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CYCLIC CARBOXYLIC MONOIMIDES

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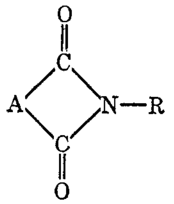
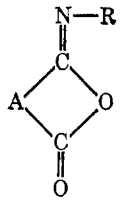
Contents

I. Introduction

The chemistry of aliphatic imides has been briefly reviewed up to the year 1936 by Amagat.[1] Up to that time imides were regarded as derivatives of acids and were not looked upon as a separate class of compounds with broad industrial or pharmacological applications of their own, as is now the case. As with so many other classes of compounds, reliable measurements of their physical properties have only been available within the last 10 years. In general imides are the diacyl derivatives of ammonia or of a primary amine. This review has been confined essentially to monocyclic dicarboxylic monoimides of general formula I, where A is an aliphatic, alicyclic, or aromatic divalent group. These restrictions were imposed so as to exclude compounds like uric acid, alloxan, barbiturates, and others on which there is also an extensive literature. The N-halo derivatives of imides have also been largely excluded, because separate reviews of the reactions of these are available.[2–4] To a minor extent this review does include isoimides of the formula II.



I



II

Monocyclic carboxylic imides may be regarded as compounds derived from the corresponding dicarboxylic acids and ammonia by the elimination of water, and, since many aliphatic dicarboxylic acids are known by common names, we have classified the imides in terms of the common names of the parent acids. This system is not in conflict with the IUPAC nomenclature because the discussion is mainly confined to ring systems with less than seven atoms in the ring. For example, the names malonimide, succinimide, glutarimide, maleimide, phthalimide, and naphthalimide are in common use. The locations of substituents on carbon are indicated by numbers taking one of the carboxyl carbons as position 1, following the usual practice for the acids. If the location of a substituent on carbon is unambiguous, the number is omitted. Substitution of simple groups on nitrogen is denoted by the prefix N. 2-Aminosuccinimide and 2,3-dihydroxysuccinimide are named aspartimide and tartrimide, respectively.

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(1) P. Amagat, "Traite de Chemie Organique," Vol. XIII, V. Grignard, Ed., Masson, Paris, 1941, pp 502–521.

(2) C. Djerassi, *Chem. Rev.*, **43**, 272 (1948).

(3) L. Horner and E. H. Winkelmann in "Newer Methods of Preparative Organic Chemistry," Vol. III, W. Foerst Ed., Academic Press, New York, N. Y., 1964, p 151.

(4) R. Filler, *Chem. Rev.*, **63**, 21 (1963).

Substituents on the carbon of aromatic imides are numbered so that position 1 is the point of attachment of one of the carbonyl groups, as for the corresponding acids, and the orientation of the imide ring with respect to the fused aromatic ring is indicated by numbers if necessary. This system is generally simpler to comprehend than the standard heterocyclic nomenclature. For example, N-ethyl-3-nitrophthalimide is more immediately informative than 2-ethyl-5-nitroisoindole-1,3-dione, and methylmaleimide (citraconimide) is simpler than 3-methylpyrrole-2,5-dione.

In general, our literature survey comprises material available in *Chemical Abstracts* up to May 1969. In our discussion of chemical properties, only the imide function is generally considered and not the properties of other functional groups, but the properties of the imide function are, of course, affected by substitution on the nitrogen and on adjacent carbon atoms. Thus, while N-substituted[5] and C-substituted[6] derivatives of a stable monomeric malonimide have been known for many years and are quite stable, the existence of the parent compound is doubtful.[7] Likewise, the N-substituted tartrimides[8] and malimides[9] have been known for many years, while the parent compounds have only recently been prepared.[10] Also, for example, measurements of the rates of alkaline hydrolysis of tartrimide and malimide show that their ring systems are much less stable than that in succinimide.[7]

It is perhaps curious that simple cyclic imides do not occur either free or in the combined state in nature as do other classes of organic compounds such as carbohydrates, esters, acids, etc. This is particularly curious because the –CONH– sequence occurs in proteins. Succinimide was prepared as early as 1835,[11] not long after the first synthesis of an organic compound from inorganic material by Wohler in 1829.

It is, however, only in recent years that the study of the chemistry of imides has been given particular impetus, because of the discovery of their pharmacological and other industrial uses. For example, derivatives of imides have proved to be important medicinal agents and have been suggested for use in the treatment of arthritis,[12] tuberculosis,[13] convulsions, and epilepsy,[14] to mention only a few. Succinimide, glutarimide, maleimide, and a variety of their derivatives have been investigated for their usefulness in this connection. A number of imides can be used to stimulate the growth of plants and seedlings during the early stages of germination; *e.g.*, 2,4-dichlorophenylsuccinimide stimulates the growth of wheat and radish seedlings.[15] Conversely, other imide derivatives have been used as fungicides[15] and as herbicides.[16] The surface active properties of some imides assist their insecticidal and fungicidal properties, but N-alkyl sulfonate derivatives of succinimide can be used simply as detergents.[17]

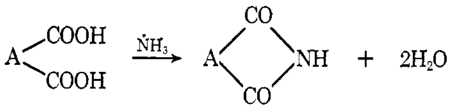
Aromatic imides are used successfully as brightening agents in the laundry and allied industries.[18] N-Vinylimides may be polymerized alone or copolymerized with, for example, ethylene to give useful polymers of high molecular weight, which may be converted into further derivatives.[19, 20]

II. Synthesis of Imides

A. GENERAL METHODS

There are a number of related methods of general applicability which may be used for the preparation of most simple aliphatic imides, and these are discussed below in this section. Section II.B lists, under the name of the imide concerned, methods of less general applicability, and this section particularly applies to aromatic and alicyclic imides in which the nature of the ring system sometimes allows special methods to be used.

1. Reaction of the Corresponding Acid with Ammonia



Where the raw materials are readily available, the most suitable starting point for the cyclization necessary to produce an imide is the corresponding acid. This may be heated to a temperature of not more than 200° with an equimolecular proportion of ammonia[21] or a compound which can produce ammonia, or a substituted derivative of ammonia, such as urea,[22] thiourea,[23] formamide,[24] dicyandiamide,[25] nitriles,[26] dicyanide,[27] sulfamic acid,[28] ethnanolamine,[29] sodium azide,[30] or ammonium carbonate.[31] It has been suggested that the reaction of the acids may in some cases proceed *via* the formation of the acid anhydride. Satisfactory yields (60–80%) of succinimide, glutarimide, maleimide, phthalimide, and their N-substituted derivatives may be obtained this way. This method is also satisfactory for the cyclization of aliphatic acids that are substituted on carbon by alkyl or aryl groups, and of aromatic acids with a wide range of substituents like

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(5) W. H. Warren and R. A. Briggs, *Ber.*, **64B**, 26 (1931).

(6) G. Zinner and R. Moll, *ibid.*, **99**, 1292 (1966).

(7) H. R. Dave and M. K. Hargreaves, unpublished work.

(8) P. F. Frankland and A. Slator, *J. Chem. Soc., London, Trans.*, **83**, 1349 (1903).

(9) A. E. Arppe, *Ann.*, **96**, 110 (1855).

(10) H. R. Dave and M. K. Hargreaves, *Chem. Commun.*, 743 (1967).

(11) F. Darcet, *Ann. Chim. Phys.*, **58**, 294 (1835).

(12) O. H. Buchanan and R. H. Freyberg, *J. Pharmacol. Exp. Ther.*, **82**, 391 (1944).

(13) D. Twomey, *Proc. Roy. Irish Acad., Sect. B*, **57**, 39 (1954).

(14) D. T. Davidson and C. Zombroso, *New Engl. J. Med.*, **251**, 853 (1954).

(15) S. E. Allen and F. Skoog, *Plant. Physiol.*, **27**, 179 (1952).

(16) E. J. Frazza and L. Rapoport (to American Cyanamid Co.), U. S. Patent 2,992,223 (1961); *Chem. Abstr.*, **56**, 332 (1962).

(17) V. R. Gaertner (to Montsanto Chemical Co.), U. S. Patent 3,029,250 (1962); *Chem. Abstr.*, **57**, 3583 (1962).

(18) T. Maruyama, D. Kohayashi, N. Kuroki, and K. Kohishi, *Kogyo Kagaku Zasshi*, **68**, 1707 (1965).

(19) D. D. Reynolds and W. O. Kenyon (to Eastman Kodak Co.), U. S. Patent 2,566,250 (1951); *Chem. Abstr.*, **46**, 778 (1952).

(20) W. E. Hanford and J. R. Roland (to E. I. du Pont de Nemours and Co.), U. S. Patent 2,402,136 (1946); *Chem. Abstr.*, **40**, 5602 (1946).

(21) R. R. Buckles and W. J. Probst, *J. Org. Chem.*, **22**, 1728 (1957).

(22) A. Rahman and M. O. Farooq, *Curr. Sci.*, **21**, 338 (1952).

(23) A. Rahman, M. A. Medrano, and O. P. Mittal, *Rec. Trav. Chim. Pays-Bas*, **79**, 188 (1960).

(24) S. Sugasawa and H. Shigehara, *J. Pharm. Soc. Jap.*, **62**, 531 (1942).

(25) M. T. Dangyan, *Bull. Arm. Br. Acad. Sci. USSR*, No. 9/10 (23/24) 53 (1942); *Chem. Abstr.*, **40**, 3399 (1946).

(26) R. Seldner, *Amer. Chem. J.*, **17**, 533 (1895).

(27) J. Mathews, *ibid.*, **20**, 654 (1898).

(28) A. V. Kirsanov and Y. M. Zolotov, *Zh. Obshch. Khim.*, **20**, 1145 (1950).

(29) A. O. Jaeger and L. C. Daniels (to Selden Research and Engineering Corp.), U. S. Patent 1,968,253 (1931); *Chem. Abstr.*, **28**, 5835 (1934).

(30) S. Marburg and P. A. Grieco, *Tetrahedron Lett.*, 1305 (1966).

(31) V. M. Rodionov and A. M. Fedorova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 247 (1950); *Chem. Abstr.*, **44**, 9395 (1950).

NO_2, NH_2, halogens, and alkyl groups.[32,33] A modification which may enable the reaction temperature to be lowered involves the heating of a neutral[34,35] or acid ammonium salt[36] of the corresponding acid.

2. *Action of Ammonia on the Acid Halide*

The heating of the appropriate acid halide with an ammonium halide under anhydrous conditions can bring about the formation of cyclic imides such as succinimide, phthalimide, and tetrahydrophthalimide, as well as certain straight-chain imides.[37]

3. *Action of Sodium Ethoxide on the Diester*

The cyclic imide is frequently obtained when the appropriate diester is warmed with sodium ethoxide solution in the presence of ammonia or other compounds such as urea,[38] thiourea,[38] or sodium benzamide.[39]

4. *From the Corresponding Amido Ester*

A method which has the advantage of working at room temperature or thereabouts is the cyclization of the half-ester half-amide with sodium alkoxides,[40] alkalis,[41] or the alkali metals[36] in nonaqueous media to remove the elements of water or alcohol.

