Dipole Moments of Some 3- and 4-Substituted Phthalimides and Phthalic Anhydrides. Influence of Steric and Resonance Effects

Lyman R. Caswell,* Lily Y. Soo,[1] Daisy H. Lee,[2] Rosemary G. Fowler,[3] and Jo-Anne B. Campbell

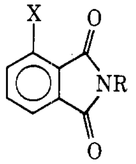
Department of Chemistry, The Texas Woman's University, Denton, Texas 76204

Received April 10, 1973

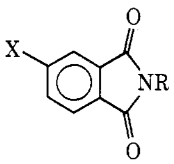
The dipole moments of phthalimide, phthalic anhydride, and 16 derivative compounds in dioxane solution have been measured and compared. The predicted moments of the derivatives have also been calculated from group moments. There is good agreement between the experimental and predicted dipole moments only for 3-methylphthalic anhydride, 3-fluorophthalimide, 4-methylphthalimide, 3-fluorophthalic anhydride, and 4-methylphthalic anhydride. The Zhdanov–Minkin equation for calculating resonance interaction moments has been applied for all of the derivative compounds. Arguments are presented for designating the numerical results of this calculation as *ring polarization moments.* The results of these calculations show that interaction resonance is significant only for 4-chlorophthalic anhydride. Steric and resonance effects are both small or absent as influences upon the dipole moments of 3-fluorophthalic anhydride, 3-fluorophthalimide, and of all methyl derivatives. Steric interaction between ortho substituents appears to be large only in the cases of 3-nitrophthalimide and 3-nitrophthalic anhydride.

The compilation of experimental dipole moments by McClellan[4] records data for a moderate number of cyclic imides, including a portion of the results of two systematic studies of the dipole moments of these compounds. The first of these studies, by Lumbroso and his coworkers,[5-7] dealt primarily with N-substituted succinimides and phthalimides. The second group of studies, by Lee and Kumler,[8-11] was concerned principally with nonaromatic imides, both cyclic and acyclic. The dipole moments of only the most common cyclic anhydrides have been determined, and no comparable systematic examination of these results has been published.

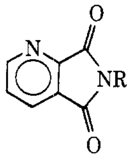
In the course of a series of studies[12-17] of the chemical and spectrophotometric properties of 3-substituted phthalimides **1** and 4-substituted phthalimides **2**, it was of interest to have dipole moment data for these compounds as an aid in the interpretation of the experimental results. Data for only three of these compounds could be found in the literature, namely, the dipole moments measured by Lumbroso and Dabard[5] for 3-chlorophthalimide (**1**, R = H; X = Cl), 4-chlorophthalimide (**2**, R = H; X = Cl), and 4-nitrophthalimide (**2**, R = H; X = NO_2), together with the moments for the *N*-methyl (R = CH_3) and *N*-phenyl (R = C_6H_5) derivatives of these compounds.



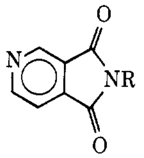
1



2

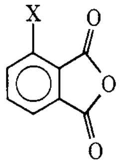


3

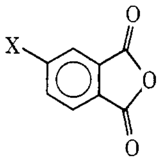


4

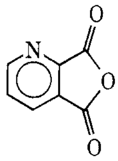
We have therefore measured the dipole moments of a more extended series of 3- and 4-substituted phthalimides and also of the pyridine analogs of phthalimide, quinolinimide (**3**), and cinchomeronimide (**4**). Since it was necessary in most cases to prepare the corresponding anhydrides as precursors to the imides, it was convenient to measure also the dipole moments of a number of 3-substituted phthalic anhydrides **5**, 4-substituted phthalic anhydrides **6**, and quinolinic anhydride **7**.



