(14) J. W. Bolger, U. S. Patent 3,257,397; *Chem. Abstr.*, **65,** 8933*b* (1966).

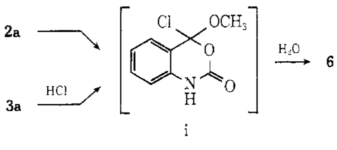
(15) The NH protons in **8a** and **8b** are readily exchanged with D_2O, and are apparently exchanging too rapidly in solution for splitting of the methine protons to be observed.

(16) It is interesting to note that imino acid **9a** exists as a zwitterion. The infrared spectrum (Nujol) of **9a** shows two broad bands at 2700–2200 and 2000–1800 cm, characteristic of the protonated imine moiety.[17]

(17) (a) B. Witkop, *Experientia*, **10,** 420 (1954); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 260.

(18) G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung.*, **48,** 77 (1966).

(19) Mechanisms which require water were necessarily excluded because of the anhydrous reaction conditions. Isatoic anhydride (**6**) was formed *in situ*, which eliminated the possibility of an intermediate such as i being converted to **6** on exposure to moisture during work-up.



i

(20) The 28-day reaction in Scheme I was monitored by ir. During the first half of the reaction, the concentration of **2a** was greater than that of **3a**, and the converse was true during the latter half. Therefore, it is conceivable that both **2a** and **3a** contributed to the formation of **6**.

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(22) (a) H. Leuchs, *Ber.*, **39,** 857 (1906); (b) H. Leuchs and W. Manasse, *ibid.*, **40,** 3235 (1907); (c) H. Leuchs and W. Gieger, *ibid.*, **41,** 1721 (1908).

(23) A satisfactory elemental analysis was obtained.

(24) (a) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9,** 55 (1944); (b) E. C. Wagner and M. F. Fegley, *Org. Syn.*, **27,** 45 (1947).

(25) D. L. Hunter, K. Kitasaki, and C. W. Hunter, French Patent 1,509,718; *Chem. Abstr.*, **70,** 37822*r* (1969).

(26) *n*-Butyl anthranilate was prepared from anthranilic acid in the usual manner[27] in 44% yield, bp 135° (1.3 mm) [lit.[28] bp 182° (760 mm)].

(27) A. J. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956, p 1000.

(28) H. C. Brill, *J. Amer. Chem. Soc.*, **43,** 1320 (1921).

(29) The glpc system of choice was 5% Carbowax 20M, 8 ft × 0.125 in., 50°, 30 cc/min of He.

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Carbon Magnetic Resonance Spectra of 2-Pyrones

W. V. Turner and W. H. Pirkle*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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The cmr spectra of 21 2-pyrones or sulfur-containing analogs of 2-pyrones are assigned by selective proton decoupling, multiplicity, and uniformity of chemical shift or J_{CH} values. Cmr spectroscopy is a useful tool in establishing the structures of unknown 2-pyrones, complimenting pmr spectroscopy in this regard.

Substituted 2-pyrones occur commonly in nature, and this ring system has recently been found to have synthetic value and to undergo highly varied thermal and photochemical reactions. Our interest in 2-pyrones led to pmr studies[1] which we have now extended to cmr. Just as proton–proton coupling constants often allow unique assignment of 2-pyrone substitution patterns, carbon-13 chemical shifts and carbon-13 proton coupling constants prove to be especially informative, thus strongly complementing pmr as a tool for 2-pyrone characterization. Several sulfur-containing analogs of 2-pyrones have been included in this study for comparative purposes.

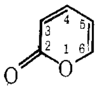
Experimental Section

Most of the 2-pyrones used in this study have been described previously. The thiones were prepared by action of P_2S_5 on the corresponding pyrones; thiapyran-2-ones were prepared by thermal isomerization of thiones.[2]

Cmr spectra were obtained with a Varian Associates Model XL-100-15 25.1-MHz spectrometer coupled with a Digilab NMR-3 Fourier transform system. The samples were quite concentrated (1.5–5.5 *M*) to minimize the time required to obtain selectively decoupled or undecoupled spectra. In several instances, solvents other than chloroform-*d* were used for increased solubility or for optimum separation of proton resonances for selective decoupling. Both 2-pyrone and 4,6-dimethyl-5-carbethoxy-2-pyrone were run almost neat (10% internal acetone-d_6 was used as a lock signal) to allow the recording of spectra in the continuous wave mode.

Results

Table I records chemical shifts for 2-pyrone ring carbons as parts per million downfield of TMS. The compounds in part A of the table are unsubstituted or monosubstituted pyrones (or sulfur analogs) for which each unsubstituted carbon resonance was identified by selective proton decoupling. Since the carbonyl carbon (C-2) chemical shift remains almost constant, the assignment of the substituted carbon is apparent.