5. *From the Corresponding Diamide or the Ammonium Salt of the Monoamide*

These substances are simply heated.[42,43] In certain instances the reaction has been assisted by the addition of substances

$$NH_2COACONH_2 \xrightarrow{\text{heat}} \underline{COACONH} + NH_3$$

$$NH_2COACOONH_4 \xrightarrow{\text{heat}} \underline{COACONH} + NH_4OH$$

such as zinc chloride or phosphorus pentoxide.[44]

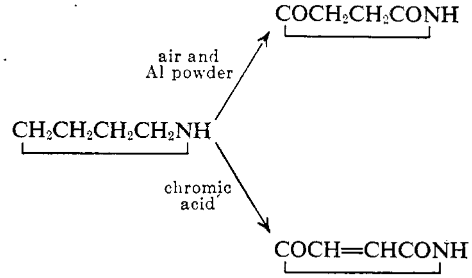
6. *Partial Hydrolysis of the Nitrile and Cyclization of the Half-Nitrile Half-Amide*

The dinitrile can be treated with an acidic hydrolyzing agent such as hydrochloric or sulfuric acid in water.[45] Succinimide can be prepared, for example, by treatment of a solution of acrylonitrile in dilute sulfuric acid with sodium cyanide.[46] Succinimide has also been prepared by the heating of succinonitrile with water and the salts or oxides of di- or trivalent metals.[47]

$$CNACN \xrightarrow{H_2O} CNACONH_2 \xrightarrow{H_2O} \underline{COACONH} + NH_3$$

7. *Oxidation Methods*

The oxidation of α-nitronaphthalene[48] with air, or *o*-xylene[49] with air in the presence of ammonia and a metal oxide catalyst (*e.g.*, V_2O_5), yields phthalimide. Similarly, succinimide has been obtained by the oxidation of pyrrole with hydrogen peroxide,[50] or by passage of pyrrole over aluminum powder in air.[51] Piperidine yields glutarimide by the same process.[52]



The use of chromic acid for the oxidation of pyrrole yields maleimide.[53] Electrolytic oxidation of a pyrrolidonecarboxylic acid in dilute sulfuric acid, with lead oxide, platinum, or carbon electrodes, gives succinimide.[54]

8. *Preparation of Imides from Alkanes*

The possibility of the manufacture of imides from alkanes has been shown by developments in the petrochemical industry. Alkanes, cycloalkanes, or olefins containing at least seven carbon atoms can be treated in the vapor phase with ammonia and oxygen to yield small amounts of imides in the presence of one or more of the following metals or compounds thereof as catalysts: copper, silver, tin, vanadium, uranium, and metals of the fifth, sixth, seventh, and eighth groups of the periodic table.[55]

9. *Reaction of Unsaturated Aliphatic Amides with Carbon Monoxide*

This reaction is carried out under pressure in the presence of catalysts such as Raney cobalt, cobalt salts, or cobalt carbonyls.[56] The yield varies from 65 to 96%, and the imides

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(32) G. Ya. Kondrat'eva and C.-H. Huang, *Zh. Prikl. Khim.* (Leningrad), **35**, 199 (1962).

(33) A. P. Karishin and D. M. Kustol, *Zh. Obshch. Khim.*, **28**, 692 (1958).

(34) A. Freund, *Ann.*, **69**, 402 (1849).

(35) O. Bernheimer, *Gazz. Chim. Ital.*, **12**, 281 (1882).

(36) H. Werbin and P. E. Spoerri, *J. Amer. Chem. Soc.*, **69**, 1681 (1947).

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(38) G. Roeder, *Ber.*, **46**, 2563 (1913).

(39) A. W. Titherley, *J. Chem. Soc.*, **85**, 1673 (1904).

(40) A. T. de Mouilpied and A. Rule, *ibid.*, **91**, 178 (1907).

(41) F. S. Legagneur, *Bull. Soc. Chim. Fr.*, 411 (1956).

(42) C. Bulow, *Ann.*, **236**, 188 (1886).

(43) G. Paris, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **33**, 1724 (1955).

(44) P. Bruylants and J. Jennen, *Bull. Cl. Sci. Acad. Roy. Belg.*, **22**, 1141 (1936).

(45) E. N. Zilberman and P. S. Pyryalova, *Zh. Org. Khim.*, **1**, 983 (1965).

(46) Ciba Ltd., Swiss Patent 275,798 (1951); *Chem. Abstr.*, **47**, 1732 (1953).

(47) H. Bergs, German Patent 730,518 (1942); *Chem. Abstr.*, **38**, 381 (1942).

(48) A. G. Green and S. J. Green (to British Dyestuffs Corporation Ltd.), British Patent 183,044; *Chem. Abstr.*, **16**, 4215 (1922).

(49) D. J. Hadley and B. Wood (to Distillers Co. Ltd.), U. S. Patent 2,838,558 (1958); *Chem. Abstr.*, **52**, 17191 (1958).

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(51) A. C. Ray and S. B. Dutt, *J. Indian Chem. Soc.*, **5**, 106 (1928).

(52) R. Wolffenstein, *Ber.*, **25**, 2777 (1892).

(53) G. Plancher and F. Cattadori, *Atti Reale Accad. Lincei*, [5] **13**, I, 490 (1904).

(54) H. Tunoda and S. Ono (to K. K. Suzuki Shôten), Japanese Patent 93,991 (1931); *Chem. Abstr.*, **27**, 1365 (1933).

(55) Toyo Rayon Co., French Patent 1,336,453 (1963); *Chem. Abstr.*, **60**, 2861 (1964).

(56) J. Falbe and F. Korte, *Ber.*, **95**, 2680 (1962).

which have been obtained are succinimide, methylsuccinimide, cyclohexane-1,2-dicarboximides, and glutarimide as shown below, *e.g.*

$$CH_2{=}CHCH_2CONH_2 + CO \longrightarrow \underline{COCH_2CH_2CH_2CONH}$$

B. SPECIAL METHODS

1. *Succinimide*

Succinonitrile may be treated in dry methanol solution with liquid ammonia to yield 2,5-diiminopyrrolidine, which may then be hydrolyzed in two steps to give succinimide.[57] Succinonitrile reacts with hydroxylamine in warm aqueous alcohol solution to give 5-hydroxyimino-2-pyrrolidone, which can then be treated with sodium nitrile in aqueous acid so that succinimide is obtained.[57]

$$CNCH_2CH_2CN \xrightarrow[-NH_3]{\substack{+NH_2OH \\ +H_2O}}$$

$$\underline{CNOHCH_2CH_2CONH} \xrightarrow[\substack{-N_2 \\ -H_2O \\ -NO_3^-}]{\substack{+HNO_2 \\ +NO_2^-}}$$

$$\underline{COCH_2CH_2CONH}$$

It is claimed that the treatment of 3-cyanopropionaldehyde with silver oxide yields almost 50% of succinimide.[58] The refluxing of aqueous sodium cyanide and bis(2-chloroethyl) ether is reported to yield some succinimide.[59] Sulfur mono chloride (S_2Cl_2) in dioxane can be used to promote the intramolecular elimination of ammonia from succinic acid diamide to give succinimide.[60] (Attempts have been made to apply this method to a wide range of diamides, but it has been successful only in the cases of succinimide and glutarimide). Succinimide may be obtained by the oxidation of 2-formylpyrrole with hydrogen peroxide.[61] The condensation of chloroacetamide with ethyl sodioacetoacetate gives acetylsuccinimide.[62]

2. *Glutarimide*

Glutarimide has been obtained by the distillation of a mixture of γ-butyrolactone and powdered anhydrous sodium cyanide at 200°,[63] and by the action of S_2Cl_2 in dioxane on glutaric acid diamide, as mentioned above in section B.1.[59]

3. *Adipimide*

This imide can be obtained in 25% yield by the heating of the wet hydrochloride of 5-cyano-1-hydroxypentylidenimine at 180°.[64] Also, adipimide can be prepared by the action of

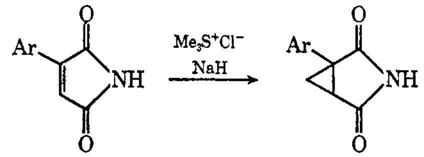
$$CN(CH_2)_4C(OH){=}NH_2^+Cl^- + H_2O \longrightarrow \underline{CO(CH_2)_4CONH} + NH_3 + HCl$$

heat on cyanovaleric acid at 230°.[65] The Beckmann rearrangement of 1,2-cyclohexanedione dioxime in liquid sulfur dioxide yields 1-aza-7-oximocycloheptan-2-one, which is cyclized by thionyl chloride to adipimide.[66]

4. *Alicyclic Imides*

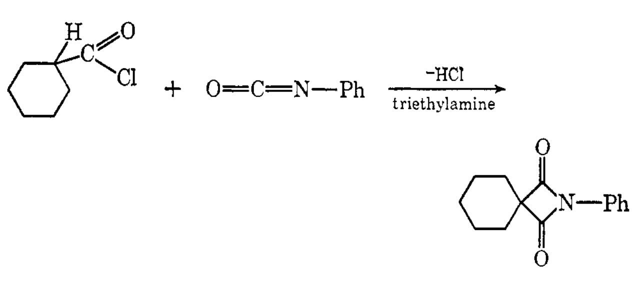
In general, these may be prepared by the methods discussed above in sections B.1, 2, and 3. Some more specialized methods are given below. The spiroimides with various ring sizes may also be obtained by the general methods.

1,2-Cyclopropanedicarboximide is only known in the form of its substituted derivatives. 1-Aryl-1,2-cyclopropanedicarboximides have been obtained by the addition of trimethylsulfoxonium chloride to a suspension of sodium hydride in tetrahydrofuran, followed by addition of the corresponding arylmaleimide; the mixture was first refluxed and then cooled.[67]



The *cis* and *trans* 1,2-dimethylcyclopropane-1,2-dicarboxylic acid anhydrides can be obtained by the condensation of diazomethane with the dimethyl ester of dimethylmaleic acid; each anhydride can then readily be heated with aniline to convert it to the corresponding N-phenyl-1,2-dimethylcyclopropane-1,2-dicarboximide.[68]

cis-Cyclohexene-1,2-dicarboximides can be prepared by the general methods and hydrogenated to the cyclohexane derivatives over platinum in acetic acid.[69] Phthalimide may be similarly reduced. An interesting example of the preparation of a cyclohexane-1,1-dicarboximide derivative has been demonstrated fairly recently.[70] Cyclohexanecarbinyl chloride is condensed with phenyl isocyanate in benzene solution at 25° by the addition of triethylamine:



The reaction may proceed by way of the benzoyl carbonium ion (or its ion pair with triethylamine) which may add to the nitrogen of the isocyanate, but there appears to be no precedent on which to base such a supposition. Alternatively, the condensation may take place through pentamethyleneketene,

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(57) J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 442 (1954).

(58) T. Komatsu, R. I. Wanaga, and J. Kalo (to Ajinomoto Co. Inc.), Japanese Patent 26,357 (1963); *Chem. Abstr.*, **60**, 5343 (1964).

(59) H. Wolz, German Patent 713,748 (1941); *Chem. Abstr.*, **38**, 1533 (1944).

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(61) R. Scarpati and C. Santacroce, *Rend. Accad. Sci. Fis. Mat., Naples*, **28**, 27 (1961).

(62) H. Gault and J. Champion, *C. R. Acad. Sci., Paris*, **232**, 851 (1951).

(63) W. Reppe, *Ann.*, **596**, 198 (1955).

(64) A. E. Kulikova and E. N. Zilberman, *Zh. Obshch. Khim.*, **30**, 596 (1960).

(65) E. N. Zilberman, *ibid.*, **25**, 2127 (1955).

(66) N. Tokura, R. Tada, and K. Yokoyama, *Bull. Chem. Soc. Jap.*, **34**, 1812 (1961).

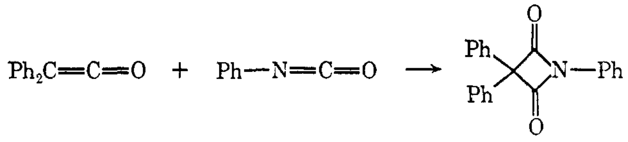
(67) P. T. Izzo, *J. Org. Chem.*, **28**, 1713 (1963).

(68) K. von Auwers and O. Ungemach, *Ann.*, **511**, 152 (1934).

(69) H. R. Snyder and G. I. Poos, *J. Amer. Chem. Soc.*, **72**, 4104 (1950).