5



6



7

The majority of these compounds are sufficiently soluble in only two of the solvents suitable for dipole moment measurements for such measurements to yield useful results. These solvents are benzene and dioxane. Neither of these solvents possesses the inertness desirable in a solvent for dipole moment measurements, since benzene acts as a donor in charge-transfer interactions with phthalic anhydride[18] and a number of its derivatives,[19] while dioxane, in addition to its usual disadvantages,[20] can presumably be hydrogen bonded to the N protons of the imides. Ultimately, dioxane was chosen as the solvent in order to provide the best comparability of the results with those of the previous studies.[5-11]

The method applied for the measurements was that of Guggenheim,[21] as presented by Oehme and Wirth.[22] The rapidity with which the measurements can be made by this method provides a definite advantage for studies involving a highly hygroscopic solvent like dioxane and the moisture-sensitive anhydrides.

Experimental Section

Anhydrides and Imides. The majority of the compounds used in this study were prepared from commercially available 3- and 4-substituted phthalic acids. These acids were converted to the anhydrides either by the action of acetic anhydride or by thermal dehydration in a sublimation apparatus. 3-Fluorophthalic anhydride was prepared by dehydration of 3-fluorophthalic acid with an excess of trifluoroacetic anhydride at room temperature.[23] Phthalimide and the nitrophthalimides were purchased. The remaining imides were prepared from the anhydrides by heating with an equimolar quantity of urea until gas evolution ceased. All of the compounds were purified by recrystallization and sublimation until published melting points or satisfactory microanalyses were obtained. A final purification by sublimation at 1 Torr was always done within 12 hr of the measurements, and the sublimates were kept under vacuum in the sublimator until time for preparation of the solutions.

3-Fluorophthalimide. A mixture of 9 g of 3-fluorophthalic anhydride, 3.6 g of urea, and 50 ml of nitrobenzene was heated 3 hr at 170–180°. The precipitate obtained from the cooled reaction mixture was recrystallized twice from benzene and then sublimed *in vacuo* to give fine, yellowish needles, mp 179.5–180.5°. The yield was 81%. *Anal.* Calcd for $C_8H_4FNO_2$: C, 58.19; H, 2.44; N, 8.48; F, 11.51. Found:[24] C, 58.34; H, 2.28; N, 8.48; F, 11.44.

Table I
Dipole Moments of 3- and 4-Substituted Phthalimides and Phthalic Anhydrides in Dioxane

Compd	Registry no.	Dipole moment, D		Ring polarization moment, D
		Exptl	Predicted	
Phthalimide	85-41-6	2.17[a]		
3-Methylphthalimide	7251-82-3	2.39	2.21	+0.4
3-Fluorophthalimide	51108-29-3	2.60	2.65	−0.1
3-Chlorophthalimide	51108-30-6	2.41[b]	2.72	−0.6
3-Nitrophthalimide	603-62-3	3.90	4.63	*c*
Quinolinimide	4664-00-0	2.97	3.16	*c*
4-Methylphthalimide	40314-06-5	2.53	2.55	<0.0
4-Nitrophthalimide	89-40-7	2.96[d]	2.46	+0.4
Cinchomeronimide	4664-01-1	2.22	1.18	+1.0
Phthalic anhydride	85-44-9	5.34		
3-Methylphthalic anhydride	4792-30-7	5.46	5.36	+0.2
3-Fluorophthalic anhydride	652-39-1	5.44	5.56	−0.3
3-Chlorophthalic anhydride	117-21-5	5.31	5.59	−0.6
3-Nitrophthalic anhydride	641-70-3	5.95	6.73	*c*
Quinolinic anhydride	699-98-9	5.54	5.80	*c*
4-Methylphthalic anhydride	19438-61-0	5.66	5.72	−0.1
4-Chlorophthalic anhydride	118-45-6	4.54	4.00	+0.5
4-Nitrophthalic anhydride	5466-84-2	2.87	2.60	+0.4

[a] Reported values: 2.14 D,[5] 2.91 D.[10] [b] Reported: 2.28 D.[5] [c] Imaginary. [d] Reported: 2.60 D.[5]

Solvents and Apparatus. Spectrophotometric quality 1,4-dioxane[25] was refluxed in contact with sodium metal until the floating globules of molten sodium remained bright.[20] The dioxane was distilled through an 18-in. Vigreux column, and only the middle third of the distillate was used in the measurements. This distillation was always done on the same day on which the measurements were made.

