[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF FLORIDA STATE UNIVERSITY]

Structural, Solvent and Salt Effects in a Unimolecular Reaction

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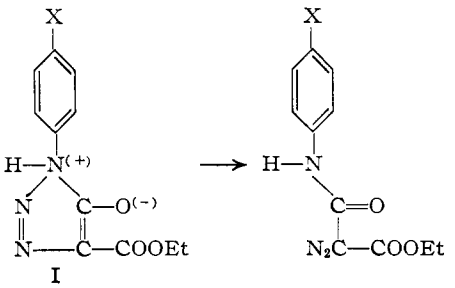
RECEIVED OCTOBER 20, 1955

The Dimroth triazole rearrangement is decelerated by electron-supplying substituents and by good solvents for the triazole. This deceleration is largely an activation enthalpy effect. The deceleration by salts, on the other hand, is largely an activation entropy effect. The enthalpy of activation is an approximately linear function of the entropy of activation in both cases, but two lines are required for the correlation, one for solvent and structure as the independent variables, the other for the nature and concentration of added salt as the independent variables. The interaction between solvent effects and structural effects is discussed.

Introduction

The Dimroth[1,2] rearrangement of aryl triazoles is a theoretically important limiting case because changes in the free energy of the transition state can be neglected in comparison with changes in the free energy of the ground state. A considerable simplification is thereby achieved in the interpretation of the dependence of the reaction rate on reagent structure, solvent, the nature and concentration of added salts, and on the temperature. The reason for the preponderant influence of the ground state on the reaction rate in this case is the highly polar nature of the reagent I in contrast to the transition state, in which the strong dipole has largely collapsed.



I

The independent variables producing changes in the rate have been studied together rather than separately because of the probable importance of interactions among them. For example the effect of a structural or solvent change will usually be different at different temperatures, sometimes even different in sign.[3] Also, a substituent might exert a large part of its effect by modifying the role of the solvent, or *vice versa*.[4]

Substituent and Solvent Effects.—At ordinary temperatures the Dimroth rearrangement is accelerated by electron-withdrawing substituents and decelerated by electron-releasing substituents.[1] As Dimroth has shown already, the reaction is also faster in poor (usually less polar) solvents for the triazole than in good (polar) solvents. Acetonitrile is a faster solvent for the reaction than is dimethylformamide; acetonitrile has a higher dielectric constant but a lower dipole moment than dimethylformamide. The solubility is so high in both solvents as to make its measurement of no theoretical interest, however. With solvent and structure (the nature of the substituent X) as the variables, both the activation enthalpy and the activation entropy are changed, but in compensating directions. At ordinary temperatures the effect of the activation enthalpy is the more important and hence the reactions of higher activation enthalpy are the slower ones. Figure 1 shows the trend of activation enthalpy with activation entropy. The slope, or *isokinetic temperature*,[3] of this line is about 600°K. Dimroth's data for the isomerization of a related compound, 1-benzyl-4-carbethoxy-5-hydroxy-1,2,3-triazole in the four solvents methanol, acetone, ethanol and chloroform also show a linear relationship.[5,3] We mention the existence of the latter correlation to justify our assumption that the correlation of Fig. 1 is more than a coincidence and that it would continue to obtain if data were available for more solvents.

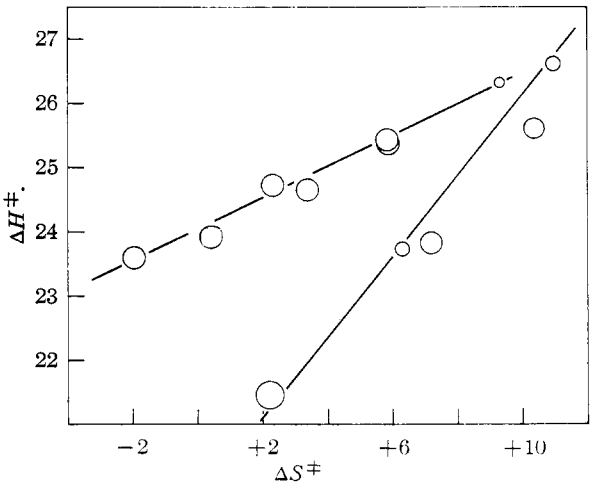
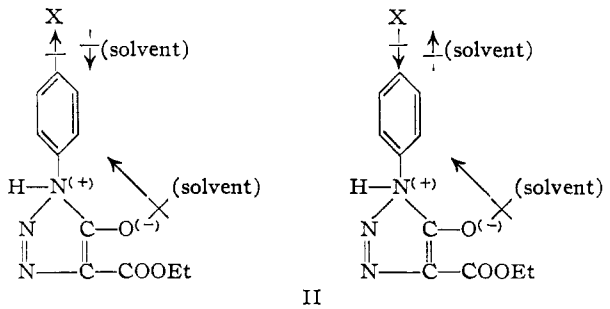