2-pyrone

Like the corresponding proton resonances, the C-4 and C-6 resonances of 2-pyrone are downfield of those of C-3 and C-5. This order has also been observed in 2-pyridone.[3]

Single-bond carbon-13 proton coupling constants (J_{CH}, hertz) for most of the 2-pyrones appear in parentheses in Table I. They provide a means of identifying C-6 when it bears hydrogen. The ranges of values of J_{CH} for C-3 and C-5 are similar and larger than the usual values for C-4, although some overlapping occurs. The values for 2-pyrones may be compared with J_{CH} for 4-pyrone (200 Hz for C-2 and 169 Hz for C-3)[4] and furan (201 Hz for C-2 and 175 Hz for C-3).[5] A value of *ca.* 200 Hz is typical for J_{CH} of carbon atoms attached to oxygen in aromatic heterocycles.[6] J_{CH} values for sulfur analogs of 2-pyrones are similar to those of 2-pyrone, except that J_{CH} for C-6 of the thiapyran derivatives is *ca.* 180 Hz. (*Cf.* J_{CH} of 185 Hz for the α carbons of thiophene.[6]) Two exceptions to this pattern emerge from Table I. The unusually small J_{CH} of C-3 of 4-methylthiapyran-2-one and the unusually large J_{CH} for C-4 of coumalyl chloride are unexplained.

Significant longer range coupling is also observed, but this varies with the nature of the substituents. Thus, in 4-methyl-2-pyrone C-6 is coupled (J = 7 Hz) to some proton other than H-6, while in 4-methyl-6-chloro-2-pyrone the C-6 resonance is a singlet (J < 1 Hz). Because of

Table I
Chemical Shifts of Ring Carbons in 2-Pyrones and Some Sulfur Analogs

Compd	Chemical shift (J_{CH})						Registry no.
	C-2	C-3	C-4	C-5	C-6	CH_3	
A. 2-Pyrone[a,l]	162.0	116.7 (170)	144.3 (163)	106.8 (173)	153.3 (200)		504-31-4
4-Methyl-2-pyrone[b]	161.8	113.7 (169)	156.1	109.3 (169)	151.1 (199)	21.1	22682-12-8
3-Hydroxy-2-pyrone[b]	161.8	142.7	115.2 (166)	107.3 (170)	142.3 (205)		496-64-0
3-Methoxy-2-pyrone[b]	158.6	145.9	112.9	106.0	142.9	56.0	51270-28-1
3-Acetoxy-2-pyrone[b,d]	157.6	137.3	131.2	105.4	149.1	20.2	51270-29-2
Coumalyl chloride[b,e]	158.2	115.3 (175)	140.3 (170)	116.6	163.0 (203)		23090-18-8
Thiapyran-2-one[c]	183.7	124.9 (169)	140.9 (163)	118.7 (169)	137.4 (180)		6788-51-8
Pyran-2-thione[c]	196.9	131.8	134.4	109.6	155.6		23639-33-0
4-Methylthiapyran-2-one[b]	184.3	123.8 (161)	153.4	122.2 (166)	136.0 (183)	24.1	51270-30-5
4-Methylpyran-2-thione[b]	197.0	130.2 (172)	149.2	113.2 (170)	155.0 (202)	21.1	51270-31-6
B. 5-Methyl-2-pyrone[b]	161.2	115.7 (171)	146.5 (162)	114.7	148.0 (197)	14.4	51270-32-7
6-Methyl-2-pyrone[b]	162.0	112.6 (171)	144.1 (162)	103.4 (171)	162.9	19.8	4394-76-7
4-Chloro-6-methyl-2-pyrone[b,f]	160.9	110.8 (177)	151.8	106.1 (176)	162.9	19.8	17422-72-9
4-Methyl-6-chloro-2-pyrone[b]	160.6	110.4 (171)	157.5	107.1 (176)	148.7	21.4	22682-15-1
4-Methoxy-6-methyl-2-pyrone[b]	162.1	87.3 (172)	171.4	100.3 (168)	164.6	55.9 19.7	672-89-9
4-Methoxy-6-(4-methoxystyryl-2-pyrone (yangonin)[b,g]	160.9	88.4	171.3	100.4	163.9		500-62-9
4,6-Dimethyl-5-carbethoxy-2-pyrone[a,h]	159.6	111.9 (170)	154.4	112.9	165.1	21.0 (4) 19.6 (6)	3385-34-0
4,6-Dimethyl-5-carbethoxypyran-2-thione[b,i]	195.7	128.6 (173)	146.8	116.6	168.4	20.5 19.9	51270-33-8
Thiapyran-2-thione[b]	205.2	139.3 (169)	132.6 (163)	122.7 (169)	141.8 (180)		930-72-3
Coumarin[b,j]	160.5	116.4 (172)	143.5 (164)	118.8	153.9		19-64-5
Benzopyran-2-thione[k]	198.5	130.2 (176)	133.0 (164)	121.3	157.2		3986-98-9