A minimum of five solutions of each of the freshly sublimed compounds in the freshly distilled dioxane was prepared. Weight fractions of solutes fell in the range 10^{-3}–10^{-1}. The refractive indices of the dioxane and of the solutions were measured at 20.00° with either a Bausch and Lomb Type 3L Abbé refractometer or with a Bellingham and Stanley high-precision refractometer. The dielectric constants of dioxane and of the solutions were measured with a WTW Type DM01 dipolmeter,[26] using a Type DFL1 sample holding cell, also at 20.00°.

The dipolmeter was calibrated with spectrophotometric quality cyclohexane, benzene, carbon tetrachloride, and *n*-butyl ether, all of which had been stored over Type 4A molecular sieve for at least 1 week prior to the measurements. Dielectric constants for these liquids at 20° were those quoted by Oehme and Wirth.[22] This calibration was done six times at random intervals during an 8-month period, using new stocks of reference liquids, and found to be reproducible.

Results and Discussion

Calculations. The data from all of the calibration measurements were combined, and the method of least squares was applied to convert these measurements to a calibration equation for translating the dipolmeter readings to dielectric constants. The differences between the dielectric constants of the solutions and the solvent, $\epsilon_2 - \epsilon_1$, and the differences between the squares of the refractive indices, $n_2^2 - n_1^2$, were plotted against weight fraction of solute. If either of these plots showed curvature, sharp breaks, or scatter or failed to go through the origin, the entire set of measurements was repeated with fresh materials.

The slopes, a_n and a_ϵ, of the two plots were determined by the method of least squares. The dipole moment was then calculated from the difference $a_\epsilon - a_n$ by the equation[27]

$$\mu^2 = \frac{27kT}{4\pi N}\cdot\frac{M_2}{d_1(\epsilon_1 + 2)^2}\cdot(a_\epsilon - a_n) \qquad (1)$$

in which μ is the dipole moment in esu cm, k is the Boltzmann constant, T is the absolute temperature, N is Avogadro's number, M_2 is the molecular weight of the solute, d_1 is the density of dioxane at 20°, and ϵ_1 is the dielectric constant of dioxane at 20°.

The precisions of a_ϵ and a_n were calculated from the standard deviations of these slopes and the t factors at the 95% confidence level for the appropriate number of degrees of freedom. These limits were carried through the final calculations, and dipole moment values having precision limits wider than ±0.03 D were discarded. The results of the surviving measurements are presented in Table I.

Sources of Error. Early in this study a few sets of solutions were prepared on the night before the day on which the measurements were to be made. These measurements were later repeated with freshly purified materials and with all of the manipulations being done within 3–4 hr. The redeterminations gave dipole moments which were from 0.1 D larger for imides to as much as 0.7 D larger for anhydrides. The smaller values obtained in the earlier measurements were attributable to the effects of atmospheric oxygen and moisture on the dioxane and subsequent hydrolysis of the anhydrides by the absorbed moisture. It is felt that these effects have been satisfactorily minimized by the use of a short working time.

A source of difficulty inherent in the Guggenheim method lies in the problem of determining refractive indices with a sufficient degree of exactness.[20] The choice of dioxane as solvent has provided an advantage in this respect, since its refractive index is smaller than those of other suitable solvents, thereby giving larger values for $n_2^2 - n_1^2$ than would otherwise have been obtained. The compounds themselves provided a second minimization of this source of error, in that the slope a_ϵ was always one order of magnitude larger than the slope a_n and two orders of magnitude larger in the cases of the anhydrides.