Fig. 1.—Upper line, effect of the nature and concentration of added salt on the activation parameters for the rearrangement of 1-anisyl-4-carbethoxy-5-hydroxy-1,2,3-triazole: lower line, effect of structural and solvent changes on the activation parameters for the rearrangement of substituted 1-phenyl-4-carbethoxy-5-hydroxy-1,2,3-triazoles. The upper three points near this line are for reactions in dimethylformamide while the lower three points are for acetonitrile.

The probable explanation for the higher activation enthalpy of the methoxy and methyl compounds as compared with the bromo compound is that increases in the activation enthalpies in this case tend to parallel reductions in the potential energy of the reagent molecules. An electron-releasing substituent lowers the potential energy of the protonated nitrogen next to the benzene ring.

(1) O. Dimroth, *Ann.*, **373**, 349 (1910).
(2) O. Dimroth, *ibid.*, **377**, 131 (1910).
(3) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).
(4) J. Gripenberg, E. D. Hughes and C. K. Ingold, *Nature*, **161**, 480 (1948).
(5) O. Dimroth, *Ann.*, **373**, 367 (1910).

A suitably oriented solvent molecule might do much the same thing, and a single correlation for both structural and solvent effects is therefore not surprising. It will be noted (Fig. 1) that in the slower solvent, dimethylformamide, the points corresponding to various substituents bunch together more than they do in acetonitrile. A decelerating solvent tends to lessen the effect of a substituent; the solvent and substituent effects are not entirely additive. This is understandable if a solvent that stabilizes the zwitterion at the reaction site by forming a dipole–dipole complex with it can also partly neutralize the substituent's dipole (II)



II

Although the transition state is much less polar than the ground state of the triazole, there is one type of solvation that might be more important in the transition state than in the ground state, namely the formation of a π-complex with the benzene ring. Trinitrobenzene will form complexes with benzene derivatives to an extent that depends on the electron density of the substrate ring. Complex formation is hindered by positive charge adjacent to the ring; the complex once formed reduces the electron density of the ring. Hence trinitrobenzene should form very little π-complex, if any, with the triazole zwitterion, but any complex should rearrange very rapidly, as does the nitro-substituted zwitterion. Table I shows that trinitrobenzene had no detectable effect.

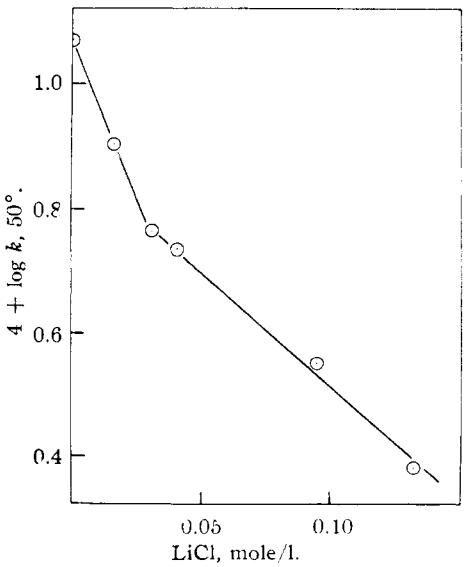


Fig. 2.—Effect of lithium chloride on the rate of rearrangement of 1-anisyl-4-carbethoxy-5-hydroxy-1,2,3-triazole in dimethylformamide at 50°.

Salt Effects.—The salt effect has been studied with the methoxy compound in dimethylformamide. Salts added to the solvent decelerate the reaction, the logarithm of the first-order rate constant being at least approximately a linear function of the salt concentration in most cases. Small ions have a greater effect at a given concentration than do large ones. The most effective salt studied, LiCl, gave a decidedly non-linear log k *vs.* salt concentration curve (Fig. 2) at 50°.[6] At 25° the salt effect was smaller and the curvature less apparent. Lithium nitrate, a less effective salt, gave a straight line within experimental error even at 50°.

