

17447-74-4; dimethyl 2-*n*-butylthio-3-butenylmalonate
17447-75-5.

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The Tscherniac-Einhorn Reaction. I. Equilibria in Solutions of N-Hydroxymethylphthalimide in Strong Sulfuric Acid

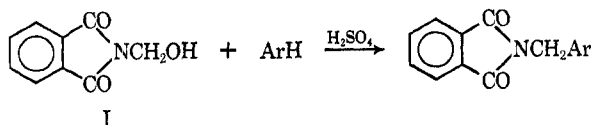
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Nmr, uv, and cryoscopic measurements have been combined with chemical methods to study the behavior of solutions of N-hydroxymethylphthalimide (I) in strong sulfuric acid. In 75% sulfuric acid the protonated substrate II begins to equilibrate rapidly with detectable amounts of the corresponding protonated sulfate ester III. Conversion into III is virtually complete in 94% acid, but over the range 75–100% acid, III also is in rapid equilibrium with the protonated bis(phthalimidomethyl) ether (IV). The ratio of III to IV (~2.3–2.5) appears to be relatively independent of acid concentration.

In 1901, Tscherniac reported the condensation of N-hydroxymethylphthalimide (I) with a series of aromatic compounds in strong sulfuric acid.¹ Later



Einhorn extended the reaction to a series of readily available N-hydroxymethylamides.² This aromatic substitution process thus has come to be known as the Tscherniac-Einhorn reaction.³ Of exceptional interest, however, is the powerful electrophilic reactivity of Tscherniac's original reagent, I, in strong sulfuric acid. More recent work has shown, for example, that benzoic acid undergoes *meta* substitution in 60% yield in 95% sulfuric acid at 10–15°. In 20% oleum at 50–60° even nitrobenzene is attacked at both *meta* positions,⁵ and 2,4-dinitrophenol is quantitatively substituted by I in 5% oleum at 100°. It was the purpose of the present work to study the behavior of I in strong sulfuric acid and to identify potentially reactive species or their precursors. A companion paper⁷ describes a kinetic study of the reaction of I with 2,4-dinitrophenol and the most likely mechanism.

Experimental Section

Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer. A Cary Model 14 spectrometer was used for the ultraviolet absorption spectra.

(1) J. Tscherniac, German Patent 134979 (1901); *Chem. Zentr.*, II, 1084 (1902).

(2) A. Einhorn, E. Bischoff, C. Ladisch, T. Mauermayer, G. Schupp, E. Spröngerts, B. Szelinski, and M. Göttler, *Ann. Chem.*, **343**, 207 (1905); **361**, 161 (1908); *Ber.*, **42**, 4837 (1909).

(3) (a) H. Hellmann, *Angew. Chem.*, **69**, 463 (1957); (b) R. Schröter in Houben-Weyl's "Methoden der organischen Chemie," Vol. 11, part I, E. Müller, Ed., 4th ed, G. Thieme, Stuttgart, 1957, pp 795–805; (c) H. E. Zaugg and W. B. Martin, *Org. Reactions*, **14**, 63 (1965).

(4) R. Oda, K. Teramura, S. Tanimoto, M. Nomura, H. Suda, and K. Matsuda, *Bull. Inst. Chem. Res., Kyoto Univ.*, **33**, 117 (1955); *Chem. Abstr.*, **51**, 11355b (1957).

(5) S. R. Buc, U. S. Patent 2,593,840 (1952); *Chem. Abstr.*, **46**, 6844 (1952).

(6) M. Yamaguchi, *Nippon Kagaku Zasshi*, **73**, 393 (1952); *Chem. Abstr.*, **47**, 10497e (1953).

(7) H. E. Zaugg, R. W. DeNet, J. E. Fraser, and A. M. Kotre, *J. Org. Chem.*, **34**, 14 (1969).

Materials.—Benzamide, mp 130°, was purified by recrystallization of the commercial material. N-Methylphthalimide, mp 133–134°, was prepared by alkylation of potassium phthalimide with dimethyl sulfate using the general method of Sheehan and Bolhofer.⁸ N-Hydroxymethylbenzamide, mp 103–105°,^{9a} and N-hydroxymethylphthalimide (I),⁹ mp 144–146° (from isopropyl alcohol), were prepared by reported methods.