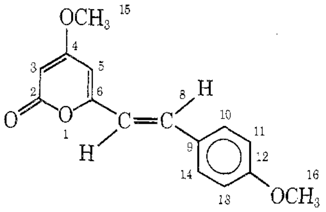
[a] As a 90% solution in acetone-d_6. [b] As $CDCl_3$ solution. [c] As solution in $CDCl_3$–CCl_4. [d] Acetate carbonyl at δ 167.8. [e] COCl at δ 162.7. [f] It is not obvious which of the resonances at δ 160.9 and 162.9 is C-2 and which C-6, or which of those at δ 106.1 and 110.8 is C-5 and which C-3. [g] In addition to the 2-pyrone ring carbons, we observed the following resonances: δ 55.4 and 55.8 (2 OCH_3), 114.5 (C-11 and C-13), 116.6 (C-7), 128.2 (C-9), 129.0 (C-10 and C-14), 135.4 (C-8), and 159.2 (C-12). The assignments agree well with those reported for *p*-methoxystyrene in K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **44,** 2855 (1966), and P. C. Lautebur, *Ann. N. Y. Acad. Sci.*, **70,** 841 (1958). [h] Carbonyl at δ 165.2. [i] Carbonyl at δ 164.6. [j] Other resonances at δ 116.5, 124.4, 128.0, and 131.7. This has been reported before (ref 3, p 333) and is included for comparison. [k] Other resonances at δ 116.9, 126.3, 129.0, and 135.6; dilute in acetone. [l] A solvent effect is reflected in the chemical shifts of 2-pyrone carbons in dilute $CDCl_3$ solution: δ 117.0, 142.8, 106.0, and 152.0 for C-3, C-4, C-5, and C-6, respectively. C-2 was not observed.

uncertainties in the assignment of a number of the longer range couplings, these values have not been tabulated.

Assignments in part B of Table I are based on chemical shift data from part A, coupling constants, multiplicity in undecoupled spectra, and, where possible, selective decoupling.

The resonances of the methyl carbons attached to the ring in 4,6-dimethyl-5-carbethoxy-2-pyrone were identified by selective proton decoupling, the order of the carbon resonances being reversed from that of the corresponding protons. The original identification of the methyl proton resonances was based on the *ca.* 1 Hz coupling of 4-CH_3 to H-3, which is observed in a number of 4-methyl-2-pyrone derivatives.

The natural product yangonin[7,8] was prepared for this study. With 4-methoxy-6-methyl-2-pyrone and 4-methoxystyrene[10] as models, the interpretation of the spectrum is quite straightforward, although questions arise concerning C-2 and C-6.



yangonin

The greatest difficulty arose in interpreting the spectrum of 4-chloro-6-methyl-2-pyrone. Although it is clear from multiplicities which two resonances arise from C-3 and C-5, further assignment cannot be made *via* selective decoupling since the proton resonances have not been assigned. The order of proton and carbon resonances is, however, the same. The downfield carbon resonances arise from C-2 and C-6, leaving the resonance at δ 151.8 for C-4. This assignment means that the substitution of chlorine at C-4 results in a downfield shift of 7.5 ppm, while at C-6 it causes an upfield shift of 4.6 ppm.

Thiapyran-2-thione is not included in part A of Table I because the complexity of its proton spectrum precluded selective decoupling. The resonance at δ 205.2 represents C-2, and a tentative assignment of the other resonances follows from the assumption that the effects of the two sulfur substitutions are additive. Chemical shifts predicted in this way, based on 2-pyrone in $CDCl_3$ solution, are 140.0, 131.0, 121.5, and 139.7 ppm for C-3 and C-6, respectively; these are very close to the observed values. The observed J_{CH} values support the assignment.

Charge distribution in the 2-pyrone ring is indicated by the downfield shifts of C-4, C-6, H-4, and H-6 relative to C-3, C-5, H-3, and H-5 and also by the chemical shifts of methyl substituents. Thus, 4-methyl and 6-methyl carbons appear at 21 and 20 ppm downfield of TMS, respectively, but 5-methyl carbon appears at 14 ppm. Smaller differences also appear in pmr shifts of these methyl groups.

Localization of the double bonds of 2-pyrones is suggested by the observation that in the proton spectra of methyl pyrones H-3, but not H-5, is coupled to a 4-methyl group. In 2-pyrone cmr spectra, methyl substitution causes an upfield shift of the β carbon on the same double bond. However, both 4-methyl and 5-methyl substituents are observed to shift the remaining β carbon downfield. This effect is particularly noteworthy for 4-methoxy-6-methyl-2-pyrone, where the methoxy group causes an upfield shift of C-3 of almost 30 ppm, but shifts C-5 upfield only 3 ppm. This effect has been discussed previously in the case of proton spectra.[11]

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References and Notes

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(3) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," Wiley, New York, N. Y., 1972, p 107.