All of the salts studied at more than one temperature, including lithium chloride, gave enthalpies of activation linearly related to the entropies of activation. Points corresponding to different salts or to different concentrations of salt fell on a single line (Fig. 1). The slope or *isokinetic temperature* of that line is about 240°K. The significance of this value for the isokinetic temperature is that at all temperatures above −30° the reaction rates are entropy controlled, the faster reactions being those of more positive entropy of activation rather than those of lower enthalpy of activation. At temperatures below −30° salts should accelerate rather than decelerate the reaction. At −30° they should have no effect.

The order of increasing activation enthalpy and entropy for equal concentration of different salts is lithium chloride < lithium nitrate < sodium nitrate < potassium nitrate ≈ ammonium nitrate < no salt. The position of potassium nitrate in the series is estimated from a comparison of rates at only one temperature, a procedure justified by the correlation of higher rate with higher activation enthalpy and entropy for temperatures above −30°.

Strong acids might affect the reaction rate in two ways, by repressing any dissociation of the triazole or by exerting a salt effect. Although the triazole is itself a strong acid in water it is not expected to dissociate extensively in the solvents studied in the present paper. Hence added strong acids should not be able to affect the rate by changing the proportion of triazole in the associated form, I. The lack of effect of added acid (Table I) is consistent with the first-order kinetics in the solvents studied by us.[7] The salt effect of strong acids should also be small since the solvated proton is a rather large ion, and even ions of the size of potassium and ammonium show rather small effects. The concentration at which added acids could be studied was low because of interference with the analytical method for the triazole.

The fact that the salt effect activation parameters require a separate isokinetic line from that used for the structural and solvent points (Fig. 1) is an

(6) S. Winstein, E. Clippinger, A. A. Fainberg and G. C. Robinson, THIS JOURNAL, **76**, 2597 (1954), have observed a similar large and non-linear salt effect stabilizing solvent-separated ion pairs. The triazole zwitterion might be expected to interact with salts in much the same way. Intimate ion pairs, on the other hand, would be less subject to the salt effect because of their partially covalent character or mutual polarization.

(7) B. R. Brown and D. H. Hammick, *J. Chem. Soc.*, 1384 (1947), reported that the triazole rearrangement is second order in water.