(70) A. C. Poshkus and J. E. Herweh, *J. Org. Chem.*, **30**, 2466 (1965).

by analogy with the observed reaction of diphenylketene with phenyl isocyanate to yield N-phenyldiphenylmalonimide,[71] although this appears to require vigorous conditions (220°).[72]



Saturation of a solution of cycloheptanone and ethyl cyanoacetate in absolute ethanol with ammonia at 0° is reported to give, after acidification, the imide of cycloheptane-1,1-bis(cyanoacetic acid).[72]

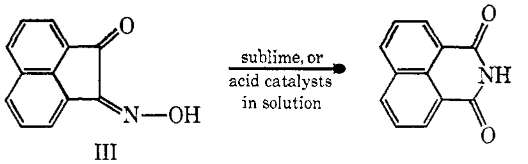
5. *Phthalimide*

This is most straightforwardly obtained by the general methods, of course, but it has also been obtained from a number of unusual starting materials and routes. The treatment of ethyl phthalate with magnesium aminoiodide in ether and decomposition of the product with water yields phthalimide.[73] Isatoic anhydride (N-carboxyanthranilic acid anhydride) yields a certain amount of phthalimide by reaction with ammonia, the yield being determined by the relative concentration of the latter.[74] The catalytic vapor-phase oxidation of isoquinoline yields phthalimide as a major product, with pyridine as a by-product.[75]

6. *Naphthalimides*

The 1,2-, 2,3-, and the 1,8-naphthalimides may be obtained by the general methods. For example, 1,8-naphthalamide at high temperatures gives 1,8-naphthalimide.[76]

Acenaphthenequinone monoxime (III) rearranges when it is heated in a tube at 250° to give a sublimate of 1,8-naphthalimide;[77] alternatively, this Beckmann transformation may be brought about when the monoxime is heated with acetic acid, HCl gas in acetic anhydride, sulfonyl chloride in dry pyridine, or 70% sulfuric acid.[78,79] Also, N-amino-1,8-naphthalamide can be heated with sodium nitrate and acetic acid, or with sodium hypobromite in alkali, to give 1,8-naphthalimide.[80] The N-aminonaphthalamide is obtained by the action of hydrazine sulfate on the naphthalenedicarboxylic acid or anhydride.



III

1,2-Naphthalimide may be obtained when 1,2-dibromonaphthalene is heated with copper cyanide and pyridine in a sealed tube at 200° and the reaction mixture is treated with dilute HCl.[81]

7. *2,2′-Diphenyldicarboximide*

This may be obtained by the general methods and also when 2,2′-diphenyldicarboxylic acid is heated with acetonitrile in a tube at 225–240°, or through a Beckmann transformation effected by the heating of 9,10-phenanthraquinone monoxime with HCl gas in an acetic acid–acetic anhydride mixture at 130–140°.[82]

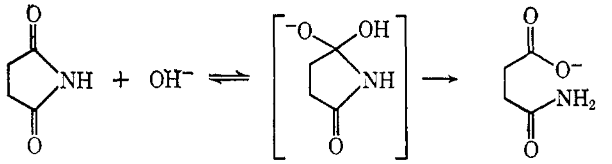
III. Chemical Properties

A. RING-OPENING REACTIONS

1. *Saponification by Alkalies*

It has been known since the latter part of the 19th century that treatment of succinimide with mild alkalies such as $Ba(OH)_2$, $Ca(OH)_2$, or PbO, in the presence of warm water, yielded the corresponding metal salt of succinamic acid.[83] The action of aqueous or alcoholic sodium hydroxide on phthalimide and maleimide gave the salts of phthalimidic and maleamic acids.[84,85] It was also well recognized that more vigorous treatment of imides with alkali would continue hydrolysis of the open-chain half-amide to yield the salt of the appropriate dibasic acid.[83,86]

The alkaline saponification of imides is a simple and quantitative process, and accurate kinetic data have been collected in the course of various investigations of relative reaction rates (Table I). The rates in dilute aqueous solution are proportional to the concentrations of imide and hydroxide ion, and the kinetics are straightforwardly of the second order. The basic hydrolysis of open-chain amides is characterized by exchange of the carboxyl oxygen with oxygen of the aqueous solvent and by attack of hydroxide ion on the carboxyl carbon.[87,88] There appears little reason to doubt that the saponification of imides occurs by a similar mechanism, as illustrated below ($B_{Ac}2$ by the Ingoldian classification).



succinimide intermediate succinamate ion

Possibly, the second slow step occurs by way of further intermediates arriving through proton exchange. Whether the consecutive hydrolysis of the half-amide is comparatively rapid or not does not affect the kinetics of the initial process.

The kinetic effects of substitution of the hydrogens in the 2 and 3 positions by alkyl groups in succinimide are not large

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(81) H. de Diesbach and E. von der Weid, *Helv. Chim. Acta*, **10**, 888 (1927).

(82) P. Wegerhoff, *Ber.*, **21**, 2356 (1888).

(83) R. Teuchert, *Ann.*, **134**, 140 (1865).

(84) M. Landsberg, *ibid.*, **215**, 197 (1882).

(85) J. Tscherniac, *Ber.*, **36**, 218 (1903).

(86) W. Kuster, *Z. Physiol. Chem.*, **55**, 523 (1908).

(87) M. L. Bender, R. D. Ginger, and K. C. Kemp, *J. Amer. Chem. Soc.*, **76**, 3350 (1954).

(88) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," 3rd ed, revised by I. T. Millar and H. D. Springall, Clarendon Press, Oxford, 1966, Chapter 7.

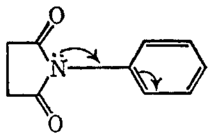
and are no doubt mainly connected with the degree of strain in the ring[89,90] (Table I[89–93]). Most notable is the enhanced rate of reaction of *trans*-cyclohexane-1,2-dicarboximide, by a factor of more than 100 compared to succinimide; the cyclohexane ring fused *trans* to the imide ring must impart severe twist and strain to the latter, so making the carboxyl carbon both more accessible to a nucleophilic reagent and less strongly bound to the nitrogen. The six-membered-ring imide, glutarimide, is also less stable than succinimide by a factor greater than 100. The chair-form glutarimide ring presents quite different geometry to an attacking reagent than the flat, five-membered imide ring of succinimide.[91,92] Disubstitution at the 3 position in the glutarimide ring evidently introduces severe steric hindrance to the attack by hydroxide ions on the carboxyl carbon. The substitution of the N-hydrogen by phenyl in succinimide, to give succinanil, causes a striking increase in the rate of ring opening by hydroxide ion; no doubt this occurs because the electron-withdrawing effect of the phenyl group makes the imide ring less stable owing principally to conjugation of the lone-pair electrons of nitrogen with the phenyl ring (IV). This view is supported by the observation that electron-withdrawing substituents, such as the nitro substituent on the phenyl ring, increase the rate of saponification, whereas electron-releasing substituents decrease it,[94] and these characteristics are paralleled by the behavior of N-phenylamides.[95] Similarly, it appears plausible that the substitution of hydrogens by hydroxyl in succinimide causes relative instability to alkali in the derived malimide and tartrimide.[7]

Table I

Second-Order Rate Coefficients (k, l. mol^{-1} sec^{-1})[a] for the Reaction of Imides with Hydroxide Ion in Water at 25°

Imide	*10^3k*
Succinimide[89,93]	8
Methylsuccinimide[89]	5
Ethylsuccinimide[89]	17
dl-2,2-Dimethylsuccinimide[89]	10
cis-Cyclohexane-1,2-dicarboximide[93]	11
trans-Cyclohexane-1,2-dicarboximide[89]	830
Succinanil[90]	5450
Glutarimide[91]	820
3-Methylglutarimide[91]	240
3-Ethylglutarimide[91]	530
3,3-Dimethylglutarimide[91]	42
Dimethylmaleimide[93]	650
Tetrahydrophthalimide[93]	1300

[a] It is necessary to multiply the coefficients recorded in the references by the factor 10 × 200/60 to obtain the standard units l. mol^{-1} sec^{-1} given here, except in the case of ref 90.



IV

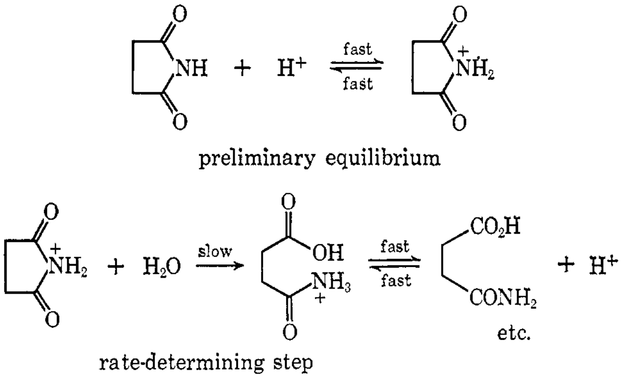
The reaction of phthalimide with hydroxide ions is complicated by the fairly acidic nature of the N hydrogen. There appears to be an approximately second-order reaction of phthalimide and hydroxide ion over the pH range 7 to about 10, but above this the rate of ring opening is almost independent of hydroxyl ion concentration.[94,96] For the pH range 7–10, electron-withdrawing substituents in the 4 position increase the rate; above this pH range, there is very little dependence of rate on the nature of the substituent on the phthalimide ring.[94] The explanation for this behavior is that at the lower pH's hydroxide ion reacts with neutral phthalimide only, but at the higher pH's the phthalimide starts to ionize to its negative ion, which may react with water.[96] More straightforward second-order kinetics are observed with respect to the concentrations of imide and hydroxide ion in the case of N-aryl-substituted phthalimide.

The energies and entropies of activation have been explored for a set of methyl-substituted succinanils.[90] The energies of activation ranged from 9 to 13 kcal/mol, and the entropies of activation were strongly negative in accord with a bimolecular rate-determining step.

2. *Acid-Catalyzed Hydrolysis and Reaction in Acid pH Ranges*

It has long been known that the prolonged heating of phthalimide with strong mineral acids yields phthalic acid.[97] This is a general reaction, and the action of strong aqueous solutions of mineral acids on N-substituted imides yields the appropriate acid and primary amine. The reaction mechanism almost certainly involves nucleophilic attack of water on the carboxyl carbon of the unstable conjugated acid of the imide ($A_{Ac}2$) (Scheme I). It is also possible that there is a contribution to the reaction through the intermediate species protonated on the oxygen of a carbonyl group. It is of interest here that acid-catalyzed hydrolysis of *amides* is thought to

Scheme I



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(90) A. K. Herd, L. Eberson, and T. Higuchi, *J. Pharm. Sci.*, **55**, 162 (1966).

(91) S. S. G. Sircar, *J. Chem. Soc.*, 600 (1927).

(92) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(93) W. Huckel and H. Muller, *Ber.*, **64B**, 1981 (1931).

(94) J. Tirouflet and E. Le Trouit, *C. R. Acad. Sci., Paris.*, **241**, 1053 (1955).

(95) E. E. Reid, *Amer. Chem. J.*, **21**, 284 (1899); **24**, 397 (1900).

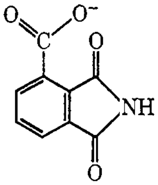
(96) P. Papoff, U. Mazzucato, A. Foffani, and G. Piazza, *Ann. Chim.* (Rome), **50**, 530 (1960).

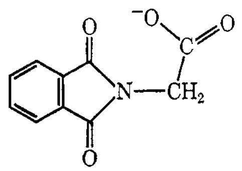
(97) O. Aschan, *Ber.*, **19**, 1407 (1886).

proceed through the less stable N-protonated amide while the O-protonated conjugate acid is relatively inert.[98]

In the case of phthalimide and concentrations of acid about 0.1 N or greater, reaction rates are proportional to the concentrations of imide and hydrogen ions, and the second-order rate coefficient for 100° is 9.83×10^{-5} l. mol^{-1} sec^{-1}.[99] The concentration of water, which is kinetically important, is constant for relatively low acidities and low concentrations of imide. (The second-order rate coefficients for the acid-catalyzed hydrolysis and the alkaline saponification cannot be compared significantly because the respective reaction mechanisms differ.) The alkaline reaction is kinetically effective at extremely low hydroxyl ion concentrations, pH 3 and above, whereas the acid-catalyzed reaction is only effective at pH's less than about 1.5. From pH 2 to 3, there is an apparently noncatalyzed reaction, the rate of which is independent of the ionic concentrations, and the first-order rate coefficient with respect to concentration of imide is 8.98×10^{-6} sec^{-1} at 100°.[99] If this reaction is considered to result from bimolecular reaction of neutral water molecules on the carboxyl carbon of the imide, then the appropriate second-order coefficient would be 1.62×10^{-7} l. mol^{-1} sec^{-1}, which may be directly compared with the value for the reaction of hydroxide ion. Water molecules are, of course, far less nucleophilic than hydroxide ions, by a factor of 2.5×10^4 here. There is some possibility that a reaction of hydroxide ions with the conjugate acid of the imide might contribute to the "non-catalyzed" reaction; this mechanism would also give reaction rates independent of the ionic concentrations.