Prediction of Dipole Moments. Predicted dipole moments of the imides and anhydrides were calculated by vectorial addition of group moments. In making these calculations, the assumptions made by Lumbroso and Dabard[5] and by Bakhshiev,[28] for predicting the dipole moments of phthalimides, were adopted and extended to the anhydrides. These assumptions are four in number. (1) The phthalimide and phthalic anhydride molecules are planar. (2) The vectors of the group moments, for the substituents used in this study, lie in the molecular plane. (3) The imide and anhydride moieties are electron withdrawing, and their group moment vectors bisect these groups. (4) The benzene ring is a perfect hexagon and makes no contribution to the total dipole moment. With these assumptions, the dipole moments of the appropriate monosubstituted benzenes may be taken as the group moments and added vectorially according to the equation[29]

$$\mu^2 = \mu_X^2 + \mu_Y^2 + 2\mu_X\mu_Y \cos\phi \qquad (2)$$

in which μ is the predicted moment, μ_X is the group moment for the substituent X, μ_Y is the imide or anhydride group moment, and ϕ is the angle between the vectors of μ_X and μ_Y. On the basis of the assumptions, an angle ϕ must be 90° for **1** and **5**, regardless of the nature of X. In the 4-substituted compounds, **2** and **6**, ϕ is 30° for electron-donating groups (X = CH_3) and 150° for electron-attracting groups (X = F, Cl, NO_2). Since the pyridine ring is not a perfect hexagon, the fourth assumption must be modified slightly for **3**, **4**, and **7**. The geometry of the pyridine ring[30] gives 89° for ϕ in **3** and **7**, and, since the pyridine nitrogen atom is electron-attracting,[31] 149° 10′ for ϕ in **4**.

The dipole moments of phthalimide, 2.17 D, and of phthalic anhydride, 5.34 D, obtained in the current study, were taken as the group moments for the imide and anhydride groups. In order to avoid discrepancies which might be introduced by differing solvent effects, or by differing procedures for evaluating dipole moments, the values for the group moments of the substituent groups were also based on data obtained for dioxane solutions, using the method and apparatus of this study to obtain the dipole moments of the appropriate monosubstituted benzenes. The resulting group moments were F, 1.53 D; Cl, 1.65 D; NO_2, 4.09 D; and the heterocyclic nitrogen of the pyridine ring, 2.27 D. These values are in good agreement with the values obtained by averaging the values listed by McClellan[4] for dioxane solutions of monosubstituted benzenes, which gave the results F, 1.51 D; Cl, 1.65 D; NO_2, 4.05 D; and pyridine, 2.22 D.

The dipole moment of toluene could not be obtained for a dioxane solution by the method and apparatus of this study. Plots of the experimental values of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction for such solutions repeatedly gave sets of random points with no recognizable linearity. Since no published value could be found for the dipole moment of toluene in dioxane, McClellan's[4] "best value" for the dipole moment of toluene, 0.43 D, was taken as the group moment for the methyl group. The difficulty of measuring the dipole moment of toluene in dioxane is apparently the result of the closeness of the dielectric constants of these two liquids, which have been reported[32] to be 2.209 for dioxane and 2.379 for toluene, at 25°. The predicted dipole moments are summarized in Table I for comparison with the experimental values.

Discussion. Earlier studies[5,10] have yielded values of 2.14 D and 2.91 D for the dipole moment of phthalimide in dioxane solution. The current finding of 2.17 D is in satisfactory agreement with the smaller of these values. The paper which reported the higher value also commented upon the tan color of phthalimide, which leads to the suspicion that the material used in that study was not pure, since pure phthalimide is white. The dipole moment of phthalimide in benzene solution has been reported[4] as 2.12 D. There have been no previous measurements of the dipole moment of phthalic anhydride in dioxane solution. Values resulting from measurements with other solvents are 4.71 D in benzene,[18] 5.29 D in benzene,[4] and 5.87 D in carbon tetrachloride.[18]

The dielectric constant data for all of the imides except phthalimide and the methylphthalimides showed changes in the slopes of the plots of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction in the vicinity of 10^{-2} weight fraction, and the measurements for these compounds were not extended to concentrations above this inflection point. This effect was particularly strong in the case of 4-nitrophthalimide, for which the plot of $n_2^2 - n_1^2$ *vs.* weight fraction also curved at the same point. The choice of concentration ranges upon which to base the dipole moment measurement apparently accounts for the differences between the dipole moments obtained in a prior study[5] and those of the current study, for 3-chlorophthalimide and 4-nitrophthalimide. The solutions utilized in the prior study fell in the concentration range 10^{-2}–10^{-1} weight fraction, above the inflection point in the dielectric constant curve.

