through the sample cavity. Temperatures were monitored by a copper–constantan thermocouple placed above the receiver coil but the actual temperature experienced by the sample was estimated by replacing the sample with a glass tube of similar construction containing another thermocouple.

The temperature of the sample did not vary by more than 1° during a determination and the values given are believed to be accurate to at least 2°. Chemical shifts and coupling constants were determined from low-temperature spectra to an accuracy of at least 1%.

Theoretical spectra were generated by an IBM 7094 II computer (coupled to a Moseley X-Y plotter) using a Fortran IV coded program based on the equations of Alexander.[27] Input to the program included an effective relaxation time, T_2, for each nucleus in the system and mean lifetimes, τ_1 and τ_2, for each AB set of nuclei. The sensitivity of the computed spectra to small variations in the mean lifetimes varied from system to system. However, it is believed that the rate constants so obtained are accurate to 20% or better.

The potential-energy calculations, the results of which are given in Table III, were performed with a slightly modified version of Wiberg's program.[18] No attempt was made to ensure that an absolute minimum had been obtained; the complexity of the system and the amount of computing time required precluded this. The initial structure input to the program had tetrahedral bond angles and equilibrium bond lengths. The structure of the molecule at the first minimum reached did not differ significantly from the original structure.

Acknowledgment. We thank Professor K. B. Wiberg for a copy of his computer program. As part of the freshman honors program, Mr. Gregory Thompson rendered valuable assistance with the synthesis of 9-ethyl-2,2-difluoro-*cis*-decalin.

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[27] S. Alexander, *J. Chem. Phys.*, 37, 974 (1962).

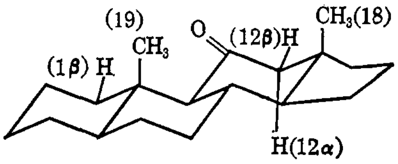
A Variable-Temperature Nuclear Magnetic Resonance Study of Toluene–Ketone Complexes[1,2a]

Pierre Laszlo[2b] and Dudley H. Williams

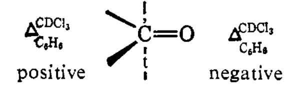
Contribution from the Centre National de la Recherche Scientifique, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, and the University Chemical Laboratory, Lensfield Road, Cambridge, England. *Received January 10, 1966*

Abstract: The temperature variations in the chemical shift of proton resonances in some steroidal ketones in toluene solution have been determined. The changes in resonance positions on passing from an "inert" solvent (carbon tetrachloride) to toluene are accentuated on cooling, since the equilibrium ketone + toluene $\rightleftharpoons$ complex is driven toward complex formation with a decrease in temperature. The temperature variation of the equilibrium constant (calculated in terms of a 1:1 complex) gives the heat of formation of the complex as -0.65 ± 0.15 kcal/mole; in view of the assumptions made in calculating ΔH, this value is probably significant only to an order of magnitude. The sign of solvent shifts induced by toluene relative to carbon tetrachloride closely follows the empirical generalization previously reported for those induced by benzene relative to chloroform.

It has recently been shown[3-5] that benzene solvent molecules can form a stereospecific complex with a ketone group in a solute molecule, in a manner which permits valuable stereochemical and structural conclusions to be made from solvent shift data. The approximate orientation of the complexing benzene molecule with respect to the carbonyl group has been evaluated[5] in the case of 5α-androstan-11-one (I) as solute, on the assumption of a 1:1 benzene–ketone complex. The 11-ketone I offers advantages over other ketones in studies of complexing since the solvent shifts of no less than five protons (18-H, 19-H, 12α-H, 12β-H, and 1β-H), variously oriented with respect to the carbonyl group (see I), can be followed. An empirical correlation has been formulated[3-6] which states that the shift of a proton resonance on passing from deuteriochloroform to benzene solution ($\Delta^{\mathrm{CDCl_3}}_{\mathrm{C_6H_6}} = \delta_{\mathrm{CDCl_3}} - \delta_{\mathrm{C_6H_6}}$ ppm) will be positive for protons lying behind a plane drawn at right angles to the C–O bond and passing through the carbonyl carbon atom, but $\Delta^{\mathrm{CDCl_3}}_{\mathrm{C_6H_6}}$ will be negative for protons lying in front of this plane (see II); protons lying approximately in the plane suffer a very small or zero solvent shift.