Protonation of Amides and Imides in Sulfuric Acid.—Four compounds, benzamide, N-hydroxymethylbenzamide, N-methylphthalimide, and N-hydroxymethylphthalimide (I), were studied by the method of Davis and Geissman¹⁰ in which differences ($\Delta\epsilon$) in ultraviolet extinction at two selected wavelengths, in water and in 20 different concentrations (1–98.5%) of aqueous sulfuric acid, were measured. Plotting $\Delta\epsilon$ vs. acid concentration gave, for the first two compounds, a typical sigmoid titration curve from which the acid concentrations at half-protonation of the substrates could be estimated. By using 225 and 240 m μ as the analytical wavelengths for benzamide, it was found that this compound is half-protonated in 36% sulfuric acid.¹¹ Similarly, using 227 and 245 m μ as the analytical wavelengths, N-hydroxymethylbenzamide was found to be half-protonated in 50% sulfuric acid. Unfortunately, the ultraviolet spectra of the two phthalimides did not change with acid concentration as much as did the spectra of the two benzamides. Consequently, sharp-breaking curves were not obtainable, and only approximations of half-neutralization points could be made. Using 320 and 325 m μ as the wavelengths for N-methylphthalimide and 220 and 228 m μ for N-hydroxymethylphthalimide it could be estimated, roughly, that these imides are half-protonated somewhere in the range 60–70% sulfuric acid.

Quenching of Solutions of N-Hydroxymethylphthalimide (I) in Sulfuric Acid. Bis(phthalimidomethyl) Ether (V).—A solution of I (0.444 g) in 97.35% sulfuric acid (5 ml) was kept at 35° for 1 hr and then poured into vigorously stirred ice-water (50 ml). The precipitate (0.038 g, 9%, mp 203–205°) was collected at the filter, washed with cold water (10 ml), and dried. Recrystallization from glacial acetic acid gave a sample, mp 207–209°, identical (ir, nmr, and mixture melting point) with an authentic sample¹² of V. In nine runs, yields of 5–17% of V were obtained in 70–100% sulfuric acid at temperatures of 20–50°. Between 60 and 70% acid, the solution rate of I was so low that much longer times (8–16 hr) were required to give comparable yields. At concentrations below 60% acid, the low solubility of I precluded the occurrence of appreciable reaction.

(8) J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, **72**, 2786 (1950).

(9) S. R. Buc, *ibid.*, **69**, 254 (1947).

(10) C. T. Davis and T. A. Geissman, *ibid.*, **76**, 3507 (1954).

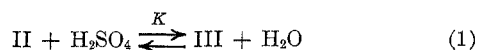
(11) Using the same conditions, J. T. Edvard and S. C. R. Meacock, [*J. Chem. Soc.*, 2000 (1957)] found that benzamide is half-protonated in 38% H₂SO₄.

(12) F. Sachs, *Ber.*, **31**, 1232 (1898); H. Bredereck, R. Gompper, H. Herlinger, and E. Weitun, *ibid.*, **93**, 2423 (1960).

Evidence for the Presence of a Sulfate Ester in Sulfuric Acid Solutions of I.—A solution of 0.4362 g (2.47 mmol) of N-hydroxymethylphthalimide (I) in 3.656 g (2 ml) of fuming sulfuric acid (0.48% SO₃) was quenched in 10 ml of cold water. Precipitated ether V (0.042 g, 10%) was removed by filtration and weighed aliquots (0.1–0.2 g) of the filtrate (13.10 g) were titrated with standard base. Over a 48-hr period the acid (H₂SO₄) titer of the filtrate increased by an amount equivalent to the hydrolysis of a 96 ± 8% yield of the sulfate ester III. A 25% yield of I (0.1114 g) also crystallized from the filtrate.

Cryoscopic Measurements.—The van't Hoff *i* factors for N-hydroxymethylphthalimide (I) and for bis(phthalimidomethyl) ether (V) in 100% sulfuric acid were determined by the method of Newman, Kuivila, and Garrett.¹³ An apparatus similar to theirs, but of all-glass construction, was obtained from Normag A.-G., West Germany. The compounds were introduced in the form of hard pellets. Three separate runs, each using three increments of I, gave a mean *i* factor of 3.46 (range 3.27–4.09) for this substance. Two runs, each using four increments, gave a mean value of 4.88 (range 4.62–5.21) as the *i* factor for V.

