A Thermodynamic Study of 1:1 Complex Formation between N-Methyl Lactams and Phenol in Carbon Tetrachloride[1]

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The relative basic character of cyclic organic compounds in which the donor atom is exocyclic has been studied for a limited number of systems.[3-8] Based on the magnitude of pK_a values, the order of basicity for N-methyl lactams is six- > seven- > five-membered ring.[6] The same order of basicity was found for the corresponding thiolactams.[7] The data for the lactams showed, also, that through the ten-membered ring, the pK_a values of the even-numbered rings were invariably larger than those of the *neighboring* odd-numbered rings.[6] This research was undertaken to confirm the relative order of basicity for the five-, six-, and seven-membered ring lactams by measuring thermodynamic constants for 1:1 complex formation with a reference acid, and to gain some insight into the curious relationship between ring size and basicity as it is reflected in the magnitude of equilibrium constants. Because previous studies had shown that 1:1 complexes are formed between phenol and amides,[9,10] phenol was selected as the reference acid.

Preliminary infrared spectral studies of N-methyl-substituted lactam–phenol systems showed that the free O–H band, at 3610 cm.$^{-1}$, disappeared and was replaced by a new, broad band at lower wave numbers. This new band has been attributed to the formation of a hydrogen bond between the phenol and a donor molecule.[11] At the same time the carbonyl band of the complexed lactam appeared as a shoulder on the low frequency side of the carbonyl band of the uncomplexed lactam. This may be interpreted as evidence for bonding of the lactam through the carbonyl oxygen rather than the nitrogen atom. Similar shifts in the carbonyl band of other complexed carbonyl compounds has been taken as evidence of bonding through the carbonyl oxygen.[12-14]

Equilibrium constant data are summarized in Table I. The invariance of the equilibrium constant with a tenfold change in the lactam concentration ($\sim$4 to 40 $\times$ 10^{-3} M) and the good agreement between the equilibrium constants obtained from spectral data taken at 1418 and at 285 mμ provide strong evidence for the existence of 1:1 complexes.

The enthalpy and entropy changes accompanying complexation were determined by a least-squares treatment of data plotted for eq. 1.

$$\ln K = -\left(\frac{\Delta H}{R}\right)(1/T) + \frac{\Delta S}{R} \qquad (1)$$

A summary of thermodynamic constants is given in Table II.

All of the N-methyl lactams possess larger equilibrium constants for 1:1 complex formation than do the N,N-dimethylamides[9,10] (see Table II). If in fact the decrease in the equilibrium constant that accompanies substitution of the propionamide for the acetamide is due to an unfavorable entropy effect arising from the methyl group on the α-carbon, suggested by Joesten and Drago, then the magnitude of the equilibrium constants involving amides with bulkier alkyl groups on the α-carbon would not be expected to exceed 107 l./mole, the value reported for N,N-dimethylpropionamide. From the limited equilibrium constant data it appears that an increase in basicity toward phenol results from cyclization of amides.

Based on the magnitude of the equilibrium constants, the order of basicity for the N-methyl lactams is six- > seven- = five-membered ring. The greater basicity of the six-membered ring indicated by previous pK_a measurements[6] has been confirmed. An explanation of this order is not readily apparent from our data. Certain variations in thermodynamic constants are significant however. Table II shows that the enthalpy and entropy changes for complex formation with N,N-dimethylamides and the seven-membered ring lactam are comparable. Assuming that solvent effects are relatively small or that these effects tend to cancel for a series of related compounds it appears that the seven-membered ring has sufficient flexibility to behave like the open-chain amides in adjusting to the orientational and spacial restrictions imposed by complex formation. The increased rigidity of the six- and five-membered rings restricts the capacity of these lactams to make similar adjustments. As a result the enthalpy and entropy changes are lowered.