I



II

It was now of interest to undertake variable-temperature nmr studies, in the hope of shifting the equilibrium (1) in favor of complex formation and so enhancing the solvent shifts. In addition, the temperature

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[1] Solvent Effects in Nmr Spectroscopy. VII. Part VI: J. H. Bowie, D. W. Cameron, P. E. Schutz, and D. H. Williams, *Tetrahedron*, in press.

[2] (a) Effet de Solvants en Resonance Magnetique Nucleaire. VIII. Part VII: P. Laszlo, *Bull. Soc. Chim. France*, in press; (b) Department of Chemistry, Princeton University, Princeton, N. J. 08540.

[3] D. H. Williams, and N. S. Bhacca, *Tetrahedron*, 21, 2021 (1965).

[4] S. Bory, M. Fetizon, P. Laszlo, and D. H. Williams, *Bull. Soc. Chim. France*, 2541 (1965).

[5] D. H. Williams and D. A. Wilson, *J. Chem. Soc.*, 144 (1966).

[6] J. D. Connolly and R. McCrindle, *Chem. Ind.* (London), 379 (1965).

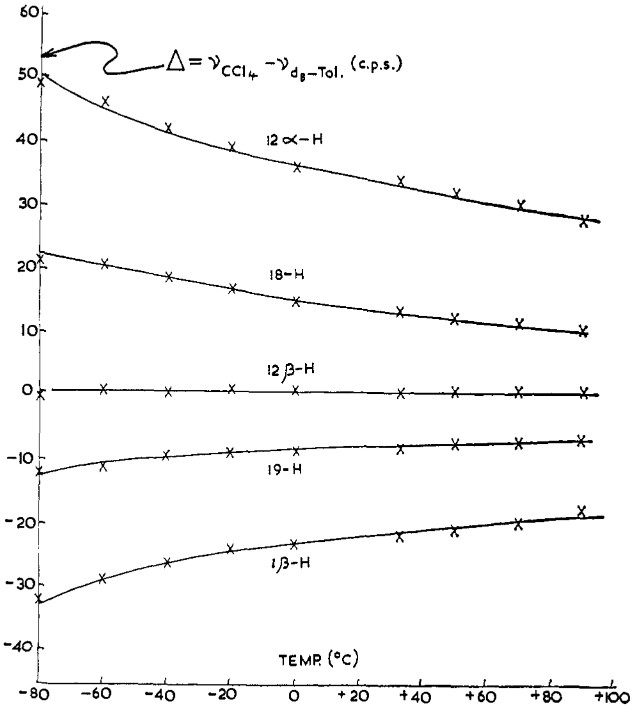


Figure 1. Temperature variation of the chemical shift of some proton resonances of 5α-androstan-11-one (I) in toluene-d_8 solution.

Table I. The Temperature Variation of the Chemical Shifts of Proton Resonances in Some Steroidal Ketones (I and III–VI) with Temperature in Toluene (or Toluene-d_8) Solution[a]

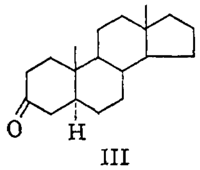
	Resonance					Temp,
Compd	19-H	18-H	12α-H	12β-H	1β-H	°C
I	105.5	55.5	190.0	217.0	262.0	+90
	106.0	54.5	188.0	217.0	264.0	+70
	106.5	53.5	186.0	217.0	265.0	+50
	107.0	52.5	184.0	216.5	266.0	+33
	107.5	51.0	182.0	217.0	267.0	0
	108.0	49.0	179.0	217.0	268.0	−20
	108.5	47.5	176.0	216.5	270.0	−40
	110.0	45.5	172.0	217.0	273.0	−60
	111.0	45.0	169.0	218.0	276.0	−80
III	61.0	61.0				+28.5
	57.5	62.0				+8
	54.0	62.5				−23
	51.5	63.0				−39
	44.5	64.0				−75
IV[b]	62.5	60.5				+100
	61.0	59.5				+90
	~59.5	~59.5				+70
	57.5	58.5				+50
	55.5	57.5				+33
	53.5	55.5				0
	51.5	54.0				−20
	49.0	52.0				−40
	46.5	50.0				−60
	45.0	49.0				−80
V	63.5	58.5				+28.5
	62.5	55.5				−39
	61.5	52.0				−74
VI	49.5	49.5				+35
	37.0	46.5				−70