Nmr Examination of the Equilibrium between N-Hydroxymethylphthalimide (I–II) and Its Sulfate Ester III.—Preliminary experiments showed that 5% solutions of I in 77.5% sulfuric acid gave a single peak for the methylene protons at 358 Hz (*vs.* TMS in capillary). In 99% acid a single peak at 386 Hz was observed. At intermediate acid concentrations in this range two peaks were present. Although they both shifted downfield slightly (6 Hz total) with increasing acid strength, they maintained a constant separation (20–22 Hz). In many spectra, an intermediate broad band overlapping both main peaks was clearly discernible. Of particular significance for the present work, however, was the behavior of the two main peaks. With increasing acidity in this range (77–99% H₂SO₄, uncorrected), the downfield peak grew at the expense of the upfield one. In view of the results of the quenching experiments, the upfield peak could be assigned to the methylene protons of II (in equilibrium with its unprotonated form, I), the downfield peak to the sulfate ester III (and its unprotonated form) and the minor, intermediate band severely complicated attempts to use integrated areas as measures of the relative amounts of the two main components. For this reason, ratios of peak heights were used in the quantitative study of equilibrium 1.



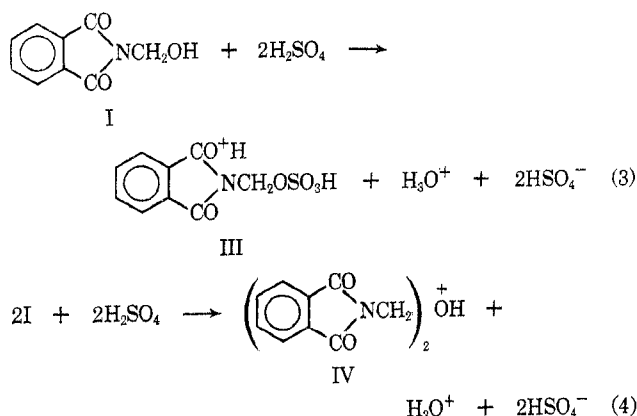
$$\log [\text{III}]/[\text{II}] = \log K - \log a_{\text{H}_2\text{O}} \quad (2)$$

Samples (50–100 mg each) of N-hydroxymethylphthalimide (I) were weighed into dry glass-stoppered weighing bottles. Sulfuric acid of known concentration (three titrations of weighed aliquots) was then weighed into each bottle in amounts sufficient to make solutions of 5 to 10% by weight. After solution was complete, samples were transferred to nmr tubes, and the nmr spectra were scanned in the region of interest (temperature of probe; 33 ± 2°). The ratio of the height of the downfield peak to that of the upfield peak was then taken as the value for [III]/[II] in eq 2. However, to determine the activity of water (*a*_{H₂O}) in each run it was necessary to know the concentration of the sulfuric acid at equilibrium. Corrections for the acid consumed and the water produced by the substrate therefore were made using two assumptions. In the range of acid concentrations covered, it was assumed that all solute species exist entirely in their monoprotonated forms,¹⁵ *i.e.*, II, III, and IV, and that

28% of the substrate exists as IV at equilibrium.¹⁶ From an expanded plot of per cent H₂SO₄ *vs.* log *a*_{H₂O}¹⁷ the equilibrium water activities could then be obtained. A total of 27 determinations were carried out covering corrected acid concentrations from 77.05% (–log *a*_{H₂O} = 1.91; log [III]/[II] = –0.7) to 92.36% (–log *a*_{H₂O} = 3.96; log [III]/[II] = 0.8). A simple linear regression analysis of a plot of –log *a*_{H₂O} *vs.* log [III]/[II] (*i.e.*, eq 2) gave a slope of 0.70 ± 0.04 (standard error) with intercept (*i.e.*, log *K*) – 2.14 (*K* = 0.0072).