A comparison of the thermodynamic data of the N-methyl-ϵ-caprolactam–phenol system with that of the ϵ-caprolactam–phenol system shows that the values of the equilibrium constants are the same within experimental error. The magnitude of the enthalpy term is increased, however, upon substitution of a methyl group on nitrogen. Such a trend would be predicted on the basis of an inductive effect. The decrease in entropy accompanying adduct formation is considerably greater for the N-methyl lactam. Qualitatively the larger entropy term for the N-methyl derivative arises from a more restricted configuration of the atoms as the complex becomes more stable (ΔH becomes a larger negative value). Apparently no adverse steric effect is caused by the introduction of the methyl group on the nitrogen.

Experimental

Reagents.—The carbon tetrachloride used in these studies was either Fisher Spectranalyzed certified reagent grade or Fisher certified reagent grade. It was used without further purification.

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(1) Abstracted in part from the Ph.D. Thesis of D. M. Hart, The Pennsylvania State University, 1963.

(2) National Science Foundation Cooperative Fellow, 1962–1963.

(3) M. Tamres and S. Searles, Jr., *J. Am. Chem. Soc.*, **81**, 2100 (1959).

(4) H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960).

(5) S. Searles, M. Tamres, and G. M. Barrow, *J. Am. Chem. Soc.*, **75**, 71 (1953).

(6) R. Huisgen, H. Brade, H. Walz, and I. Glogger, *Chem. Ber.*, **90**, 1437 (1957).

(7) J. T. Edward and H. Stollar, *Can. J. Chem.*, **41**, 721 (1963).

(8) T. Gramstad, *Spectrochim. Acta*, **19**, 497 (1963).

(9) M. D. Joesten and R. S. Drago, *J. Am. Chem. Soc.*, **84**, 2037 (1962).

(10) M. D. Joesten and R. S. Drago, *ibid.*, **84**, 2696 (1962).

(11) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

(12) D. L. Glusker, H. W. Thompson, and R. S. Mulliken, *ibid.*, **21**, 1407 (1953).

(13) C. D. Schmulbach and R. S. Drago, *J. Am. Chem. Soc.*, **82**, 4484 (1960).

(14) R. S. Drago and D. A. Wenz, *ibid.*, **84**, 526 (1962).

TABLE I

EQUILIBRIUM CONSTANTS FOR 1:1 PHENOL–LACTAM ADDUCTS IN CARBON TETRACHLORIDE[a]

t, °C.	K,[b] l./mole		$a_c - a_a$[b]		K,[c] l./mole
		N-Methyl-γ-butyrolactam			
16.0	197 ± 7		1520 ± 10		. . .
25.0	150 ± 3		1450 ± 40		149 ± 9
35.0	106 ± 7		1420 ± 30		. . .
45.0	77.3 ± 2.9		1390 ± 20		. . .
		N-Methyl-δ-valerolactam			
16.0	260 ± 12		1660 ± 20		. . .
25.0	185 ± 3		1580 ± 10		166 ± 17
35.0	145 ± 4		1450 ± 20		. . .
45.0	104 ± 5		1430 ± 60		. . .
		N-Methyl-ϵ-caprolactam			
16.0	216 ± 9		1560 ± 40		. . .
25.0	149 ± 3		1590 ± 20		146 ± 9
35.0	104 ± 2		1550 ± 20		. . .
45.0	78.9 ± 3.6		1510 ± 50		
		ϵ-Caprolactam			
15.5	205 ± 10		1500 ± 30		. . .
25.0	154 ± 5		1430 ± 20		152 ± 11
35.0	114 ± 9		1380 ± 50		
45.0	81.8 ± 5.0		1380 ± 30		. . .
		ϵ-Caprolactam[d]			
15.0	12.3 ± 0.4[e]	12.5 ± 0.7[f]	1001 ± 14[e]	679 ± 14[f]	
25.0	10.1 ± 0.4[e]	9.6 ± 0.6[f]	979 ± 32[e]	660 ± 20[f]	
34.9	8.1 ± 0.4[e]	8.2 ± 0.3[f]	996 ± 12[e]	652 ± 14[f]	
45.0	6.5 ± 0.3[e]	6.5 ± 0.2[f]	981 ± 20[e]	625 ± 8[f]	

[a] All errors are given in terms of standard deviations for a series of no less than four samples. [b] Calculated from data obtained at 285 mμ. [c] Calculated from data obtained at 1418 mμ. [d] Data for iodine–ϵ-caprolactam 1:1 adduct. [e] Calculated from data obtained at 450 mμ. [f] Calculated from data obtained at 515 mμ.