[a] Values refer to cps at 100 Mc with tetramethylsilane as internal reference; determinations were carried out in 2–4% w/v solutions. [b] The assignments of the 18-H and 19-H resonances are not unambiguous and may be reversed; the value of 0.62 ppm previously reported[3] for the H-18 resonance of IV in $CDCl_3$ is in error and should be 0.71 ppm.

variation of the equilibrium constant for the equilibrium 1 would permit an evaluation of the enthalpy of formation of the complex on the basis of an assumed 1:1 complex.[7] Obviously, benzene was not a suitable solvent for such variable-temperature studies and consequently it was decided to employ toluene as solvent. Previous temperature-variable studies in toluene solution have been carried out on methyl iodide and chloroform,[8] acetonitrile, *p*-benzoquinone, and N,N-dimethylformamide,[9] and pyrimidine[10] for the purpose of evaluating solvent–solute interactions.

$$\text{solvent} + \text{ketone} \rightleftharpoons \text{complex} \qquad (1)$$

As in previous studies, steroidal ketones were employed as solutes for reasons outlined above; in addition the steroidal ketones are conformationally rigid (with a reservation, to be made subsequently, for ring A of 5α-androstan-11-one (I)) and the C-18 and C-19 methyl groups are freely rotating and therefore give sharp resonance lines, whose solvent shifts can easily be followed. The results for 5α-androstan-11-one (I), 5α-androstan-3-one (III), 5α-androstan-6-one (IV), 5α-androstan-17-one (V), and 5α-androstan-3,6-dione (VI) are summarized in Table I. The results for 5α-androstan-11-one (I) are also summarized graphically in Figure 1 in terms of a plot of the solvent shift $\Delta_{\mathrm{tol}}^{\mathrm{CCl_4}}$ ($\Delta_{\mathrm{tol}}^{\mathrm{CCl_4}} = \nu_{\mathrm{CCl_4}} - \nu_{\mathrm{tol}\text{-}d_8}$ cps at 100 Mc) against temperature. To enable the solvent shifts of all the pertinent resonances of I to be followed toluene-d_8 was used as solvent in this case. The H-18 and H-19 resonances of I occur at the same chemical shift in toluene and toluene-d_8 solutions (measurements at the normal probe temperature of 33°) and therefore no significant secondary deuterium isotope effect seems to be operative. The location of the resonances in carbon tetrachloride (chosen as an "inert" reference solvent) at 33° are given in Table II. The most striking results are those obtained for 5α-androstan-11-one (I, see Figure 1). At low temperatures the equilibrium (1) is shifted in favor of complex formation. The negative solvent shifts of 1β-H and 19-H (which lie in front of the reference plane) are therefore accentuated, as are the positive solvent shifts of 12α-H and 18-H (these protons lie be-



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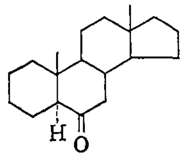
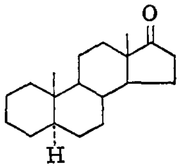
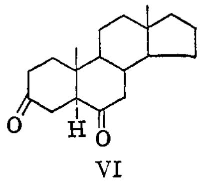


IV



V



VI

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(7) In the specific instance of 5α-androstan-11-one (I), it is difficult to visualize other than a 1:1 solvent–solute interaction. A benzene molecule can approach the C=O group from the α face, but approach from the β face is virtually impossible due to the steric bulk of the C-18 and C-19 angular methyl groups (as indicated by Dreiding models). It is emphasized that in an earlier paper (ref 5), the term "complex" was used in a different context to represent the averge picture due to the equilibrium (1) at 33°.

(8) R. J. Abraham, *Mol. Phys.*, 4, 369 (1961).

(9) J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, 40, 1285 (1962).

(10) J. N. Murrell and V. M. S. Gil, *Trans. Faraday Soc.*, 61, 402 (1965).