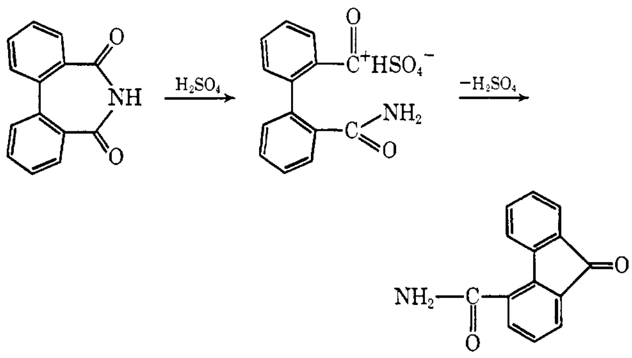
The participation of the carboxyl group as a "neighboring group" enhancing the reaction rate has been observed in the cases of the anions of 2-carboxyphthalimide (V) and phthaloylglycine (VI).[99,100] For 2-carboxyphthalimide, the rate coefficients for the acid and alkaline reactions are about as for phthalimide, but over the pH range 1–4 the reaction is faster by a factor of very roughly 10, and there is a rate–pH contour with minima at pH 1 and 4.2 and a maximum at pH 2.9. It has been suggested that this behavior is due to the participation of the *o*-carboxylic acid group and various zwitterions in a many-stepped reaction mechanism, which will not be detailed here.[99] Clearly, the participation of the ionized carboxyl group as an intramolecular catalyst is opportune in the two cases V and VI; the carboxylate group may also act as a general base in the removal of a proton from an intermediate, and the un-ionized carboxyl group may act as a general acid.[99,100] The pH range over which the hydrolysis of phthaloylglycine depends on the carboxyl group extends from 2 to 7.[100]


V


VI

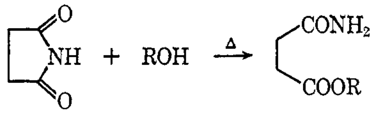
In the absence of deliberately added acidic or basic reagents, N-arylmonothiosuccinimides have been shown to hydrolyze faster than N-alkylmonothiosuccinimides; there arises in these cases the possibility of nucleophilic attack by water on the carbon of the C=S group.[101]

Akin to an acid-catalyzed hydrolysis is the reaction of 2,2′-diphenyldicarboximide in sulfuric acid at 100° to give a fluorenonecarboxamide[82] probably as follows.



3. *Reaction with Organic Nucleophiles: Alcohols, Ammonia, and Amines*

Many imides react with alcohols to yield the ester–amide derivative:



Succinimide must be heated with methanol under pressure at temperatures in the range 150–200° for the reaction to take place to give methyl succinamate.[102] Tartrimide yields ethyl tartramate with ethanol in the cold.[7] Maleimides may also undergo ring opening with cold ethanol.[103]

In a solution of ammonia in methanol, succinimide reacts to give some methyl succinamate, which can be recovered from the mother liquor, but a good yield of succinamide is precipitated, because ammonia is more nucleophilic than the alcohol.[104] Succinamide is obtained also when succinimide is heated alone with ammonia at temperatures in the range 100–200°. Tartrimide with alcoholic ammonia also gives the diamide.[10] Phthalimide and 2,2′-diphenyldicarboximide react with concentrated aqueous ammonia at room temperature to give the respective diamides.

N-Substituted phthalimides react with primary aliphatic amines to give diamides. The reaction involves ring closure, as shown in Scheme II, and if the first amine is present in large excess, the isolated di-N-alkylamide will contain only this. Tetrachlorophthalimide has been observed to react with alkylamines to yield N,N-dialkylamides.[105]

N-Substituted phthalimides react generally with hydrazine to give an amine and 1,4-phthalazinedione. Phthalimide reacts with phenylhydrazine to form first phthalamic acid hydrazide, and then phthaloylphenylhydrazine and 2-hydro-3-phenyl-1,4-phthalazinedione are formed[106] (Scheme III).

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(99) B. Zerner and M. L. Bender, *J. Amer. Chem. Soc.*, **83**, 2267 (1961).

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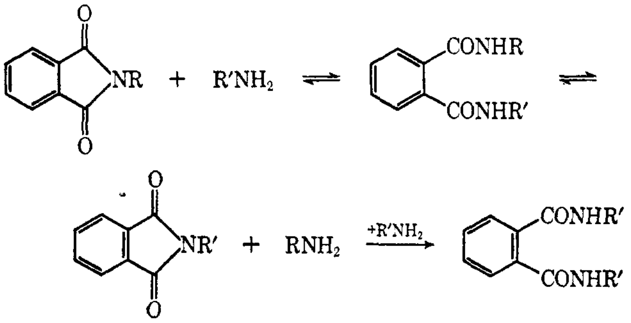
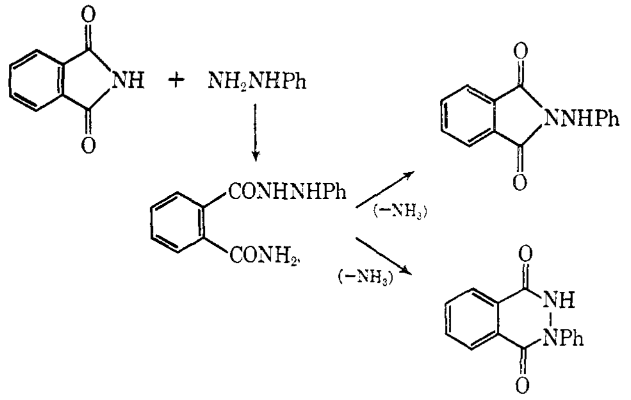
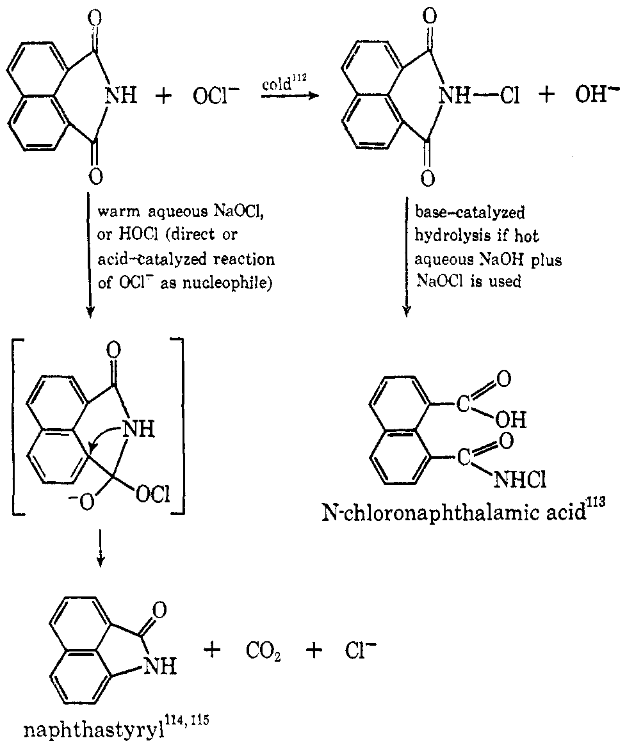
Scheme II



Scheme III



Scheme IV



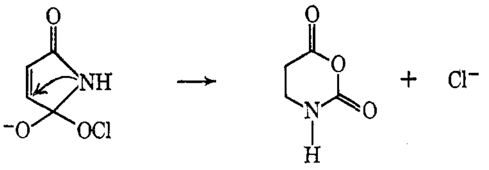
Succinimide reacts quantitatively with aqueous methylamine to give N-methylsuccinamide,[107] and N-vinylsuccinimide reacts with amines to give substituted amides.[108] Succinimide reacts with one molecular proportion of hydrazine hydrate in cold alcohol to give succinic acid monohydrazide, while 2 molar equiv of hydrazine in boiling alcohol yields the dihydrazide.[109]

Maleimide polymerizes under basic conditions; in the reaction of amines with maleimide, ring opening apparently occurs as a first step, but this is followed by polymerization.[110] However, maleimide does react with phenylhydrazine to give maleamic acid phenylhydrazide.[111]

4. Reaction with Hypohalites

When low temperatures (0°) are employed and strongly hydrolytic conditions are avoided, the product from the reaction of hypohalites with imides is generally the N-haloimide, as discussed in a later section. However, when higher temperatures are used, the action of the hypohalite (and hydroxide) ion as a nucleophile becomes important and the predominant reactions involve opening or alteration of the imide ring. An interesting early example is the action of hypochlorite on 1,8-naphthalimide under various conditions (Scheme IV). In contrast to the nucleophilic action of hydroxide ion, hypochlorite causes the elimination of carbon dioxide (probably from the intermediate indicated in square brackets) and formation of a lactam ring. Similarly, when warmed with aqueous sodium hypochlorite, phthalimide can yield anthranilic acid, the hydrolysis product of the unstable lactam.[116] If ethanolic reagents are used, for example, phthalimide yields ethyl anthranilate, the alcoholysis product of the lactam.[117]

This type of rearrangement appears to be fairly general. Succinimide warmed to 60° with aqueous KOBr and KOH yields 3-aminopropionic acid,[118] no doubt through the lactam. A curious but consistent rearrangement occurs in the case of the reaction of maleimide with aqueous NaOCl-NaOH at 0°.[119] Elimination of carbon dioxide from our proposed intermediate does not occur in this case, because the unsaturated



2,6-dioxo-2,3-dihydro-3-oxazine[119]

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(107) F. S. Spring and J. C. Wood, *J. Chem. Soc.*, 625 (1945).

(108) A. F. Nikolaev, N. V. Daniel, and V. M. Urigovera, *Zh. Obshch. Khim.*, **34**, 3087 (1964).

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(110) D. G. Smyth, A. Nagamatsu, and J. S. Fruton, *J. Amer. Chem. Soc.*, **82**, 4600 (1960).

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(112) L. Francesconi and F. Pirazzoli, *Gazz. Chem. Ital.*, **33**, I, 44 (1903).

(113) L. Francesconi and V. Recchi, *Atti Reale Accad. Lincei*, [5] **10**, II, 91 (1901).

(114) F. Ullmann and E. Cassirer, *Ber.*, **43**, 440 (1910).

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(116) Badische Anilin- & Soda-Fabrik A.-G., German Patent 55,988 (1890).

(117) Basler Chem. Fabik, German Patent 139,218 (1902).

(118) S. Hoogewerff and W. A. van Dorp, *Rec. Trav. Chim. Pays-Bas*, **10**, 4 (1891).