TABLE II

THERMODYNAMIC DATA FOR 1:1 ADDUCT FORMATION BETWEEN PHENOL AND LACTAMS OR AMIDES IN CARBON TETRACHLORIDE[a]

Lactam or amide	K (25°), l./mole	$-\Delta H$, kcal./mole	$-\Delta S$, e.u.	$-\Delta F$[b](25°), kcal./mole
N-Methyl-γ-butyrolactam	150 ± 3	5.95 ± 0.15	10.04 ± 0.49	2.95 ± 0.15
N-Methyl-δ-valerolactam	186 ± 3	5.62 ± 0.12	8.42 ± 0.40	3.11 ± 0.12
N-Methyl-ϵ-caprolactam	149 ± 3	6.41 ± 0.11	11.52 ± 0.38	2.98 ± 0.11
ϵ-Caprolactam	154 ± 5	5.67 ± 0.12	9.05 ± 0.49	2.97 ± 0.12
ϵ-Caprolactam[c]	10.1 ± 0.4	3.98 ± 0.08	8.50 ± 0.27	1.36 ± 0.08
N,N-Dimethylacetamide[d]	134 ± 3	6.4 ± 0.3	11.7 ± 0.6	
N,N-Dimethylpropionamide[d]	107 ± 2	6.4 ± 0.2	12.1 ± 0.6	
N,N-Dimethylformamide[d]	64 ± 1	6.1 ± 0.4	12.1 ± 0.7	

[a] From data collected at 285 mμ. Errors for our data are given in standard deviations. [b] Value of ln K obtained from least-squares line of ln K *vs.* $1/T$ plot. [c] Data for iodine–ϵ-caprolactam 1:1 adduct provided for comparison only. [d] See ref. 10.

Baker and Adamson reagent grade phenol was distilled under atmospheric pressure to give white crystals, m.p. 40–41°. The reported melting point is 40.9°.[15]

The compound N-methyl-γ-butyrolactam (General Aniline and Film Corp.) was twice distilled under nitrogen atmosphere. The constant boiling middle fraction, $n^{25}\mathrm{D}$ 1.4678, was collected. Reported values of $n^{25}\mathrm{D}$ are 1.4666[16] and 1.469.[17]

The n-methyl-ϵ-caprolactam was obtained by one of the procedures described by Benson and Cairns.[19] By this method ϵ-caprolactam (Eastman Kodak) was first converted to O-methylcaprolactam with dimethyl sulfate. The O-methyl derivative was converted to N-methyl-ϵ-caprolactam by retreatment with dimethyl sulfate. The N-methyl-ϵ-caprolactam obtained in this manner gave a value for $n^{25}\mathrm{D}$ of 1.4819. The reported values for $n^{25}\mathrm{D}$ range from 1.4812 to 1.4833.[19]

The ϵ-caprolactam was twice recrystallized from anhydrous ether. After drying for 3 hr. on a sintered-glass funnel under a steam of dry nitrogen, it gave a melting point of 68–69°, lit.[20] 68–70°.

Baker and Adamson resublimed iodine was ground together with 25% by weight of potassium iodide and 10% by weight of calcium oxide. The mixture was then sublimed. The iodine was collected and stored in a desiccator over phosphorus pentoxide.

Apparatus.—All spectrophotometric measurements were made on a Cary Model 14 recording spectrophotometer. The temperature of the cell compartment was controlled to within ±0.2° with water from a constant-temperature bath circulating through the thermostated cell compartment and cell jacket supplied with the instrument. The temperature of the cell compartment was measured directly with a thermometer graduated in units of 0.1°.