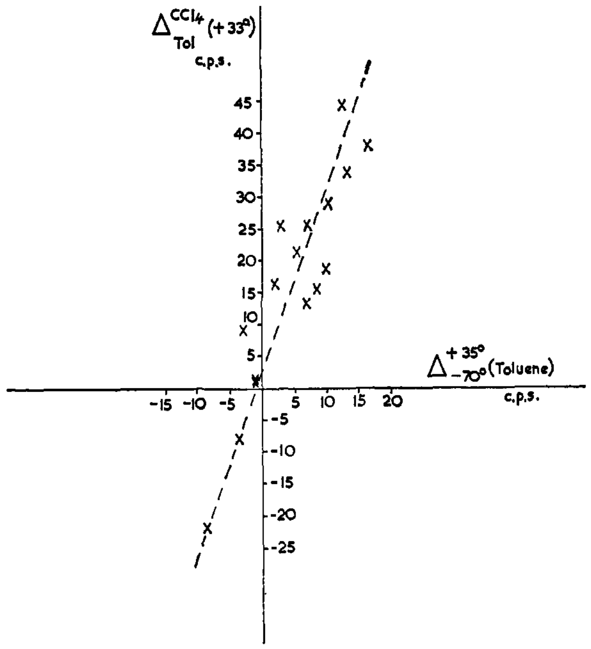

Figure 2. Plot of the temperature variation of the chemical shift of some proton resonances (in the spectra of I and III–VI) in toluene solution *vs.* the solvent shift on change of solvent from CCl_4 to toluene. (The corresponding data for the methyl resonances of camphor are also included in this figure.)

hind the reference plane); the equatorial 12β-H lies approximately in the reference plane and its resonance position is barely affected by change of solvent from carbon tetrachloride to toluene-d_8 or by change of temperature in toluene-d_8.[11]

Table II. Chemical Shifts of Proton Resonances in Some Steroidal Ketones (I and III–VI) in Carbon Tetrachloride (at 33 ± 3°)[a]

	Resonance				
Compd	19-H	18-H	12α-H	12β-H	1β-H
I	99.0	66.0	218.0	218.0	244.0
III	99.0	70.0			
IV	73.0	73.0			
V	80.0	80.0			
VI	94.0	75.0			

[a] Values refer to cps at 100 Mc with tetramethylsilane as internal reference; determinations were carried out in 2–4% w/v solution.

There is a reasonable correlation between the solvent shifts induced by toluene relative to carbon tetrachloride (at 33 ± 3°) and the *supplementary* shifts observed on cooling the toluene solutions. This correlation may be seen from Figure 2, in which the $\Delta_{tol}^{CCl_4}$ solvent shifts which are observed at normal probe temperatures have been plotted against the supplementary shifts in toluene on cooling from +35 to −70°; the data for all the compounds (I and III–VI) are included in Figure 2.

For the calculation of thermodynamic parameters on the basis of an assumed 1:1 complex, it can be shown[8] that if, in a dilute solution, a fraction p of the solute is in the complex form, then eq 2 holds, where K is the equilibrium constant for eq 1, and ΔS and ΔH are the entropy of formation and heat of formation of the complex, respectively. The value of p at any temperature