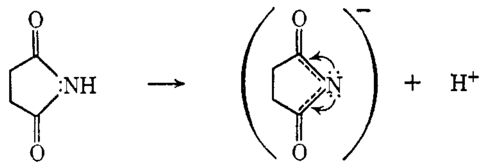
(119) I. J. Rinkes, *ibid.*, **46**, 268 (1927).

lactam may involve too much ring strain; rather, a bridging reaction appears to occur by way of the negative oxygen, while the nitrogen attaches itself to the unsaturated carbon. Additional reaction steps may be involved, and the product may possibly be an isomer of the oxazine which has been supposed to be formed. A similar reaction also appears to be undergone by phthalimide.[120,121]

B. REACTION AT THE N-HYDROGEN

1. *Ionization and Replacement by Metals*

Whereas amines are clearly basic and carboxylic acids are acidic, the amide function can be considered to be neutral or extremely weak basic. However, the introduction of an additional carboxyl function next to the nitrogen in amides produces the imide grouping with a distinctly acidic hydrogen attached to the nitrogen. A degree of resonance stabilization of the symmetrical anion occurs which cannot occur to the same extent in the amide; thus



The imides are generally very weak acids with $pK_a > 7$. Phthalimide has been studied with water and aqueous alcohol as solvents, and a number of its derivatives have been studied with aqueous alcohol only (Table II[122,123]). An idea of the values appropriate to pure water can be gained from the variation of p*K* with alcohol content of the solvent used for phthalimide. Electron-withdrawing substituents lower the p*K* of phthalimide in water from about 10 toward a value of 8. The variation of the p*K* with substituent on the aromatic ring accords with the Hammett σ constants for the influence of substituent groups on the ionization of substituted benzoic acids.[122] The N-hydroxyimides are somewhat stronger (weak) acids than the imides.

Values of pK_a reported for succinimide and glutarimide, apparently in water, are 9.35 and 11.2, respectively.[121] A set of variously substituted succinimide derivatives all have pK_a's between 7 and 10 (Table III[124]).

The acidic imide hydrogen can be replaced by metals, and many important reactions of imides are carried out *via* these salts. The salts are usually hydrolyzed in water so that their preparation and reactions must be carried out under anhydrous conditions.[125] The alkali-metal salts of, for example, phthalimide can be obtained when it is heated in alcoholic solution with the alkali-metal hydroxides, alkoxides, or hydrides.[126,127] The potassium salt is most commonly used in synthesis. The copper salt of phthalimide can be obtained by reaction of copper acetate with phthalimide.

Table II

pK_a Values at 25° for Phthalimide and Its Derivatives in Aqueous Alcohols[122]

Compound	*% alcohol (v/v)*	*pK_a*
Phthalimide	0	9.90
Phthalimide	30% ethanol	10.02
Phthalimide	78% ethanol	10.92
Phthalimide	90% ethanol	11.17
3-Nitrophthalimide	30% ethanol	8.27
3-Aminophthalimide	30% ethanol	10.81
3-Chlorophthalimide	30% ethanol	9.37
3-Acetylaminophthalimide	30% ethanol	9.53
4-Nitrophthalimide	30% ethanol	8.55
4-Aminophthalimide	30% ethanol	10.71
N-Hydroxyphthalimide[123]	50% methanol	7.00
N-Hydroxynaphthalimide[123]	50% methanol	8.25

Table III

p*K* Values[a] for Substituted Succinimides in 4% Ethanol-Water[124]

Compound	*pK*
2-Methyl-2-phenylsuccinimide	8.76
2-Benzyl-2-methylsuccinimide	9.30
2,2-Diphenylsuccinimide	8.28
2-Benzyl-2-phenylsuccinimide	8.40
2-Cyano-3-phenylsuccinimide	7.62
2-Cyano-3,3-diphenylsuccinimide	5.18
2-Carboxamido-3-phenylsuccinimide	7.60

[a] Presumably at room temperature.

The copper, mercury, and silver salts of succinimide can be obtained easily when it is heated with the appropriate metal oxide or hydroxide.[128] The metal acetate may also be used as the starting material; for example, the mercuric salt of succinimide can be formed from succinimide and alcoholic mercuric acetate.[129] However, the alkali metal salts of succinimide are more difficult to obtain.

The structure of such salts is not clear. Since both imides and their anils have been observed to form compounds with sodium and potassium hydroxides, it has been suggested that the carbonyl groups of the imides may be involved in salt formation rather than the NH group.[130]

2. *Replacement of Imidic Hydrogen by Alkyl and Aryl Groups*

The potassium salt of an imide reacts with alkyl or aryl halides to give N-substituted derivatives; *e.g.*, potassium phthalimide reacts with methyl iodide, ethyl iodide, or *sec*-butyl bromide, at 150°, with benzyl chloride at 180°, or with benzoyl chloride at lower temperatures to give the corresponding N-substituted phthalimides.[131] Potassium naphthalimide reacts similarly with methyl, ethyl, or benzyl iodide to give the N-substituted derivative.[125] Two moles of potassium phthalimide react

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(120) E. Mohr, *J. Prakt. Chem.*, **79**, 281 (1909); **80**, 1 (1909).

(121) E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Amer. Chem. Soc.*, **71**, 150 (1949).

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(126) D. L. Hammik and G. H. Locket, *J. Chem. Soc.*, **121**, 2362 (1922).

(127) J. Pfleger and E. Scheller (to Roessler and Hasslacher Chemical Co.), U. S. Patent 1,816,911 (1931); *Chem. Abstr.*, **25**, 5434 (1931).

(128) V. Dessaignes, *Ann.*, 82, 234 (1852).

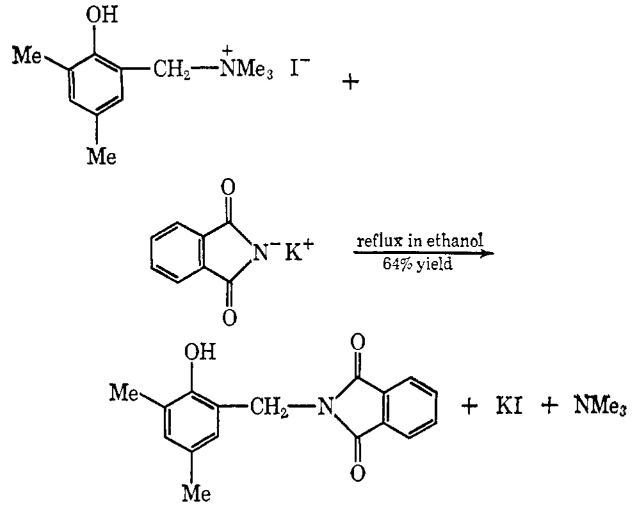
(129) N. V. S. Rao and T. R. Sheshadri, *Proc. Indian Acad. Sci.*, **10A**, 1 (1939).

(130) T. W. Evans and W. M. Dehn, *J. Amer. Chem. Soc.*, **52**, 1028 (1930).

(131) S. Gabriel, *Ber.*, **20**, 2227 (1887).

with diiodomethane to give N,N-methylenediphthalimide under anhydrous conditions.[132] Succinimide reacts with ethylene dibromide in the presence of sodium ethoxide to give N-2-bromoethyl derivatives. Trimethylene bromide gives similarly the N-3-bromopropyl derivative.[133]

Potassium phthalimide reacts with quaternary ammonium salts with the elimination of the volatile tertiary amine, as in the following example.[134]



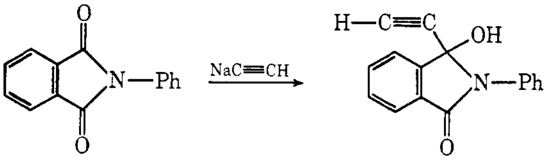
The silver derivatives of imides react with aryl or alkyl halides to give the N-arylated or N-alkylated product in the absence of moisture.[135] Silver phthalimide warmed with ethyl iodide in benzene gives N-ethylphthalimide.[135] Silver succinimide reacts slowly with ethyl iodide in chloroform to give 2-ethoxypyrrole and a little N-ethylsuccinimide;[136] in the presence of moisture succinimide is formed. Silver succinimide heated at 100° with an alkyl iodide gives the N-alkylsuccinimide.[135]

Certain organic halides react with phthalimide in dimethylformamide in the presence of anhydrous potassium carbonate to give alkylated products (Gabriel synthesis); *e.g.*, benzyl chloride gives N-benzylphthalimide.[137] Potassium phthalimide reacts with chloroacetone at 120° to give N-acetonylphthalimide. With 2-bromoacetophenone at 150° N-phenacylthalimide is formed.[138] Tropylsuccinimide is formed in good yield when succinimide is heated with tropyl bromide in pyridine.[139]

Phthalimide can be alkylated by reaction with acetone under 100 atm pressure in the presence of a catalyst, formed from 0.04% of platinum supported on alumina at a temperature of 160°, to give N-isopropylphthalimide. N-Isobutylsuccinimide is similarly obtained from succinimide and isobutyraldehyde.[140]

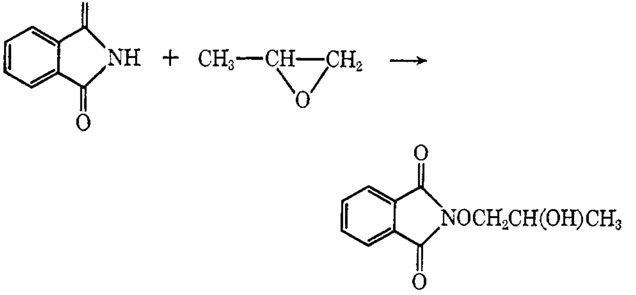
Phthalimide reacts with 40% formaldehyde solution at 150–160° to give N-methylphthalimide.[141] In the presence of piperidine or dilute alkali, phthalimide reacts with 40% formaldehyde to give piperidinophthalimidomethane, and only when the mixture is heated at 100° for several hours is a small yield of N-methylphthalimide formed.[142] Succinimide reacts with 40% formaldehyde at 150–160° to give N,N-methylenedisuccinimide.[141] It is of interest here that phthalimide heated with hexamethylenetetramine at 130° gives N,N-methylenediphthalimide and a small amount of N-ethylphthalimide.[143]

Imides react with diazomethane to give the N-methyl derivatives; *e.g.*, phthalimide reacts with an ethereal solution of diazomethane to give N-methylphthalimide. The same reaction with succinimide is much slower than with phthalimide.[144] Phthalimide reacts with acetylene at high temperature and pressure, in the presence of catalysts such as cadmium acetate, to give N-vinylphthalimide.[145] It is also of some interest that N-arylphthalimides react with acetylene, in the presence of lithium or sodium in ammonia at −40°, to give N-aryl-1-ethinyl-1-hydroxy-3-oxyisoindoles, which can be reduced catalytically with hydrogen to the 1-ethyl derivatives.[146]



3. *Preparation of N-Alkylimides in Which the Alkyl Group is Substituted by the Hydroxyl or Amino Group*

Phthalimide reacts with 10% formaldehyde solution at 100° to give N-hydroxymethylphthalimide (*cf.* section 2).[142] Phthalimide reacts with 40% formaldehyde plus 30% dimethylamine solution at room temperature to yield N-dimethylaminomethylphthalimide, and if the reaction is carried out at much higher temperatures N-hydroxymethylphthalimide is the major product.[147] Phthalimide heated at 170° with propylene oxide gives only a small yield of the normally expected product N-propoxyphthalimide. A substantial



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(132) A. Neumann, *Ber.*, **23**, 1002 (1890).

(133) K. Nakajima, *Nippon Kaguku Zasshi*, **81**, 323 (1960).

(134) A. Butenandt, U. Renner, H. Henecka, and H. Timmler (to Farbenfabriken Bayer A.-G.), German Patent 933,339 (1955); *Chem. Abstr.*, **52**, 16303 (1958).

(135) H. Wheeler, *Amer. Chem. J.*, **23**, 148 (1900).

(136) W. Comstock and H. Wheeler, *ibid.*, **13**, 522 (1891).

(137) J. H. Billman and R. Vincentcash, *Proc. Indiana Acad. Sci.*, **62**, 158 (1952).

(138) C. Goedeckemeyer, *Ber.*, **21**, 2684 (1888).

(139) W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **79**, 352 (1957).

(140) L. Schmerling (to Universal Oil Products Co.), U. S. Patent 3,274,211 (1966); *Chem. Abstr.*, **66**, 2229 (1967).

(141) J. Breslauer and A. Pictet, *Ber.*, **40**, 3784 (1907).

(142) F. Sachs, *ibid.*, **31**, 3230 (1898).

(143) M. Passerini, *Gazz. Chim. Ital.*, **53**, 338 (1923).

(144) G. Labruto, *ibid.*, **63**, 266 (1933).