TABLE I

RATE CONSTANTS FOR THE REARRANGEMENT OF SUBSTITUTED 1-PHENYL-4-CARBETHOXY-5-HYDROXY-1,2,3-TRIAZOLES

Substituent and solvent	Temp., °C.	Mean[a] k, sec.$^{-1}$
p-Methoxy in dimethylformamide	19.60	$(1.45 \pm 0.02) \times 10^{-5}$
	34.01	$(1.28 \pm .01) \times 10^{-4}$
	49.98	$(1.13 \pm .00) \times 10^{-3}$
p-Methyl in dimethylformamide	13.23	$(7.20 \pm 0.04) \times 10^{-6}$
	25.00	$(4.67 \pm .04) \times 10^{-5}$
	34.10	$(1.87 \pm .02) \times 10^{-4}$
p-Bromo in dimethylformamide	2.35	$(5.05 \pm 0.05) \times 10^{-6}$
	13.46	$(3.16 \pm .05) \times 10^{-5}$
	25.00	$(1.92 \pm .00) \times 10^{-4}$
p-Methoxy in acetontrile	3.65	$(2.44 \pm 0.04) \times 10^{-5}$
	12.37	$(9.57 \pm .15) \times 10^{-5}$
	24.99	$(5.79 \pm .00) \times 10^{-4}$
p-Methyl in acetonitrile	3.48	$(3.32 \pm 0.00) \times 10^{-5}$
	13.30	$(1.49 \pm .02) \times 10^{-4}$
	19.60	$(3.83 \pm .02) \times 10^{-4}$
	24.95	7.21×10^{-4}
p-Bromo in acetonitrile	2.26	$(1.59 \pm 0.00) \times 10^{-4}$
	12.31	$(6.55 \pm .06) \times 10^{-4}$
p-Methyl in acetonitrile with 0.0313 *M* 1,3,5-trinitrobenzene	13.30	1.51×10^{-4}
	24.95	7.22×10^{-4}
p-Methyl in acetonitrile with 0.0501 *M* 1,3,5-trinitrobenzene	24.95	7.28×10^{-4}
p-Methoxy in dimethylformamide with 0.064 *M* 1,3,5-trinitrobenzene	19.60	1.41×10^{-5}
p-Methoxy in dimethylformamide		
with 0.074 *M* $HClO_4$	25.00	3.18×10^{-5}
with 0.037 *M* $HClO_4$	25.00	3.26×10^{-5}
with no $HClO_4$	25.00	3.36×10^{-5}[b]
p-Methoxy in dimethylformamide[c]		
with 0.040 *M* LiCl	25.00	2.15×10^{-5}
0.068 *M* LiCl	25.00	1.81×10^{-5}
.114 *M* LiCl	25.00	1.18×10^{-5}
.129 *M* LiCl	25.00	1.02×10^{-5}
no salt	50.21	11.8×10^{-4}[b]
.016 *M* LiCl	50.21	7.99×10^{-4}
.031 *M* LiCl	50.21	5.80×10^{-4}
.041 *M* LiCl	50.21	5.45×10^{-4}
.095 *M* LiCl	50.21	3.55×10^{-4}
.132 *M* LiCl	50.21	2.45×10^{-4}
with the sodium salt of 1-*p*-anisyl-4-carbethoxy-5-hydroxy-1,2,3-triazole[c]		
0.041 *M*	25.00	2.86×10^{-5}
.098 *M*	25.00	2.79×10^{-5}
with 0.251 *M* $LiNO_3$[c]	25.00	1.38×10^{-5}
.239 *M* $LiNO_3$	50.21	4.08×10^{-4}
.172 *M* $LiNO_3$	50.21	5.17×10^{-4}
.113 *M* $LiNO_3$	50.21	6.30×10^{-4}
.052 *M* $LiNO_3$	50.21	9.73×10^{-4}
.035 *M* $LiNO_3$	50.21	10.22×10^{-4}
with 0.094 *M* $NaNO_3$	25.00	2.82×10^{-5}
.093 *M* $NaNO_3$	50.21	8.72×10^{-4}
with 0.103 *M* NH_4NO_3	25.00	2.91×10^{-5}
.111 *M* NH_4NO_3	50.21	8.73×10^{-4}
with 0.100 *M* KNO_3	50.21	8.59×10^{-4}

[a] Mean rate constants and the probable errors of individual rate constants are given. The probable errors are based on populations consisting of rate constants for runs of initial triazole concentration ranging from 0.01 to 0.1 molar. There is no observable correlation between the initial concentration and the first-order rate constant. [b] Estimated from data at other temperatures. [c] Initial concentration of triazole about 0.03 molar.

indication of an important qualitative difference between the interaction of the triazole zwitterion with relatively weak dipoles (substituents or solvent molecules) and with strong dipoles. This qualitative difference and the lowering of both the activation enthalpy and the activation entropy by salts can be explained as follows: in the ground state an intimate association of the triazole zwitterion with the salt ion-pairs deprives both of these strong dipoles of a good deal of their solvation. With the collapse of the triazole zwitterion in the transition state there is an increase in solvation of the unneutralized salt ion-pair with a resulting lowering of the activation enthalpy and of the activation entropy.

TABLE II

ACTIVATION PARAMETERS FOR THE REARRANGEMENT OF SUBSTITUTED 1-PHENYL-4-CARBETHOXY-5-HYDROXY-1,2,3-TRIAZOLES

Substituent and solvent[a]	Enthalpy of activation and probable error[b]	Entropy of activation and probable error[b]
p-Bromo in acetonitrile	21.47 ± 0.11	2.23 ± 0.46
p-Methyl in acetonitrile	23.81 ± .12	7.21 ± .41
p-Methoxy in acetonitrile	23.74 ± .06	6.34 ± .22
p-Bromo in dimethylformamide	25.62 ± .10	10.4 ± .4
p-Methyl in dimethylformamide	26.61 ± .07	11.0 ± .2
p-Methoxy in dimethylformamide	26.33 ± .04	9.32 ± .13
p-Methoxy in dimethylformamide with added salt		
0.016 *M* LiCl	24.65 ± .1	3.40 ± .35
.040 *M* LiCl	23.93 ± .1	0.41 ± .35
.115 *M* LiCl	23.58 ± .1	−1.94 ± .35
.103 *M* NH_4NO_3	25.38 ± .1	5.9 ± .35
.251 *M* $LiNO_3$	24.74 ± .1	2.3 ± .35
.094 *M* $NaNO_3$	25.41 ± .1	5.9 ± .35

[a] The activation parameters at a given salt concentration were calculated by correcting the observed rate constant for any difference from the indicated salt concentration, assuming a linear dependence of log k on the salt concentration. [b] From a least squares calculation using the individual rate constants, given equal weight, rather than the mean rate constants of Table I.