Procedure for Ultraviolet Spectral Measurements.—Stock solutions of phenol were prepared by direct weighing of the phenol into a volumetric flask on an analytical balance and adding carbon tetrachloride to the mark. The stock solutions were used immediately. Solutions of known lactam concentration were prepared by direct weighing of the lactam into clean, dry volumetric flasks that had been flushed with nitrogen. Aliquots of

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(15) R. R. Dreisbach and R. A. Martin, *Ind. Eng. Chem.*, **41**, 2875 (1949).

(16) "Dictionary of Organic Compounds," Vol. II, I. M. Heilbron, Ed. Oxford University Press, London, 1946, p. 806.

(17) E. Fisher, *J. Chem. Soc.*, 1382 (1955).

(18) "Dictionary of Organic Compounds," Vol. II, I. M. Heilbron, Ed. Oxford University Press, London, 1946, p. 796.

(19) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).

(20) C. E. Dalgliesh, A. W. Johnson, and L. J. Haynes, "Chemistry of Carbon Compounds," Vol. IB, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1952, p. 840.

the phenol stock solution, measured to ±0.02 ml., were added from a 10-ml. buret to the flasks containing the lactam, and carbon tetrachloride was added nearly to the mark. Carbon tetrachloride was added to the mark after the sample had come to thermal equilibrium at the temperature spectral measurements were to be run. This procedure was used to eliminate concentration corrections arising from temperature-dependent volume changes of the solution. The spectra were measured with carbon tetrachloride in the reference cell. Cells of 1-cm. path length fitted with ground-glass stoppers were used. The absorbance of the solution containing only the Lewis acid was also obtained.

The phenol–lactam complexes absorb in the same region as free phenol, but the former have larger extinction coefficients than free phenol. Spectra of phenol–lactam solutions were recorded at a constant wave length of 285 mμ. This wave length was chosen, after studying numerous spectra of lactam–phenol mixtures between the wave length of 300 and 270 mμ, because it was the wave length at which the difference between the extinction coefficient of the phenol and the complex was the greatest. Similar findings have been reported in connection with amide complexes of phenol.[9,10] Experiments on solutions which contained only lactam indicated that absorption due to free lactam was negligible at 285 mμ; thus, the following (eq. 2) applies.[21]

$$K^{-1} = \frac{C_aC_b}{A - a_aC_a}(a_c - a_a) - C_a - C_b + \frac{A - a_aC_a}{a_c - a_a} \quad (2)$$

Here, K is the equilibrium constant for 1:1 complex formation, C_a is the initial concentration of the Lewis acid, C_b is the initial concentration of the Lewis base, A is the absorbance at a specified wave length, a_a is the extinction coefficient of the Lewis acid, and a_c is the extinction coefficient of the 1:1 adduct at the specified wave length. In the derivation of eq. 2, Rose and Drago have assumed that the sole product species is a 1:1 complex, and that the Beer–Lambert law is obeyed by all absorbing species.

The graphical method described by Rose and Drago was replaced by a more rapid and precise analytical solution adaptable to computer programming. The simultaneous solution of eq. 2 for two sets of experimental data, denoted by subscripts 1 and 2, results in the quadratic expression that follows (eq. 3),

$$\left[\left(\frac{C_{a1}C_{b1}}{A_1 - B_1}\right) - \left(\frac{C_{a2}C_{b2}}{A_2 - B_2}\right)\right]D^2 + [(C_{2a} + C_{b2}) - (C_{a1} + C_{b1})]D + [(A_1 - B_1) - (A_2 - B_2)] = 0 \quad (3)$$

where $D = a_c - a_a$. The two values of D obtained from the solution of the quadratic equation are substituted into eq. 2 to solve for K^{-1}. The true values for K^{-1} and D for the system are obtained by inspection. Ideally, one true value of K^{-1} and corresponding value of D should be obtained. Practically, it is necessary to take the average of the K^{-1} values obtained from each pair of experimental values. Data for the ε-caprolactam–iodine adduct were obtained at 515 and 450 mμ, the wave lengths for the maxima of the free and the complexed iodine bands, respectively. Values of K were obtained by the use of eq. 2.