In the case of 4-chlorophthalimide, the plot of $\epsilon_2 - \epsilon_1$ *vs.* weight fraction failed to go through the origin but was linear, at least up to 2×10^{-2} weight fraction, while the plot of $n_2^2 - n_1^2$ showed slight curvature at the higher concentrations. These results were reproducible. The slopes of the linear portions of the curves gave an apparent dipole moment of 1.01 D for 4-chlorophthalimide, which is smaller than the calculated value of 1.10 D, and appreciably smaller than the previously reported[5] value of 1.43 D, which was obtained from measurements made on more concentrated solutions.

No similar deviations were observed in the measurements made with the anhydrides or with the reference compounds. It is thus probable that the deviations observed with the phthalimide derivatives are the result of hydrogen-bonding interactions, either between the imides and dioxane, or between two imide molecules, or both. In very dilute solution, the predominant H-bonded species must be an association of one imide molecule with one dioxane molecule, and it is actually this species whose dipole moment was measured in this study.

Examination of the results reported in Table I shows that there is good agreement between the experimental and predicted dipole moments only for the 4-methyl compounds and for 3-fluorophthalimide and 3-methylphthalic anhydride. Fair agreement is observed with 3-fluorophthalic anhydride, 3-methylphthalimide, and quinolinimide. At the other extreme, agreement is very poor for 4-nitrophthalimide and 4-chlorophthalic anhydride, and extremely poor for both 3-nitro compounds and for cinchomeronimide. The general lack of agreement between experiment and prediction may indicate errors in the values used in eq 2 or the presence of factors not accounted for by this calculation.

The assumptions, upon which the predictive eq 2 is based, might better be called approximations, and they are not always good ones.[33] The assumptions adequately insert into the calculation the inductive effects of the substituent groups and the contributions to the dipole moment resulting from overlap of the π-electron cloud of the ring with π- or nonbonding electron clouds of individual substituent groups, that is, the mesomeric moments of these groups. The calculation does not allow for the transfer of charge across the π system of the ring from one group to another (the so-called interaction resonance), for any distortions in the geometry of the ring resulting from additional substitutions and probably not adequately for any major reorientations of the π-electron distribution of the ring resulting from the placement of two strongly electron-donating, or two strongly electron-attracting, substituents on the ring at an angle to each other. In the cases of compounds with substituents on adjacent carbon atoms, the calculation should provide adequately for ortho induction, but not for ortho-resonance interaction, for steric or electrostatic interactions through the space between the groups, or for intramolecular hydrogen bonding.

Two of the compounds with best agreement between predicted and experimental values are 4-methylphthalimide and 4-methylphthalic anhydride. For these compounds, all of the neglected factors must be absent, ex-

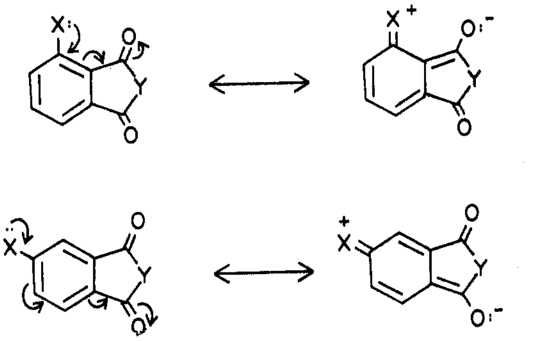


Figure 1. Resonance interactions in substituted phthalic anhydrides and phthalimides.

cept for the possibility of interaction resonance. Such interaction in these cases requires a contribution from π-σ conjugation or hyperconjugation. This always has an extremely small effect, whose contribution, beyond that already provided for in the group moment of the methyl group, must be less than the experimental error.

The remaining compounds with fair to good agreement between the experimental and calculated values include the 3-methyl and the 3-fluoro derivatives of phthalimide and phthalic anhydride. For these cases, the principal factor not considered in eq 2 is steric interaction between the substituent and the carbonyl group ortho to it. This interaction appears to have only a small effect.