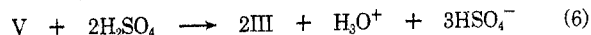
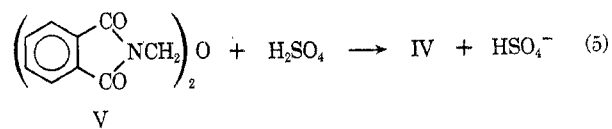
Results and Discussion

Interpretation of the Cryoscopic Results.—The quenching, nmr, and titration studies clearly show that strong sulfuric acid (>75%) converts N-hydroxymethylphthalimide (I) into a mixture of its sulfate ester and bis(phthalimidomethyl) ether (V) with the former predominating. Furthermore, the uv protonation work, as qualitative as it is, show that *at these acid concentrations* all species present must be substantially protonated. Thus, when I is dissolved in ~100% sulfuric acid, reactions 3 and 4 proceed essentially to completion.



Reaction 3 has a theoretical *i* factor of 4 and reaction 4 an *i* factor of 2. On this basis the observed *i* factor (3.46) indicates that in ~100% acid, 73% of the substrate exists as III.

Similarly, when the ether V is dissolved in the acid, reactions 5 and 6 occur. These processes have theo-



retical *i* factors of 2 and 6, respectively. Again, on this basis, the experimental *i* factor (4.88) indicates that 72% of the substrate exists as III, in good agreement with the result obtained from I.

It should be noted, however, that the ether V contains more than one basic center¹⁸ and, conceivably, could exist in a diprotonated form. On this basis, the reactions leading to a diprotonated ether from I and V would have theoretical *i* factors of 2.5 and 3,

(16) This again is an assumption possibly leading to error. However, the quenching experiments gave comparable yields of V over the whole range of acid concentrations used in the nmr study, and the experimentally more reliable measure of the equilibrium concentration of IV (*i.e.*, 28%) derived from the cryoscopic work in ~100% acid provides the more dependable estimate.

(17) N. C. Deno and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **76**, 244 (1954).

(18) J. L. O'Brien and C. Niemann [*ibid.*, **79**, 1388 (1957)] showed that phthalimide is monoprotonated in 100% sulfuric acid. Hence, in this system, the two carbonyl groups serve as a single basic center.

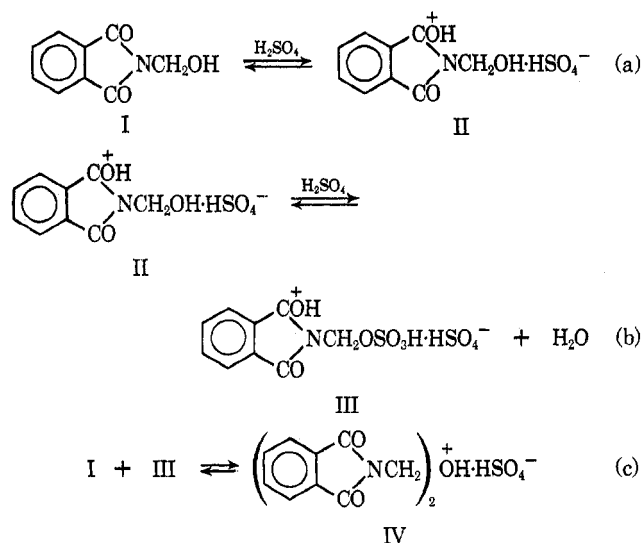
(13) M. S. Newman, H. G. Kuivila, and A. B. Garrett, *J. Amer. Chem. Soc.*, **67**, 704 (1945).

(14) These assignments also are consistent with the observed relative chemical shifts (in CDCl₃ *vs.* TMS in solution) of the methylene protons of the following compounds: I, 316 Hz; V, 319 Hz; I acetate, 344 Hz; I trifluoroacetate, 357 Hz. The minor downfield shift (~6 Hz) with increasing acidity observed for the two main peaks in sulfuric acid can be viewed as a manifestation of increased protonation of the two chief components, *i.e.*, II and III.

(15) Admittedly, this is a simplifying assumption that introduces the possibility of error, especially at the lower end of the acid concentration range. However, sample calculations showed that errors arising from the consequence of assuming 100% protonation as opposed to 50% protonation (certainly a lower limit in view of the ultraviolet studies) are small relative to the errors inherent in the measurement of relative nmr peak heights.

respectively; the observed results would lead to 64 and 63%, respectively, as the calculated proportion of the substrate existing as the sulfate ester III. The nmr results, as interpreted in the following section, favor the first alternative (*i.e.*, monoprotonation of V).