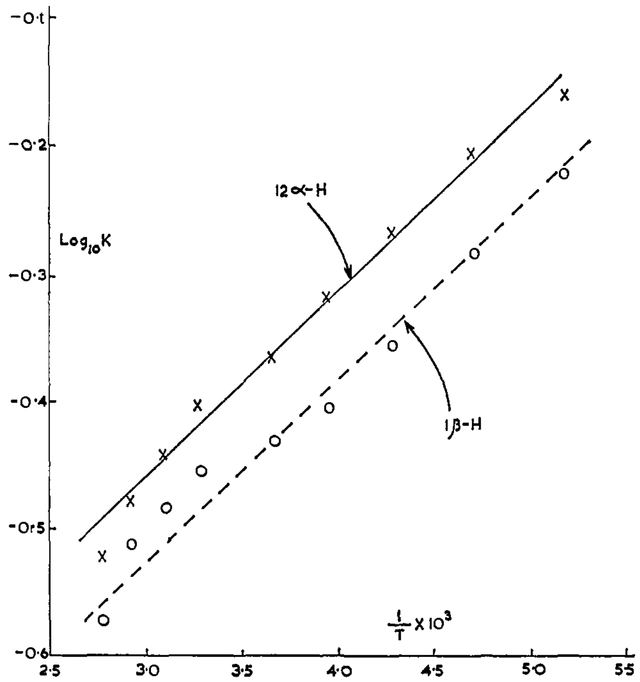

Figure 3. Plot of log K *vs.* $1/T$ based on data for 1β-H and 12α-H resonances of 5α-androstan-11-one (I).

$$K = \frac{p}{1 - p} = \exp\left(\frac{\Delta S}{R}\right) \exp\left(-\frac{\Delta H}{RT}\right) \qquad (2)$$

(t) may be found from eq 3, in which ν_c is the chemical shift of a proton resonance in the pure complex, ν_0 is the corresponding chemical shift in the absence of complexing, and ν_t is the observed value at a temperature t.

$$p = \frac{\nu_t - \nu_0}{\nu_c - \nu_0} \qquad (3)$$

If the position of the resonance in the "inert" solvent carbon tetrachloride is taken to give ν_0, and this is then arbitrarily taken as zero, then eq 4 follows.

$$p = \frac{\nu_t}{\nu_c} \qquad (4)$$

By use of eq 2 and 4, plots of log K against $1/T$ (Figure 3) have been obtained for the 12α-H and 1β-H resonances of 5α-androstan-11-one (I). Estimates of ν_c (relative to carbon tetrachloride solution) for these proton resonances are ν_c(12α-H) = +120 ± 20 cps and ν_c(1β-H) = −85 ± 15 cps, obtained by extrapolation of the curves given in Figure 1 to 0°K. The plot of log K against $1/T$, using the data for the 12α-proton, is approximately linear and gives $\Delta H = -0.65 \pm 0.15$ kcal/mole. This result is practically independent of the value of 110 cps $\leqslant \nu_c \leqslant$ 130 cps, the calculated entropy of formation, on the contrary, being obviously sensitive to this parameter; the best fit of log K against $1/T$ to a common line for 12α-H and 1β-H corresponds to the respective values of ν_c = 110:−70; 120:−77; and 130:−83. This value of ΔH should however only be

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(11) The reference plane represented by a dotted line in II has of course been proposed in terms of $\Delta_{C_6H_6}^{CDCl_3}$ solvent shifts.[3,4,6] However, it comes as no surprise that $\Delta_{tol}^{CCl_4}$ solvent shifts apparently permit a similar empirical correlation, since deuteriochloroform, although not an "inert" solvent, causes only relatively small shifts relative to carbon tetrachloride.[12]

(12) P. Laszlo, *Bull. Soc. Chim. France*, 2658 (1964).

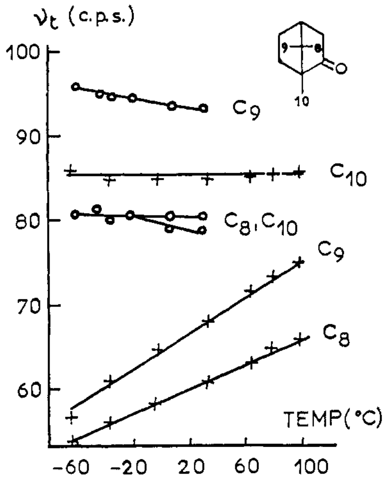

Figure 4. Temperature variation of the chemical shift of the methyl resonances of camphor in carbon disulfide solution (○) and in toluene solution (+).

regarded as an order of magnitude, since there are several possible perturbing phenomena, *e.g.*, simultaneous cccurrence of 1:1, 1:2, etc., complexes[13] and temperature shifts associated with dispersion forces.