The disagreements between the experimental and predicted moments can be treated quantitatively as an apparent interaction resonance. The interaction effects can be formally represented as depicted in Figure 1, which shows transfer of nonbonding electron charge from the substituent to a specific carbonyl oxygen. The interaction is ortho in the cases of the 3-substituted compounds and para for the 4-substituted compounds. No such formal transfer of charge can be proposed for the nitro compounds or the pyridine derivatives, since there is no basis for supposing electron donation by the nitro group, by the heterocyclic nitrogen, or by the carbonyl group in the electronic ground energy state. The competing attractive forces of these groups for electrons will, however, produce a rearrangement of the electron density distribution in the aromatic ring. There are probably also distortions in the geometries of both rings accompanying all rearrangements in electron distribution, but no estimates of this effect can be made from existing data. Since the three effects considered in this paragraph cannot be separately estimated, we propose to consider them together under the label of *ring polarization effects* and to calculate these effects for all of the compounds under consideration.

Minkin, *et al.*,[33] have proposed a relationship for calculating the interaction moments of para-disubstituted benzenes. For the reasons given above, we will redefine the values provided by this equation as *ring polarization moments.* This equation is

$$\mu_I^2 + 2\mu_I(\mu_X \cos\theta_X + \mu_Y \cos\theta_Y) + \mu_C^2 - \mu_E^2 = 0 \quad (3)$$

where μ_I is the ring polarization moment, μ_C is the predicted dipole moment, μ_E is the experimental dipole moment, μ_X and μ_Y are group moments of the interacting groups X and Y, and θ_X and θ_Y are the angles the vectors of these group moments make with the axis joining the ring carbons to which the interacting groups are bonded.

Since resonance interaction involves only one of the two carbonyls of the imide and anhydride groups, the group moments of these moieties must be resolved into two components to provide suitable values for use in eq 3. Models of the phthalimide and phthalic anhydride molecules showed that the angle between the two legs of the imide or anhydride groups is approximately 30°. Application of eq 2 with this angle and the experimental dipole moments of phthalimide and phthalic anhydride gave a moment of 1.12 D along each leg of the imide group and a moment of 2.76 D along each leg of the anhydride group. These values were defined as μ_Y in eq 3, and the previously defined group moments were defined as μ_X. The angles θ_X and θ_Y, respectively, were estimated as 0 and 15° for the 4-substituted compounds and 60 and 45° for the 3-substituted compounds. The ring polarization moments calculated for these values are listed in the last column of Table I. These results are felt to be meaningful only to the nearest 0.1 D at best, as the result of the uncertainties introduced in the values of θ_X and θ_Y, as well as in the calculation of μ_C.

True interaction moments are positive,[33] since they represent the transfer of charge across the ring, from a donor group to an acceptor group, with resulting enhancement of the dipole moment. Among the compounds considered in this study, this effect is certain only in the case of 4-chlorophthalic anhydride but may be a contributor in the cases of the 3-methyl compounds.

One possible interpretation of a negative ring polarization moment is that resonance interaction between a substituent and the ring has been reduced or suppressed. This must be the explanation for the negative ring polarization moments of the 3-fluoro and 3-chloro compounds. Steric interference between the halogen atom and the *o*-carbonyl reduces the interaction between the nonbonding pair and the π cloud. This effect is naturally larger with chlorine than with fluorine, since the larger chlorine atom is more subject to steric hindrance.

The small negative ring polarization moments observed for the 4-methyl compounds, on the other hand, are the result of the lack of a satisfactory group moment for the methyl group. If it is assumed that the ring polarization moments of the 4-methyl compounds are actually zero, then application of eq 2 with the experimental moments gives an average value of 0.39 D as the group moment for the methyl group for measurements made on aromatic compounds in dioxane solution. This is not really a significant change from the value of 0.43 D, since it reduces the calculated moments of the 3-methyl compounds by only 0.01 D.