(145) J. Furukava and A. Onishi, *Bull. Inst. Chem. Res., Kyoto Univ.*, **25**, 74 (1951).

(146) W. Ried and W. Fastabend, *Ber.*, **95**, 1562 (1962).

(147) R. O. Atkinson, *J. Chem. Soc.*, 1329 (1954).

amount of a quite unexpected product, N-(2-hydroxyethyl)-phthalimide, is also reported to be formed in this reaction.[148]

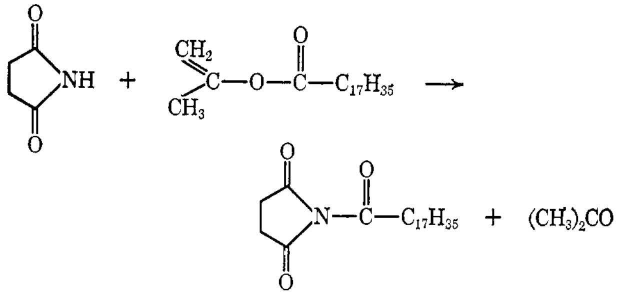
In the presence of potassium carbonate, in boiling formaldehyde, succinimide gives N-hydroxymethylsuccinimide.[149] Succinimide reacts with one molecular proportion of formaldehyde and one of a primary arylamine to give N-arylaminomethylsuccinimide; in contrast, the reaction with aliphatic amines consumes two molecular proportions of these and two of formaldehyde and yields a bis(succinimido)alkylamine.[150] Condensation of succinimide with N,N-diethylaminoethanol has been reported to give N-(2-diethylaminoethyl)succinimide.[138]

Maleimide reacts with formaldehyde in the presence of a trace of potassium carbonate to give the N-hydroxymethyl derivative.[151]

Imides react with ethylene carbonate in the presence of 0.5% Na_2CO_3 at 190° to give N-hydroxyethylimides; *e.g.*, succinimide and naphthalimide give N-hydroxyethylsuccinimide and N-hydroxyethylnaphthalimide, respectively.[152]

4. *N-Acetylation*

Imides like phthalimide and succinimide can be acetylated on heating with acetic anhydride.[125] Imides can also be acetylated by reaction with ketenes through a sodium acetate catalyst. The compounds which have been acetylated by this method include phthalimide, tetrahydrophthalimide, 4-nitrophthalimide, naphthalimide, and succinimide.[153] Brief fusion of a mixture of isopropenyl stearate and an acid catalyst with cyclic imides such as succinimide, maleimide, and phthalimide causes the elimination of acetone if the temperature exceeds 150–175° and gives high yields of the stearylated imide:[154]



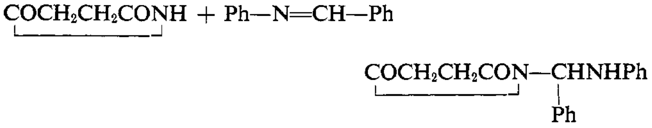
N-Stearoylsuccinimide readily undergoes ring opening on refluxing with methanol to give N-succinoylstearamide methyl ester, and this may complicate the recrystallization of the N-acylated imide from methanol.[154]

5. *Reaction of the Imidic Hydrogen with Amines*

At a fairly high temperature imides react with amines to form N-substituted derivatives; *e.g.*, phthalimide reacts with aniline or aniline hydrochloride to give N-phenylphthalimide.[155] With phenylhydrazine, it gives N-anilinophthalimide.

$$\underline{\mathrm{COC_6H_4CONH}} + \mathrm{PhNHNH_2} \longrightarrow \underline{\mathrm{COC_6H_4CON}}\mathrm{NHPh} + \mathrm{NH_3}$$

Succinimide reacts with N-benzylidineaniline to give N-(α-anilinobenzyl)succinimide; a nitro group in either ring apparently facilitates the addition.[156]



$$\underline{\mathrm{COCH_2CH_2CONH}} + \mathrm{Ph{-}N{=}CH{-}Ph} \longrightarrow \underline{\mathrm{COCH_2CH_2CON}}\mathrm{{-}\underset{\displaystyle Ph}{\underset{|}{C}}HNHPh}$$

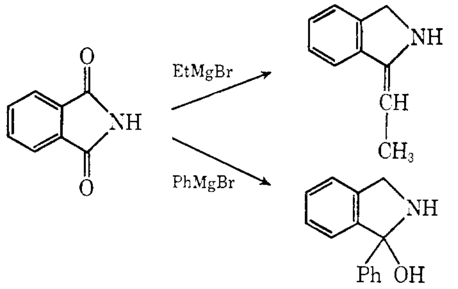
6. *Replacement of the Imidic Hydrogen by Halogens*

The action of hypohalous acid on an aqueous suspension of an imide yields the N-haloimide; *e.g.*, succinimide and phthalimide react with HOCl or HOBr to give the corresponding N-chloro or N-bromo imides.[157] Succinimide reacts with calcium oxychloride in acetic acid to give N-chlorosuccinimide.[158] Succinimide reacts with alkali and bromine or with N-bromoacetamide to give N-bromosuccinimide.[159] Silver succinimide reacts in acetone with iodine to give N-iodosuccinimide.[160] One of the naphthalimides is reported to give the N-chloro derivative by reaction with chlorine in alkali at 3°.[161] Potassium phthalimide in aqueous solution or in chloroform reacts with chlorine or bromine, or with iodine in the presence of chlorine or bromine, to give N-chloro-, N-bromo-, or N-iodophthalimide, respectively.[162]

C. SUBSTITUTIONS ON CARBON IN IMIDES

1. *Reaction of Imides with Grignard Reagents*

Phthalimide reacts with methylmagnesium iodide in pyridine to give only methane. With ethylmagnesium bromide, however, 3-ethylidinophthalimidine is obtained.[163] Phenylmagnesium bromide and phthalimide yield 3-hydroxy-3-phenylphthalimide.[164]



Similarly, N-phenylsuccinimide in benzene added to ethylmagnesium bromide in ether reacts to give 2-ethyl-2-hydroxy-

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(148) L. Smith and B. Platnon, *Ber.*, **55**, 3151 (1922).

(149) E. Cherbuliez and G. Sulzer, *Helv. Chim. Acta*, **8**, 568 (1925).

(150) M. B. Winstead, K. Anthony, W. Thomas, and R. Strachan, *J. Chem. Eng. Data*, **7**, 414 (1962).

(151) P. O. Tawney (to U. S. Rubber Co.), U. S. Patent 2,526,517 (1950); *Chem. Abstr.*, **45**, 2502 (1951).

(152) K. Yanagi and S. Akiyoshi, *J. Org. Chem.*, **24**, 1122 (1959).

(153) R. E. Dunbar and W. M. Swenson, *ibid.*, **23**, 1793 (1958).

(154) E. S. Rothman, S. Serota, and D. Swern, *ibid.*, **29**, 646 (1964).

(155) A. Piutti, *Ber.*, **16**, 1322 (1883).

(156) C. T. Chen, H. T. Ruan, and F. T. Wu, *J. Org. Chem.*, **30**, 2090 (1965).

(157) F. Longfeld and J. Stieglitz, *Amer. Chem. J.*, **15**, 215 (1893).

(158) G. Bender, *Ber.*, **19**, 2273 (1886).

(159) T. Seliwanow, *ibid.*, **26**, 425 (1893).

(160) N. Bunge, *Ann., Suppl. Vol.*, **7**, 117 (1870).

(161) Y. Tamazaki, T. Ishii, and S. Takuchi, *Yuki Gosei Kagaku Kyokai Shi*, **15**, 35 (1957).

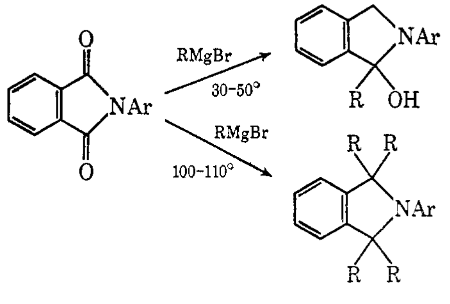
(162) J. Bredt and H. Hof, *Ber.*, **33**, 23 (1900).

(163) C. Beis, *C. R. Acad. Sci., Paris*, **138**, 988 (1904).

(164) C. Beis, *ibid.*, **139**, 62 (1904).

1-phenylpyrrolidine. Yet arylmagnesium bromides react with N-substituted maleimides to yield N-substituted 5-aryl-5-hydroxy-2-pyrrolidones.[165]

N-Aryl-substituted phthalimides react with alkyl Grignard reagents at 30–50° to give 2-aryl-3-alkyl-3-hydroxyphthalimidines, but at 100–110° 2-aryl-1,1,3,3-tetralkylisoindoles are formed.[166]



Under some conditions, the imide ring is opened by the Grignard reagent. Thus, for example, N-methylsuccinamate has been reported as the product from reaction of N-methylsuccinimide with ethyl magnesium bromide.[167] However, this imide can give either a cyclic isoindole derivative (with certain aromatic Grignard reagents) or an acyclic amide depending on the nature of the Grignard reagent.[168]

Diphenyl- and diethyl-substituted N-phenylmalonimides react with three molecular proportions of aryl Grignard reagents to give the disubstituted N-phenylacetoamides and the tertiary carbinols derived from the Grignard reagents.[169]

2. *Reactions with Phosphorus Halide and Sulfide*

Glutarimide reacts with PCl_5 to give 2,3,6-tribromopyridine, whereas with PBr_5 at 80–90° it gives 2,3,6-tribromopyridine and 2,3,5,6-tetrabromopyridine.[119,170]

Phthalimide refluxed in xylene with P_2S_5 gives dithiophthalimide.[171] N-Alkyl- or N-arylsuccinimides react with P_2S_5 in toluene or xylene to give N-alkyl- or N-arylthiosuccinimides.[172]

3. *Reaction with Halogens*

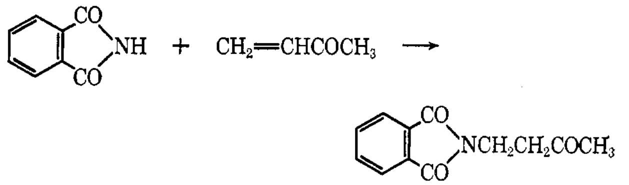
Chlorine gas led through boiling succinimide at 160° gives chloromaleimide and dichloromaleimide; bromine gives similar, brominated products.[173] Aqueous bromine also reacts with maleimide to give dibromomaleimide.[174] Methylmaleimide (citraconimide) reacts at 140° with bromine to give 2-bromo-3-methylmaleimide and 2,3-dibromo-3-methylsuccinimide.[175]

4. *Nitration of Imides Containing an Aromatic Group*

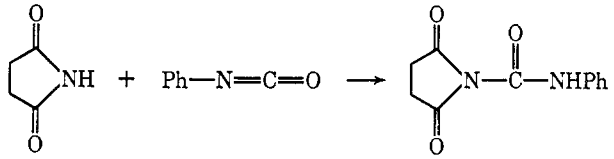
N-Methylnaphthalimide boiled with a mixture of acetic and nitric acids gives a nitro derivative.[176] 2-Ethyl-2-phenylglutarimide is nitrated at −10° by a mixture of sulfuric and nitric acids to yield mainly 2-ethyl-2-(*p*-nitrophenyl)glutarimide. Some 2-ethyl-(*o*-nitrophenyl)glutarimide can be obtained from the mother liquor.[177] All three N-tolylsuccinimide isomers are nitrated by fuming nitric acid: the *ortho* and *para* derivatives nitrate in the *meta* position, while N-*m*-tolylsuccinimide is nitrated in the *ortho* and *para* positions.[178]

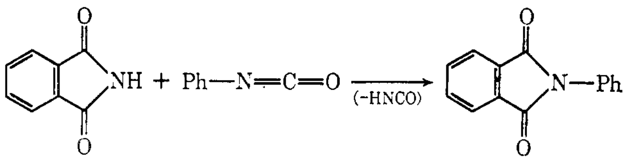
D. REACTIONS OF IMIDES WITH UNSATURATED COMPOUNDS

Imides act as acids to the C=C double bond in diverse substances. Thus, with acrolein and 2-methylacrolein succinimide gives 3-succinimidopropionaldehyde and 2-methyl-3-succinimidopropionaldehyde, respectively. Phthalimide with the same reagents gives analogous products.[179] The addition of phthalimide to the C=C double bond in esters of unsaturated acids can be brought about in the presence of a Rodionov catalyst.[180] Phthalimide reacts with certain unsaturated compounds in the presence of a basic catalyst such as KCN, K_2CO_3, pyridine, or piperidine at temperatures in the range 80–120°; thus, methyl vinyl ketone reacts with phthalimide to give 1-phthalimido-3-butanone.[181]



Succinimide refluxed with phenyl isocyanate in toluene for 7 hr gives the addition product 1-succinyl-3-phenylurea, while phthalimide is reported to give N-phenylphthalimide with the same reagent.[182]





Sodium succinimide reacts with β-propiolactone by opening of the lactone ring to give 3-succinimidopropionic acid.[183]

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(165) A. Queen and A. Reipas, *J. Chem. Soc.*, 245 (1967).