Although the data for the 1β proton give a line of the same slope (see Figure 3), this result may be fortuitous for the following reasons. The circular dichroism curve of 5α-androstan-11-one (I) is temperature dependent.[14] This observation has been explained in terms of a conformational equilibrium in ring A, whereby the interaction between the 1β proton and the 11-keto group may be relieved. This hypothesis is supported by variable-temperature studies on the nmr spectrum of I in carbon tetrachloride solution; the chemical shift of the 1β-H resonance changes from 2.46 ppm at +65° to 2.41 ppm at −20°, whereas those of the 19-H resonance (0.99 ppm at +65° and 0.98 ppm at −20°) and the 12-H resonances are only slightly altered.[15] The appreciable change in the chemical shift of the 1β-H resonance with temperature *in an "inert" solvent* suggests that the average orientation of the 1β-proton with respect to the 11-keto group changes with temperature, *i.e.*, ring A is not conformationally homogeneous in I.

The possibility of an *intrinsic* effect of the temperature on the chemical shifts has also been considered. To evaluate the order of magnitude of such variations for the steroidal ketones studied, a conformationally rigid model is needed, and camphor was chosen. In Figure 4, the temperature dependence for the methyl groups of camphor in CS_2 solution[17] is compared to their temperature variation in toluene solution (the assignment of the methyl resonances in the aromatic solvent follows that of Connolly and McCrindle[6]). The observed variations in carbon disulfide solution may be a combination of intramolecular and intermolecular effects, as in a similar gas phase study;[18] their slope is opposite to that of the toluene curves, which therefore are good evidence for the postulated cyclanone–toluene complex.

The results recorded in this paper illustrate that measurements at low temperature in toluene solution may be useful to amplify the ordinary benzene shifts observed for ketones[3-6] and also to distinguish 19-H and 18-H resonances without recourse to deuteration.

Experimental Section

The spectra were determined using a Varian HA-100 instrument, fitted with a variable-temperature probe, or a Varian A-60, similarly equipped.

Solution concentrations employed were in the range 2–4% w/v and resonance positions, uniformly expressed at 100 Mcs, were measured either relative to internal TMS (for I and IV), or relative to the methyl resonance of the toluene solvent (for III, V, and VI); the latter values were subtracted from 209.5 cps to obtain the resonance position relative to TMS. Toluene-d_8 was obtained from Merck Sharp and Dohme, Montreal.

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(13) (a) A plot of the ratio of the solvent shift to the mole fraction of benzene in carbon tetrachloride against the solvent shift is a straight line for V as solute. V was arbitrarily selected for this experiment from the available ketones (I and III–VI), since the correlation in Figure 2 suggests similar values of ΔH for the different ketones. In this experiment, the negative gradient is a measure[13b] of the apparent equilibrium constant K = 0.18–0.20 l./mole, at 33°, in fair agreement with the apparent enthalpy of formation for the I–toluene complex. Nevertheless, such a fit may well be fortuitious; the complexes' stoichiometry is uncertain, since it may depend upon statistical equivalence of a "collision" complex to a "chemical" complex; furthermore, drastic hypotheses are implicit in variable-temperature experiments (ν_c is temperature independent) and in titration curve experiments (ν_c does not depend upon the composition of the solvent mixture). (b) R. Foster and C. A. Fyfe, *Trans. Faraday Soc.*, **61**, 1626 (1965).

(14) K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963).

(15) The observation that the chemical shifts of the 19-H, 12α-H, and 12β-H resonances do show a *small* (but significant) temperature variation in carbon tetrachloride solution is compatible with a very weak interaction between carbon tetrachloride and the solute molecule. This suggestion is consistent with the recent findings of Anderson.[16] However, an *intrinsic* effect of temperature is not excluded, as is indicated subsequently in the text.

(16) J. E. Anderson, *Tetrahedron Letters*, 4173 (1965); *cf.* also P. Laszlo, *Bull. Soc. Chim. France*, **85**, (1964), in which a typographical error has changed the chemical shift of C-13 in cyclohexane to 67.1, instead of the correct value of 62.4, as in Figure 1 of that paper; the possibility of charge transfer between CCl_4 and an oxygenated solute has already been discussed in ref 12.

(17) M. Fétizon, M. Golfier, and P. Laszlo, *Bull. Soc. Chim. France*, 3486 (1965).

(18) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1174 (1961); N. Muller and R. C. Reiter, *ibid.*, **42**, 3265 (1965); A. D. Buckingham, *ibid.*, **36**, 3096 (1962).