Interpretation of the Nmr Results.—The observed deviation of the water activity ($a_{\text{H}_2\text{O}}$) dependence of the ratio [III]/[II], from that required by equilibrium b, *i.e.*, 0.7 vs. 1.0, can be explained in three ways.



First, the ratio of the thermodynamic activities of III and II may not equal the ratio of their concentrations. However, in view of their close structural and charge-type similarity, a deviation of the magnitude observed appears unreasonable on this basis. Second, a 30% greater degree of hydration of III compared with II could explain the deviation, but here again structural similarity would tend to rule out this possibility especially under the prevailing conditions. In the presence of the large excess of strong sulfuric acid it is unlikely that III could undergo hydration to the required extent.¹⁹ Third, the deviation can be explained if III is partially consumed in a competing process that does not affect the equilibrium concentration of II. It is significant that such a process is pre-

(19) J. De Luis (Ph.D. Thesis, The Pennsylvania State University, University Park, Pa., 1964) studied equilibria of type $\text{R}_2\text{N}^+\text{HCH}_2\text{OH} \rightleftharpoons \text{R}_2\text{N}^+=\text{CH}_2 + \text{H}_2\text{O}$

and observed *greater* than unit slopes for plots of $\log [B]/[A]$ vs. $\log a_{\text{H}_2\text{O}}$. This deviation was ascribed to excess hydration of A over B. In this work, however, the equilibria were observable in relatively dilute (30–60%) sulfuric acid solutions in which substrate hydration is more likely.

cisely the one most likely to lead to the ether IV in a *fast* equilibrium, namely, reaction c. By reacting with an equimolar quantity of I, III perturbs equilibrium a in the reverse direction by an amount equal to the forward perturbation of equilibrium b that results from the consumption of III in reaction c. Consequently, the equilibrium concentration of II, at a given acid concentration, is the same as if reaction c did not exist. On this basis, the observed deviation (0.30) from theory should equal the fraction of III + IV that is present as IV under equilibrium conditions. The cryoscopic results (assuming formation of the monoprotonated form, IV) are in quantitative agreement with this conclusion.

Further considerations support the plausibility of this interpretation. Of the several substrate species (*i.e.*, I, II, III, and uprotonated III) present at kinetically significant concentrations in the range of acid strengths studied, the protonated ester III should be the most reactive electrophile. This follows not only from structural considerations (a good leaving group next to a proton) but from the high value (~ 140) observed for the equilibrium constant of its reaction with water to give II (the reverse of reaction b). Furthermore, the basicity of I is no greater than that of water, and is probably considerably less,^{20–22} so that concentrations of I, at any given acid strength, should be sufficient to compete with water for the available III.^{23,24}

Registry No.—I, 118-29-6; sulfuric acid, 7664-93-9.

Acknowledgment.—We are grateful to Mrs. Ruth Stanaszek and to Mr. William Washburn for the nmr and ir spectra, respectively.

(20) The basicity of water in sulfuric acid is still a matter of some doubt. Deno²¹ states that water would have a basicity comparable with alcohols (*i.e.*, half-protonation in 40–50% sulfuric acid) while Arnett²² assigns to water a pK_a of -5.9 to -6.66 (half-protonation in 60–65% acid).

(21) N. C. Deno in "Survey of Progress in Chemistry," A. F. Scott, Ed., Academic Press, New York, N. Y., 1964, pp 159, 163.

(22) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 283 (1963).

(23) This is not meant to imply that reaction c is the only one that can produce the ether V (or IV). Quenching of sulfuric acid solutions much too dilute to show (nmr) the presence of III still led to appreciable yields of V provided that sufficient time was allowed for equilibration. Thus V can be formed, presumably, by reaction of II with I or of II with the unprotonated form of III. The important point is that only equilibrium c is fast enough to perturb the other two equilibria to a significant degree.²⁴

(24) Proton transfer to and from oxygen (reaction a) are, of course, known to be very fast processes, and in all of the nmr determinations of the ratio of III to II there was no indication that anything but "instantaneous" equilibration occurred whether one started with I (reactions a and b) or with V (reactions c and b).