(166) K. Heidenbluth, H. Tonjes, and R. Scheffler, *J. Prakt. Chem.*, **30** (304), 204 (1965).

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(168) C. Lawrence and R. Chiron, *C. R. Acad. Sci., Paris, Ser. C*, **268**, 279 (1969).

(169) W. Flitsch and R. Heidhues, *Z. Naturforsch., B*, **21**, 1137 (1966).

(170) H. J. den Hertog and E. Farenhorst, *Rec. Trav. Chim. Pays-Bas*, **67**, 380 (1948).

(171) D. S. Pratt and H. S. Brill, *Chem. Zentralbl.*, **I**, 834 (1915).

(172) R. J. Cremlyn, *J. Chem. Soc.*, 5547 (1961).

(173) G. L. Ciamician and P. Silber, *Ber.*, **16**, 2394 (1883).

(174) G. Plancher and F. Cattadori, *Atti. Reale Acad. Lincei*, [5] **13**, I, 490 (1904).

(175) D. Mendini, *Gazz. Chim. Ital.*, **15**, 185 (1885).

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(179) O. A. Moe and D. T. Warner, *J. Amer. Chem. Soc.*, **71**, 1251 (1949).

(180) E. N. Alekseeva and V. A. Vaver, *Nauch. Dokl. Vyssh. Shk., Khim. Khim. Tekhnol.*, 545 (1958); *Chem. Abstr.*, **53**, 2149 (1959).

(181) E. Dreher and H. Pasedach (to Badische Anilin- & Soda-Fabrik A.-G.) German Patent 1,034,179 (1958); *Chem. Abstr.*, **54**, 13068 (1960).

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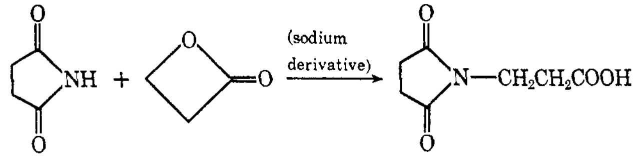
(183) T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick, F. T. Fiedorek, R. A. Bankert, J. T. Gregory, and W. L. Beears, *ibid.*, **74**, 1323 (1952).

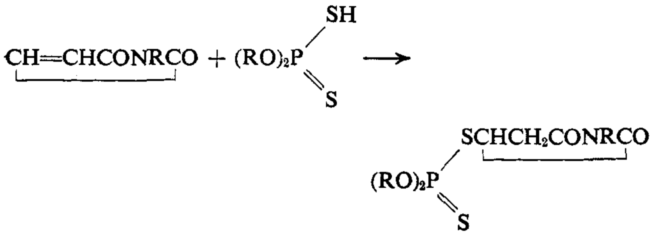


E. SPECIAL REACTIONS OF MALEIMIDE AND ITS DERIVATIVES

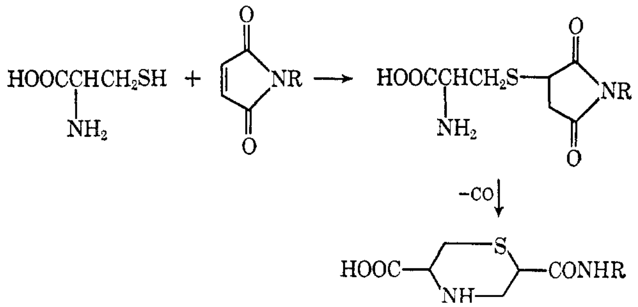
The reaction of mercaptoacetic acid, *o*-mercaptobenzoic acid, and other arylthiols with N-ethyl- or N-phenylmaleimides yields the product from addition of the S—H group to the C=C double bond:[184,185]

$$RSH + CH{=}CHCONR'CO \longrightarrow RSCHCH_2CONR'CO$$

Esters of phosphorodithioic acid add similarly to the double bond:[186]



Maleimide reacts with peptides which contain cysteine, but here the SH addition product initially formed may subsequently form a thiazine ring:[187]



The same reaction has been reported for 4-maleimidoazobenzene and for N-(2,4-dinitroanilino)maleimide.[188]

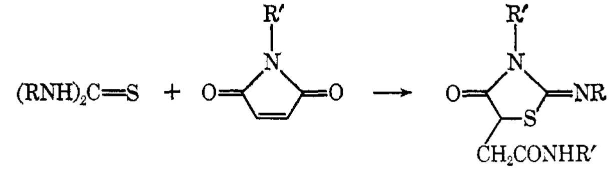
Piperidine and similar amines add to the double bond in maleimide at room temperature in the cold to give, for example, piperidinosuccinimide.[185] Phenylhydroxylamine and hydroxylamine in dry pyridine add to the double bond to give the 2-(hydroxylamino) derivative:[189]

$$RNHOH + CH{=}CHCONHCO \longrightarrow RN(OH)CHCH_2CONHCO$$

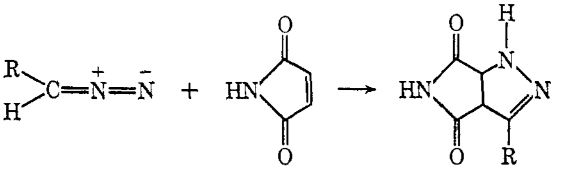
In the presence of aluminum chloride, aromatic hydrocarbons can also be made to add across the double bond in N-arylmaleimides.[185]

N-Substituted maleimides undergo Diels–Alder reactions in the usual way. 1,3-Cyclopentadiene, furan, 3,4-benzisoxazole, and various styryl-substituted compounds all give addition products. Anthracene and 2,5-dimethylfuran have been observed to add more rapidly to maleimide than to maleic anhydride.[190]

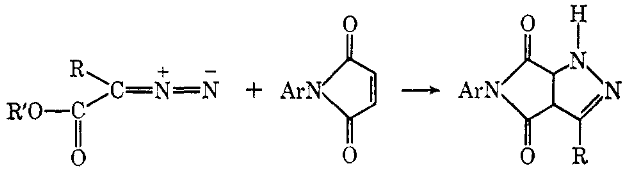
The addition of substituted thiourea derivatives to N-substituted maleimides is accompanied by opening of the imide ring, and thiazolidones result.[191] Addition of the thione group occurs across the 1 and 2 positions of the imide ring.



When aryldiazonium salts are warmed with maleimides in the presence of cuprous salts and acetone, the 2-arylmaleimides are formed.[192] However, diazoalkanes are reported to react with maleimide to give a fused Δ^2-pyrazoline ring:[193]

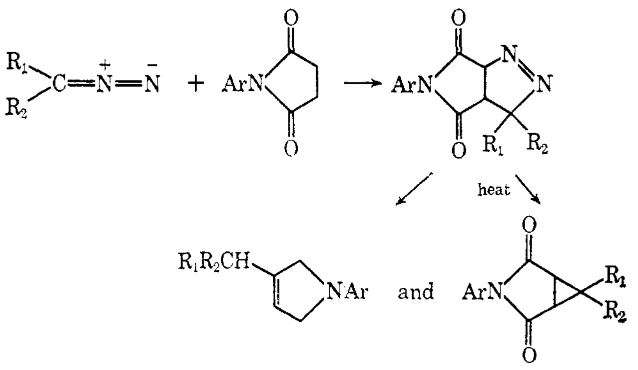


The reaction of diazo-2-alkylacetic esters with N-arylmaleimides is reported to yield the same type of product, the alkoxycarbonyl group being readily hydrolyzed off the 1-nitrogen.[194]



Diazomethane or dialkyl- or diaryl-substituted diazomethanes are reported conversely to form the Δ^1-pyrazoline ring, which is unstable to heat[194] (Scheme V). Diazofluorene, for example,

Scheme V



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(184) D. H. Marrian, *J. Chem. Soc.*, 1515 (1949).

(185) A. Mustafa, W. Asker, S. Khattab, and S. M. A. D. Zayed, *J. Org. Chem.*, **26**, 787 (1961).

(186) E. Hoegberg (to American Cyanamid Co.), U. S. Patent 2,644,002 (1953); *Chem. Abstr.*, **48**, 5206 (1954).

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(188) G. D. Clark-Walker and H. C. Robinson, *J. Chem. Soc.*, 2810 (1961).

(189) E. Jolles, *Gazz. Chim. Ital.*, **65**, 1221 (1935).

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(191) D. H. Marrian, *J. Chem. Soc*, 1797 (1949).

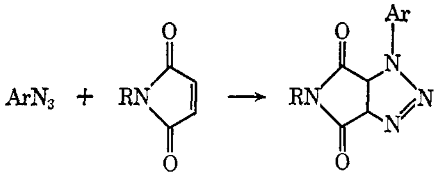
(192) C. S. Rondestvedt and O. Vogl, *J. Amer. Chem. Soc.*, **77**, 2313 (1955).

(193) A. Mustafa, S. Mohamed, A. Zayed, and S. Khattab, *ibid.*, **78**, 145 (1956).

(194) W. I. Awad, S. M. A. R. Omran, and M. Sobhy, *J. Chem. U. A. R.*, **6**, 119 (1963).

reacts with N-aryl-substituted maleimide to give a good yield of N-arylfluoren-9-ylidenesuccinimide.[194]

Aromatic azides also give fused five-membered rings:[195]



Benzaldazine is reported to add to N-butylmaleimide to yield a compound with a five-membered fused ring.[196]

F. REDUCTION OF IMIDES

1. *Reduction of Phthalimide and Its Derivatives*

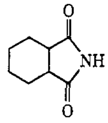
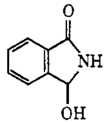
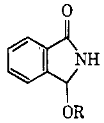
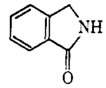
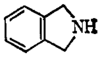
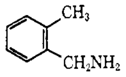
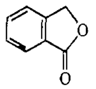
The products of reduction obtainable from phthalimide under various conditions are shown in Table IV. The reduction of derivatives of phthalimide, in which the N-hydrogen is substituted, often takes the same course as the parent imide with a particular reducing agent, but sometimes it does not. For example, N-alkyl- and the lower N-alkoxyphthalimides are reduced by lithium aluminum hydride to the corresponding N-substituted isoindolines.[197] Electrolytic reduction of N-alkylphthalimides in aqueous sulfuric acid at a zinc amalgam cathode also gives the N-alkylisoindolines.[198] When a lead cathode is used it is also possible to isolate some of the intermediate N-alkylphthalimidine, and at a copper or nickel cathode this is the major product.[198,199] However, sodium borohydride in water reduces N-ethoxyphthalimide to 2-ethoxy-3-hydroxyphthalimidine, but the methoxy derivative is reported to go to phthalide (*cf.* Table IV).[197] Sodium borohydride in methanol reduces variously N-substituted phthalimides to the corresponding N-substituted 3-hydroxyphthalimidines mixed sometimes with the N-substituted *o*-hydroxymethylbenzamides.[200]