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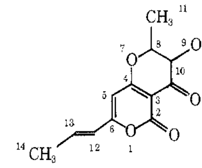
(8) The cmr spectrum of radicinin, another natural product containing a 2-pyrone ring, has been reported previously.[9] On the basis of the spectra of our model compounds, we suggest that the resonances at 188, 172, 162, and 156 are more likely to be C-10, C-4, C-6, and C-2, respectively, than C-2, C-10, C-4, and C-6, respectively. This change does not, however, affect the conclusions drawn about location of acetate units in radicinin.



radicinin

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(10) See Table I, footnote *g*.

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Possible Bifunctional Catalysis by 2-Dimethylaminoethylamine in the Dealdolization of Diacetone Alcohol[1a]

Jack Hine* and William H. Sachs[1b]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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Catalysis of the dealdolization of diacetone alcohol by *n*-propylamine, 2-methoxyethylamine, 2-trimethylammonioethylamine, and 2-dimethylaminoethylamine has been studied in water at 35°. Combination of the resultant data with literature observations shows that catalytic efficiency increases with amine basicity when steric factors are kept reasonably constant. In a plot of log k *vs.* pK_a the points for most species of the type RCH_2NH_2 lie near a straight line of slope 0.44. The activity of $Me_2NHCH_2CH_2NH_2^+$, however, is about four times as great as would be expected from the data for the other amines. This increased catalytic activity may arise from bifunctional catalysis, in which the primary amino group from the catalyst transforms the carbonyl group of diacetone alcohol to an iminium ion and the tertiary amino group removes a proton from the hydroxy group. An analysis of the propagation of errors in the determination of rate constants for acids and bases from data obtained in buffer solutions is also given.

The dealdolization of hexose derivatives brought about by Class I aldolases is thought to involve iminium-ion formation between a carbonyl group of the substrate (*e.g.*, fructose 1,6-diphosphate) and a lysine residue of the enzyme, followed by base-promoted cleavage.[2,3] The nature of the second basic group may vary from enzyme to enzyme. In the case of at least one transaldolase there is evidence that it is the imidazole ring of a histidine residue.[4] A carboxylate anion group has been postulated to be the second basic group in 2-keto-3-deoxygluconate aldolase.[5]

Observations that simple primary[6-10] and secondary[6-8] amines and amino acids,[10,11] but not tertiary amines,[7] specifically catalyze the dealdolization of diacetone alcohol have contributed to an understanding of enzymatic dealdolizations. The present study was begun with the aim of learning how polar substituents affect the efficiency of primary amine catalysis of dealdolization and of using this knowledge to tell whether a diamine may act as a bifunctional catalyst for dealdolization. After the study was largely completed, an investigation of polar substituent effects on primary amine catalysis of dealdolization was published by Pollack and Cooper.[10]

Results

The dealdolization of diacetone alcohol is known to be catalyzed by hydroxide ions.[7,12] To learn the contribution of such catalysis to reactions carried out in the presence of amines we made kinetic studies using sodium hydroxide. The reaction in aqueous solution at 35° and ionic strength 0.10 was followed by spectrophotometric measurements at 264.5 nm, where the transformation of diacetone alcohol (λ_{max} 277 nm, $\epsilon_{264.5}$ 23.7 M^{-1} cm^{-1}) to acetone (λ_{max} 264.5 nm, $\epsilon_{264.5}$ 17.9 M^{-1} cm^{-1}) is accompanied by an increase in absorbance, largely because the concentration of carbonyl groups is doubled. The kinetics were complicated by the reversible dehydration of the diacetone alcohol to mesityl oxide (λ_{max} 243 nm, ϵ_{243} 11,400 M^{-1} cm^{-1}, $\epsilon_{264.5}$ 2640 M^{-1} cm^{-1}). This caused the absorbance at 264.5 nm to increase by an amount about 47% larger than the theoretical amount for the formation of acetone only, and it caused the increase in absorbance to be accompanied by a shift in the absorption maximum to shorter wavelengths. After about 9.5 half-lives the absorbance began to decrease and the absorption maximum to move back toward longer wavelengths. Comparison of the full-length spectrum of the reaction solution after 22 dealdolization half-lives with the spectrum of aqueous acetone solutions showed that the extra absorbance of the reaction solution arose from a material with an absorption maximum at about 243 nm. To allow for this complication the kinetics of the reaction of 0.01466 M diacetone alcohol in the presence of 0.0101 M sodium hydroxide were analyzed