Experimental Part

The *para*-substituted 1-phenyl-4-carbethoxy-5-hydroxy-1,2,3-triazoles were synthesized by the method of Dimroth.[8]

Aryl Azides.—To a solution of 0.5 mole of the amine and 1.5 moles of sulfuric acid in 150 cc. of water, was added 0.5 mole of concentrated aqueous sodium nitrite dropwise at 0°. An aqueous solution of 0.5 mole of sodium azide was then added with stirring, the reaction vessel being kept in the ice-bath until nitrogen evolution ceased (3–4 hours). The aryl azide was then extracted with ether and washed with dilute sodium hydroxide until free from acid.

The aryl azides were obtained in 65–70% yield.

Diazomalonanilides.—About 0.3 mole of azide was dissolved in 50 cc. of absolute ethanol, adding a little ether if necessary, and added dropwise to an equimolar amount of the sodio derivative of diethyl malonate in ethanol. The reaction mixture was refluxed for 3–4 hours after the addi-

(8) O. Dimroth and H. Stahl, *Ann.*, **338**, 154 (1904).

tion was completed. The sodium salt of the triazole was precipitated by adding ether to the cold mixture. The salt was then dissolved in a minimum amount of water, warming if necessary, and chilled in an ice-bath. The cold salt solution was added dropwise with constant agitation to cold dilute hydrochloric acid. If the addition was too fast or the salt solution too concentrated, a plastic mass was obtained instead of the white powder form of the triazole. But in either case, one recrystallization from hot 95% ethanol yielded the yellow needles of the diazomalonanilide. The product was purified and stored in this form.

Ethyldiazomalon-*p*-aniside was obtained in 55% yield; m.p. 95–96°. *Anal.* Calcd.: C, 54.75; H, 4.98; N, 15.96. Found: C, 55.11; H, 4.85; N, 15.99. Ethyldiazomalon-*p*-toluidide, m.p. 98–99°, and ethyldiazomalon-*p*-bromoanilide,[8] m.p. 138–139°, were prepared in the same way. The corresponding triazoles melt at 91, 88 and 138°. The sample must be put into the bath just below the melting point to obtain a reproducible result.

Solvents.—Commercial acetonitrile was distilled through a helices-packed fractionating column. A middle fraction, b.p. 31–32°, d^{20} 0.7813, n^{20} 1.3450, was collected.

Commercial dimethylformamide was similarly distilled; b.p. 152–153°, d^{20} 0.9392, n^{24} 1.4282.

Kinetics.—Since the triazoles rearrange even in the solid state, they were always freshly prepared before a run. About one gram of the appropriate ethyldiazomalonanilide was dissolved in a minimum amount of hot ethanol and the solution rapidly chilled in an ice-bath. A solution of sodium ethoxide (from 0.1–0.15 g. of sodium in 4 cc. of ethanol) was added to dissolve the malonanilide, then ether was added slowly at 0° to ensure a fine white powdered precipitate of the triazole sodium salt. The salt was removed and dissolved in water, cooled to zero degrees, and added dropwise to cold dilute hydrochloric acid with constant agitation. The combined volume should not exceed 50 cc. and the salt must be added to the acid rather than *vice versa*.

The triazole thus prepared was dried *in vacuo* to constant weight. A typical sample dissolved in ethanol and quenched immediately with excess aqueous potassium iodide and iodate gave 98% or more of the theoretical amount of iodine. For the kinetic runs, a weighed sample of the triazole was dissolved in a known volume of solvent already at the desired temperature. From time to time aliquots of the thermostated solution were withdrawn with an automatic pipet and quickly transferred to a flask containing the potassium iodide–iodate solution, excess distilled water and a magnetic stirrer. The iodine, which appears instantly, was titrated with thiosulfate to a starch end-point. With dimethylformamide and other water-soluble solvents the system is homogeneous. It is doubtful whether the analytical method is fast enough for accurate results with solvents such as toluene in which the rearrangement is extremely fast and the unrearranged acid must be extracted from the hydrocarbon phase.

The runs were quite accurately first order. Rate constants and activation parameters were calculated by the method of least squares.