Application of eq 3 to the data for the 3-nitro compounds and for quinolinimide and quinolinic anhydride gave only imaginary solutions for the ring polarization moments of these compounds. We interpret this to mean that values used for the angles ϕ and θ in eq 2 and 3 for these compounds were in considerable error. Steric effects in the 3-nitro compounds must force the nitro group out of coplanarity with the ring to a sufficient degree as to suppress the resonance interaction of the nitro group with the ring, producing substantially smaller dipole moments than the predicted ones. The group moment of the nitro group in this case also will be smaller than the one assumed in this study. In the cases of the pyridine derivatives, quinolinimide and quinolinic anhydride, the error lies in the assumption that the geometries of these compounds are similar to those of phthalimide and phthalic anhydride. The available data are unfortunately not adequate for the estimation of more accurate angles.

Erroneous geometry is also a contributing factor to the very large positive ring polarization moment of cinchomeromimide. Other factors may be involved, however, with this compound and with the 4-nitro compounds, which also show positive ring polarization moments. All three of these compounds have strongly electron-withdrawing groups acting in opposition to each other, with neither steric effects nor interaction resonance being possible. In such cases the aromatic ring becomes electron deficient and may act as an acceptor in charge-transfer complexation. Whether or not this effect, with dioxane acting as donor, accounts for the large dipole moments of these molecules is problematical.

Early in this study it was speculated that an enolized form of the imide might be stabilized by intramolecular hydrogen bonding in 3-fluorophthalimide and 3-nitrophthalimide. There is no chemical evidence for such enolization, however, and concurrent ultraviolet and infrared studies by one of us (L. Y. S.) failed to reveal any spectral evidence for it. Construction of models[34] of the enol forms showed that the enol hydrogen cannot be properly oriented to permit hydrogen bonding, either to a fluorine atom or to a nitro group in the 3 position.

Acknowledgments. We thank Miss Young Hee Yoon for assistance with the calculations, Miss Dorcas R. Wallace for assistance with the measurements, and Miss Piyada Sivatanpisit for assistance with some of the organic preparations. The authors are grateful to The Robert A. Welch Foundation for their financial support of this study, through Research Grant No. M-101.

References and Notes

(1) Ph.D. Dissertation, 1972.
(2) Ph.D. Dissertation, 1971.
(3) Welch Postdoctoral Fellow, 1972.
(4) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.
(5) H. Lumbroso and R. Dabard, *Bull. Soc. Chim. Fr.*, 749 (1959).
(6) A. Arcoria, H. Lumbroso, and R. Passerini, *Bull. Soc. Chim. Fr.*, 754 (1959).
(7) A. Arcoria, J. Barassin, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 2509 (1963).
(8) C. M. Lee and W. D. Kumler, *J. Amer. Chem. Soc.*, **83**, 4586 (1961).
(9) C. M. Lee and W. D. Kumler, *J. Amer. Chem. Soc.*, **84**, 565, 571 (1962).
(10) C. M. Lee and W. D. Kumler, *J. Org. Chem.*, **27**, 2055 (1962).
(11) C. M. Lee and W. D. Kumler, *J. Org. Chem.*, **28**, 1438 (1963).
(12) L. R. Caswell and P. C. Atkinson, *J. Org. Chem.*, **29**, 3151 (1964).
(13) L. R. Caswell and P. C. Atkinson, *J. Heterocycl. Chem.*, **3**, 328 (1966).
(14) L. R. Caswell and T. L. Kao, *J. Heterocycl. Chem.*, **3**, 333 (1966).
(15) L. R. Caswell and E. D. Martinez, *J. Chem. Eng. Data*, **13**, 286 (1968).
(16) L. R. Caswell, R. A. Haggard, and D. C. Yung, *J. Heterocycl. Chem.*, **5**, 865 (1968).
(17) F. C. Lee and L. R. Caswell, *J. Heterocycl. Chem.*, **8**, 831 (1971).
(18) R. A. Crump and A. H. Price, *Trans. Faraday Soc.*, **65**, 3195 (1969).
(19) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, London, 1969, pp 52–54, 82–88.
(20) H. B. Thompson, *J. Chem. Educ.*, **43**, 66 (1966).
(21) E. A. Guggenheim, *Trans. Faraday Soc.*, **45**, 714 (1949).
(22) F. Oehme and H. Wirth, "The Determination of the Molecular Electrical Dipole Moment," Kahl Scientific Instrument Corp., El Cajon, Calif.
(23) J. D. Hoskins, private communication.
(24) Microanalysis by PCR, Inc., Gainesville, Fla.
(25) Aldrich Chemical Co., Inc., Milwaukee, Wis.
(26) Kahl Scientific Instrument Corp., El Cajon, Calif.
(27) E. A. Guggenheim, *Trans. Faraday Soc.*, **47**, 573 (1951).
(28) N. G. Bakhshiev, *Opt. Spektrosk.*, **13**, 192 (1962).
(29) V. I. Minkin, O. A. Osipov, and Y. A. Zhdanov, "Dipole Moments in Organic Chemistry," translated by B. J. Hazzard, Plenum Press, New York, N. Y., 1970, pp 89–101.
(30) B. Bak, L. Hansen, and J. Rastrup-Andersen, *J. Chem. Phys.*, **22**, 2013 (1954).
(31) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1960, pp 167–168.
(32) A. A. Maryott and E. R. Smith, *Nat. Bur. Stand. (U. S.), Circ.*, **No. 514** (Aug 10, 1951).
(33) V. I. Minkin, O. A. Osipov, and Y. A. Zhdanov, ref 31, pp 204–217.
(34) Godfrey Stereomodels, Bronwill Scientific, Rochester, N. Y.