Procedure for Near-Infrared Spectral Measurements.—As a check on the ultraviolet measurements, equilibrium constants for the phenol–lactam systems were also computed from spectral data on the first overtone band of the free O–H stretching frequency at 1418 mμ.[22] Since this band is due to *free* phenol, it is possible to measure the equilibrium phenol concentration and, by assuming 1:1 complex formation, compute the concentrations of free lactam and the 1:1 complex as well. Two restrictions on the measurement of equilibrium constants by this procedure reduced the precision of the equilibrium constants to 7–10% of the mean value (in terms of standard deviation). The small extinction coefficient of 3.45 required as large a concentration of phenol as possible, as well as a path length of 10 cm. The upper limit of phenol concentration was set at 0.006 M. Above this concentration, polymeric phenol species are reported to be present in appreciable amounts.[22] The combination of these factors required spectral measurements at low absorbance, generally no greater than 0.150.

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[21] N. J. Rose and R. S. Drago, *J. Am. Chem. Soc.*, **81**, 6138 (1959).

[22] G. Aksnes and T. Gramstad, *Acta Chem. Scand.*, **14**, 1485 (1960).

The Replacement of Phenolic Hydroxyl Groups by Hydrogen

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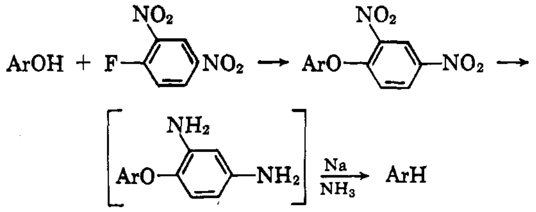
We recently required a method for the replacement of phenolic hydroxyl groups by hydrogen. There existed at the time no good general method for this simple transformation, and none of the then reported[3] procedures regularly gives high yields, although an excellent method has since been reported by Sawa[4] for removing the phenolic hydroxyl of various 3-methoxy-4-hydroxymorphinan derivatives. We have independently developed a very similar method[5] and our modification, which gives excellent yields in selected cases, notably in the morphine series[6] as does Sawa's, appears to offer some practical advantages over that of Sawa. This report deals with an attempt to define the scope and applicability of the method. We may say at the outset that, although in many cases excellent yields are obtained, the reaction is not so general as we had hoped. It appears to be most successful when methoxyl or phenyl groups are adjacent to the hydroxyl.

Our modification of the method consists of the preparation of the 2,4-dinitrophenyl ether of the phenol, its catalytic hydrogenation to the corresponding 2,4-diaminophenyl ether, and cleavage of this ether with sodium in liquid ammonia. The use of the dinitrophenyl ether offers several advantages over that of the simple phenyl ether used by Sawa.[4] Perhaps the most important is ease of preparation. Sawa's phenyl ethers were prepared by the Ullmann reaction, considerably more cumbersome than the method of Reinheimer[7] or arylation with 2,4-dinitrofluorobenzene and sodium hydride in benzene–dimethylformamide, both used in this work. The latter in particular proceeds smoothly to give excellent yields, even with highly



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[1] National Science Foundation Predoctoral Fellow, 1961–1963.

[2] Union Carbide Fellow, 1963–1964.

[3] G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S 178 (1949); G. W. Kenner and N. R. Williams, *ibid.*, 522 (1955); S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958). The classical zinc dust distillation is of course not generally useful except for the exhaustive degradation of hydroxylated substances to hydrocarbons.

[4] Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 144, 154 (1961). We are greatly indebted to Dr. Sawa for making details of his procedure available to us considerably in advance of publication.

[5] Both methods are based on the cleavage of diphenyl ethers by sodium in liquid ammonia, a reaction which has been studied at length by F. J. Sowa and his co-workers [*J. Am. Chem. Soc.*, **59**, 603, 1488 (1937); **60**, 94 (1938)].

[6] M. Gates and W. H. Pirkle, to be published. See also M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

[7] J. D. Reinheimer, J. P. Douglass, H. Leister, and M. B. Voelkel, *J. Org. Chem.*, **22**, 1743 (1957).