The salts used in the salt effect experiments were reagent grade, dried at 100–110° overnight or to constant weight and allowed to cool in a desiccator over phosphorus pentoxide.

Acknowledgment.—This work was supported by the Office of Ordnance Research, U. S. Army.

TALLAHASSEE, FLORIDA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE RICE INSTITUTE]

The Mustard Oil of *Limnanthes douglasii* Seed, *m*-Methoxybenzyl Isothiocyanate

BY MARTIN G. ETTLINGER AND ALLAN J. LUNDEEN[1]

RECEIVED SEPTEMBER 21, 1955

The seed of *Limnanthes douglasii* furnished the previously unknown *m*-methoxybenzyl isothiocyanate, obtained also by synthesis.

The meadow foam, *Limnanthes douglasii* R. Br., of the small North American family *Limnanthaceae*, is a herb native to Oregon and California. A century ago, Chatin[2] observed that the plant afforded a pungent, steam-volatile oil that appeared to be an isothiocyanate and gave with ammonia a crystalline thiourea. Guignard[3] demonstrated that the *Limnanthes* oil did not exist in the intact plant but was liberated on maceration of leaf or seed, by an enzyme that could also convert the glucoside sinigrin to allyl isothiocyanate. He noted that the oil in taste and odor resembled that of garden cress, now known to be benzyl isothiocyanate.

Dr. Joe E. Hodgkins found at Rice that the thiourea in ammoniated distillates of *Limnanthes douglasii* seed, chromatographed on paper,[4] appeared to be a single substance with R_{Ph} 1.02 ± 0.02 and was consequently distinct from all thioureas of volatile natural mustard oils of known structure.[5] In our further work, the *Limnanthes* isothiocyanate, formed in approximate amount of 0.5% of seed, was isolated and characterized as the thiourea, m.p. 101–101.5°, and the N′-phenylthiourea, m.p. 86–87°. The phenylthiourea was originally obtained from a benzene solvate as a metastable dimorph, m.p. 76.5–77°, which changed to the higher-melting form. The infrared spectra of the solid modifications differed markedly between 7.5 and 15 μ.[6]

Analyses of the mustard oil and derivatives showed that the isothiocyanate had the empirical formula C_9H_9ONS and contained one methoxyl group. The thiourea in ethanol had an ultraviolet absorption maximum at 244 mμ (log ϵ 4.15), comparable to that shown by monosubstituted thioureas with a saturated carbon atom adjacent to the chromophore,[7,8] whereas the absorption band[7,9]

(1) National Science Foundation Predoctoral Fellow.

(2) A. Chatin, *Compt. rend.*, **38**, 772 (1854); *Ann. sci. nat., Botan.*, [4] **6**, 247 (1856).

(3) L. Guignard, *Compt. rend.*, **117**, 751 (1893); *J. botanique*, **7**, 417 (1893).

(4) A. Kjaer and K. Rubinstein, *Acta Chem. Scand.*, **7**, 528 (1953).

(5) A thiourea with R_{Ph} 1.02 ± 0.01 has been derived in small amounts from turnip and rape, of the mustard family (K. A. Jensen, J. Conti and A. Kjaer, *ibid.*, **7**, 1267, 1271 (1953)), but has not been further characterized. Compare benzylthiourea, R_{Ph} 0.9; β-phenylethylthiourea, 1.1; 4-methylthiobutylthiourea, 0.97 (A. Kjaer and R. Gmelin, *ibid.*, **9**, 542 (1955)).

(6) *Cf.* infrared spectra of dimorphs of allylthiourea (A. A. Ebert, Jr., and H. B. Gottlieb, THIS JOURNAL, **74**, 2806 (1952)).

(7) A. Clow and N. L. Helmrich, *Trans. Faraday Soc.*, **36**, 685 (1940).

(8) A. Kjaer, J. Conti and I. Larsen, *Acta Chem. Scand.*, **7**, 1276 (1953).

(9) A. Kjaer, K. Rubinstein and K. A. Jensen, *ibid.*, **7**, 518 (1953). The statement that a N-methallyl (alkyl) group exerts a hypsochromic effect in a N′-phenylthiourea is formally true, but as the figure in the reference might suggest, the effect appears to be caused not by displacement of the phenylthiourea band, but by appearance of intense absorption at short wave lengths by the N-alkylthioamide group acting as a partial chromophore.