Synthesis of Phosphine Oxides from Phosphorus Esters and Alkyl Halides Using Either Sodium Bis(2-methoxyethoxy)aluminum Hydride or Sodium Aluminum Diethyl Dihydride[1,2]

Ronald B. Wetzel and George L. Kenyon*[3]

Department of Chemistry, University of California, Berkeley, California 94720, and Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143

Received February 5, 1974

Procedures are presented by which phosphorus esters (phosphates, phosphonates, and phosphinates) may be converted to phosphine oxides by reduction with either sodium bis(2-methoxyethoxy)aluminum hydride or sodium aluminum diethyl dihydride followed by addition of an appropriate primary or secondary alkyl halide. Yields are generally comparable to those obtained using a Grignard approach to the same conversions, but the procedures described offer the advantages of greater convenience and experimental simplicity. A number of examples of the synthetic method are presented including the preparations of the phosphorus-containing heterocycles, 1-phenylphospholane 1-oxide, and 1-phenylphosphorinane 1-oxide.

Only a few general approaches to the syntheses of phosphine oxides exist. The Arbuzov reaction of an alkyl halide with an ester of a phosphinous acid,[4] while giving respectable yields of phosphine oxides, is often rendered infeasible by the difficulty in obtaining the necessary phosphinate. Alkaline hydrolysis of quaternary phosphonium salts[5] likewise is only useful if an appropriate phosphonium salt is readily available. The reaction of Grignard reagents with various phosphorus esters[6] is generally more viable than the above methods, but it too has some disadvantages: there is an extra step, the synthesis of the Grignard reagent, and this reagent usually must be employed in large excess in the reaction with the phosphorus ester.[6,7]

We would like to report a new general procedure for the synthesis of phosphine oxides using the aluminum hydride reagents $NaAlH_2(CH_2CH_3)_2$ and $NaAlH_2(OCH_2CH_2OCH_3)_2$. Since some workers have encountered difficulties in attempting to carry out reactions with particular Grignard reagents or particular leaving groups on phosphorus, this new procedure complements the procedure using Grignard reagents. The procedure involves initial reaction of a phosphorus ester (phosphate, phosphonate, or phosphinate) with one of these two aluminum hydride regents to form an intermediate which subsequently reacts with an alkyl halide to form new carbon–phosphorus bonds. In Scheme I, R′ may be alkyl or aryl, and R″ may be a primary or secondary alkyl halide.

Results and Discussion

Addition of either $NaAlH_2(CH_2CH_3)_2$ or $NaAlH_2(OCH_2CH_2OCH_3)_2$ to a solution of a phosphinate