethyl)mercury Derived Dichlorocarbene

Sir:

Recently we have reported concerning the reaction of phenyl(trihalomethyl)mercury compounds with azodicarboxylate esters, which appears to take the course shown in eq 1.[1] Tentative ir and nmr spectroscopic evidence for the formation of 1,3,4-oxadiazoline intermediates (I) was available for several such reactions.

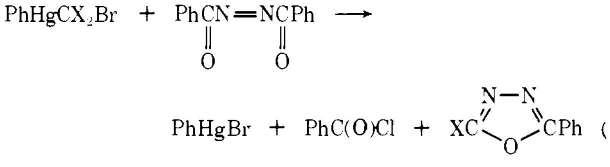


(1)

I

It was expected that such formal 1,4 addition of CX_2 might be possible with other α,β-unsaturated systems, and we report here concerning the preparation of an oxadiazole and an oxazole by similar processes.

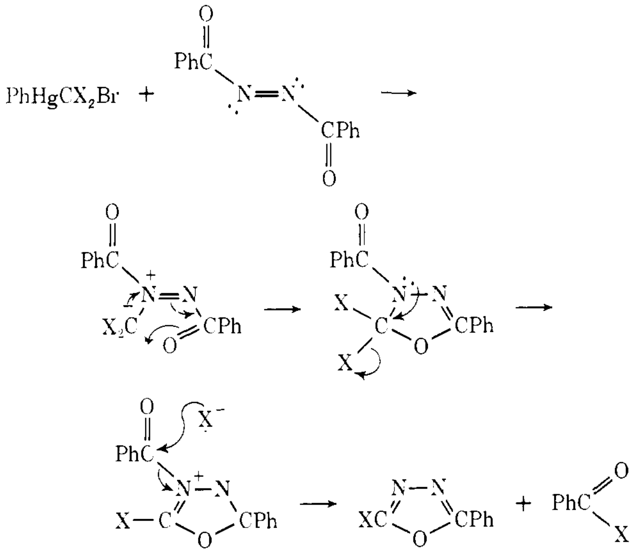
A carbon tetrachloride solution of phenyl(bromodichloromethyl)mercury and azodibenzoyl (5 mmol each) was stirred at room temperature under nitrogen for 8 days and then heated at 80° for 1 hr. Two products, identified as benzoyl chloride (66%) and 2-chloro-5-phenyl-1,3,4-oxadiazole (II, X = Cl) (54%), mp 76–78° (lit.[2] mp 75°), were obtained. An ir spectroscopic study of the reaction revealed the intervention of an intermediate with an ir band at 1610 cm^{-1}, presumably a C=N frequency. When $PhHgCBr_3$ was the mercurial used in this reaction, benzoyl bromide and 2-bromo-5-phenyl-1,3,4-oxadiazole (II, X = Br), mp 107–109°, were obtained, the latter in 80% yield. A plausible mechanism for formation of the heterocyclic products is shown in Scheme I.



(2)

II

Scheme I



1,4 addition of CX_2 also can occur with an –N=C-C=O system. The reaction of $PhHgCCl_2Br$ with $EtO_2CN{=}C(CO_2Et)_2$ or $MeO_2CN{=}C(CO_2Et)_2$ in ben-

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[1] D. Seyferth and H. Shih, *J. Amer. Chem. Soc.*, **94**, 2508 (1972).

[2] C. Ainsworth, *Can. J. Chem.*, **43**, 1607 (1965). The nmr and ir spectra of II (X = Cl) are identical with those reported here.