Electrolysis of potassium phthalimide in strong aqueous potassium hydroxide solution with platinum electrodes yields ammonia and potassium phthalate.[201]

The half-wave potentials for the polarographic reduction of phthalimide and its substituted derivatives to phthalimidines have been studied. Reduction in a slightly alkaline medium showed two one-electron waves, whereas reduction in an acid medium showed a single two-electron reduction wave.[202]

Table IV

Reduction Products from Phthalimide

Reduction medium	*Product*
Hydrogen, platinum[202] H_2, Raney Ni, alcohol [203] H_2, Raney Ni, dioxane, 160°[203] H_2, Pt, acetic acid[203]	 Cyclohexanedicarboximide
Zn, NaOH[204] Pb cathode, HCl, aq dioxane, 30°[205]	 3-Hydroxyphthalimidine
$NaBH_4$, 2-propanol (ROH), 35% yield[206] Pb cathode, alcohol (ROH)[205]	 3-Alkoxyphthalimidine
Cu cathode, aq H_2SO_4, 40°[207]	 Phthalimidine
Copper chromite, Al_2O_3, 240°, 80% yield[203] $LiAlH_4$[208] Pb cathode, 50% aq H_2SO_4, 60° [205] Zn|Hg cathode, lead anode, 12 *N* aq H_2SO_4, 80°, 0.5 A/cm^2 [198]	 Isoindoline
Na, isoamyl alcohol[209]	 *o*-Methylbenzylamine
Zn, aq NaOH, 100° [210] $NaBH_4$, H_2O, 60% yield[206]	 Phthalide

2. *Reduction of 1,8-Naphthalimide and Its N-Methyl Derivative*

1,8-Naphthalimide is similar to phthalimide in that the former is reduced at a lead cathode in 50% aqueous sulfuric acid solution at 60° to yield 2,3-dihydro-2-azaphenalene; *i.e.*, the imide ring can be completely reduced, and the aromatic rings are retained.[211,212] This product has also been obtained by reduction of 1,8-naphthalimide at a zinc amalgam cathode in alcoholic sulfuric acid.[213] When alcoholic sulfuric acid is used as the electrolytic solvent with a lead cathode, up to a 30% yield of N-methyl-1,8-naphthalimidine may be obtained from N-methyl-1,8-naphthalimide; however, when a zinc amalgam cathode is employed, the reduction proceeds further to N-methyl-2,3-dihydro-2-azaphenalene.[213]

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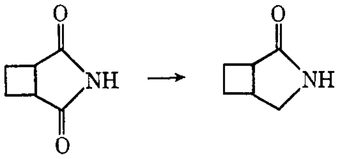
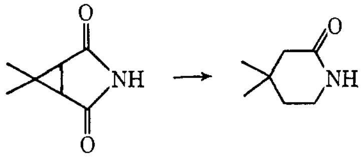
3. *Reduction Products from Succinimide and Related Compounds*

The product in which one of the carbonyl groups in succinimide is completely reduced, *i.e.*, pyrrolidone, can be obtained by reduction at either a thorium or zinc amalgam cathode in 50% aqueous sulfuric acid.[214,215] Some pyrrolidine, in which both carbonyl groups have been reduced, is also produced by this procedure, but this product is better prepared by reduction of succinimide with lithium aluminum hydride[216] or by sodium and alcohol.[217] Electrolytic reduction at a lead cathode in 50% aqueous sulfuric acid leads to opening of the imide ring with the formation of mainly 4-aminobutyric acid.[218] Some simple N-alkyl-substituted succinimides are reduced by lithium aluminum hydride to the N-substituted pyrrolidine derivatives, but the N-*t*-butyl and N-phenyl substituents cause opening of the ring in this reaction so that N-substituted 4-hydroxybutylamines are formed in part.[216] N-Tritylsuccinimide gives N-trityl-4-hydroxybutyramide entirely.[216]

One carbonyl group can be reduced in cyclobutane-1,2-dicarboximide and cyclopentane-1,2-dicarboximide at 5° in dilute sulfuric acid, so that pyrrolidone rings are formed.[219,220]



The central bond breaks when 2,2-dimethylcyclopropanedicarboximide is similarly reduced, and 4,4-dimethyl-2-piperidone is produced.[220]



4. *Reduction of Maleimide*

Hydrogenation on platinum and electrolytic reduction at a nickel cathode in dilute sulfuric acid give very good yields of succinimide if the conditions are mild.[221,222] When a zinc amalgam cathode is used, succinic acid and ammonia are formed.[222]

5. *Reduction of Substituted Glutarimide Derivatives*

There appear to be no reports of reduction products obtained from glutarimide itself, but these can be assumed to be similar to those formed from derivatives. Both N-alkyl- and N-aryl-substituted glutarimides are reduced mainly to the N-substituted 2-piperidones in 85% sulfuric acid at a lead cathode, and the reduction can be carried further to the N-substituted piperidines at a zinc amalgam cathode.[223] 2,4-Dimethylglutarimide is reduced by lithium aluminum hydride to 3,5-dimethylpiperidine.[224]

G. METAL–ORGANIC COMPLEXES OF IMIDES

The action of caustic alkalies on a solution of succinimide and copper acetate or chloride in aqueous alcohol gives a series of complexes with the formula $(C_4H_4NO_2)_4CuM \cdot nH_2O$ in which M = Li, Na, K, Rb, or Cs, and n = 1, 2, 4, or 6, depending on M. Succinimide also gives a reddish brown barium–copper complex $BaCu(C_4H_4NO_2)_4$. These complexes are crystalline and stable in dry state but are decomposed by water with separation of $Cu(OH)_2$. The potassium, rubidium, and cesium complexes have a red color with a violet tint, while the sodium and lithium complexes have a bright ultramarine color.[225] Succinimide gives a golden yellow compound, $C_4H_4O_3NHgK$, with potassium hydroxide and mercuric acetate.[226] This compound is alkaline to phenolphthalein and is decomposed by strong acids or by heat. Further treatment with KOH and mercuric acetate gives a greenish compound, $C_4H_4O_4NHg_2K$, which is stable when dry but decomposes in moisture. Chloroauric acid, gold hydroxide, a gold salt, or fulminating gold react with succinimide in the presence of a base to give complexes.[227] Succinimide is also known to form addition compounds with phenols, hydrogen peroxide, and titanium tetrachloride.[228] Periodide formation is common to all classes of organic compounds containing the C=O group; the products are called carbonyl periodides, and succinimide, for example, forms the compound $(C_4H_4NO_2)KI \cdot I_2$.[229]

Succinimide and ethylenediamine cyanide tetrahydrate form two series of complexes with Ni, one blue-green and paramagnetic and the other yellow and diamagnetic; no equilibrium appears to exist between the two forms. The analogous series of copper complexes are all paramagnetic as are the succinimide–diisobutylamine complexes, $(C_4H_4O_2N)Cu(C_4H_9NH_2)_2$.[230] Magnetic susceptibility measurements have been made for a series of aliphatic amine complexes of Cu with phthalimide of the above type. The magnetic moments fall between 1.76 and 1.9 BM, and square-planar coordination of the copper was suggested. These complexes give a typical ink-blue color in solution and show a single band in the 600–900-mμ region of the spectrum, the position of which changes with the polarity of the solvent used.[231]

Complexes of Co^{II} with phthalimide and ammonia (or ethylenediamine, 2,2′-bipyridyl, or 1,1-*o*-phenanthroline) have been isolated. They do not melt before decomposition and decompose with warm acids; their structure appears to contain the phthalimide ion and the appropriate amine in the

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coordination sphere.[232] Complexes of the type Fe^{III}(phthalimide)$_3$–(amine)·H_2O are probably nonelectrolytes with all of the species coordinated to the metal. Although the C=O group in phthalimide does not take part in the coordination, the infrared band corresponding to C=O stretching is shifted to lower frequencies compared to the noncoordinated state.[233] This bis(aliphatic amine) complexes of copper phthalimide show N–H stretching vibrations in the range 3370–3260 cm^{-1} in Nujol. The carbonyl stretching frequencies of the complexes fall within the range 1665–1640 cm^{-1}, which is well removed from the 1745-cm^{-1} band observed in phthalimide and the 1725-cm^{-1} band observed in copper phthalimide. These results have been construed as supporting a *trans* structure for the complexes.[234] In contradistinction to the copper complexes, the carbonyl frequencies of phthalimido-, diphthalimido-, diamino-, or diphthalimidoethylenediaminocobalt(II) show a band at 1725–1700 cm^{-1}. The conclusion was reached that the cobalt coordinates with the phthalimide through nitrogen.[235]

Orange and yellow colored, solid addition complexes are formed between maleimide and quinol in the molar ratios 1:1 and 2:1, respectively.[236] The complexes are held together mainly by hydrogen bonds and readily dissociate in solution. Irradiation of the 2:1 complex yields cyclobutane-1,2-*anti*-3,4-tetracarboxylic acid bisimide, which no doubt reflects a back-to-back orientation of the imide molecules in the complex.

H. PHOTOLYSIS, PYROLYSIS, AND MISCELLANEOUS REACTIONS

The photolysis of succinimide vapor by light of wavelength in the range 2300–2600 Å has been studied at temperatures up to 200°, which is below the pyrolysis range. Four different stoichiometric reactions appear to occur and the reaction products are carbon monoxide and dioxide, carboximine, ethylene, hydrogen cyanide, acrylonitrile, water, and cyanoethane.[237] The pyrolysis of succinimide vapor at temperatures in the range 425–500° is kinetically of the first order and has an activation energy of 52 kcal/mole, and the reaction products were qualitatively the same as for photolysis but had different ratios.[237] The pyrolysis and photolysis of N-methylsuccinimide were simpler, yielding chiefly CO, C_2H_4, and CH_3NCO.[237] In connection with a mass spectrometric study, the pyrolysis of several N-arylphthalimides has been shown to yield carbon monoxide and carbon dioxide among the products. The carbon dioxide must arise from some kind of rearrangement.[238]

Distillation of an imide with zinc dust gives the corresponding unsaturated heterocyclic base; *e.g.*, succinimide gives pyrrole, and glutarimide gives pyridine.[239] When heated with sodamide, naphthalimide can be stripped down to naphthalene.[239]

Many details of the polymerization of imides are beyond the intended scope of this review, although such reactions have been known for about two decades.[19] N-Substituted maleimides can be polymerized by means of free-radical and anionic catalysts.[240] Free-radical polymerization can also be induced by γ radiation.[241] The imide ring also features in some aromatic, heat-resistant polymers, which have important industrial applications.

IV. Physical Properties

A. SOME THERMODYNAMIC PROPERTIES

A selected list of available melting points is given in Table V for imides not substituted on the N-hydrogen. This table can serve as a general source of references to methods of preparation and properties. The molecules of imides are most probably associated in pairs through C=O···H—N hydrogen bonding in the solid and liquid states; all of the melting points are well above room temperature and decomposition sets in before boiling points are reached in general. Table VI gives melting points and some boiling points for N-substituted imides. In these compounds, of course, there can be no hydrogen bonding as in the simple imides.

A set of detailed vapor pressure measurements is available for phthalimide and some of its substituted derivatives, and these data are listed in Table VII.

The vapor pressures (P, mm) of liquid succinimide over the temperature range 126–177° is given by

$$\log P = 9.05 - (3530/T)$$

where T is in °K, and the function for liquid N-methylsuccinimide over the range 83–122° is

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Table V

Melting Points of Imides

Compound	*Mp, °C*
Succinimide[242]	125–126
Methylsuccinimide[104]	66
2,2-Dimethylsuccinimide[90]	105–107
cis-2,3-Dimethylsuccinimide[90]	78
trans-2,3-Dimethylsuccinimide[90]	106
2,2-Dimethyl-3-methylsuccinimide[90]	121
Tetramethylsuccinimide[90]	197
2,3-Diphenylsuccinimide[90]	196–198
Tartrimide[88]	205
Malimide[88]	96
Glutarimide[91, 121]	163–165
Carbobenzoxy-2-aminoglutarimide[243]	122–124
3-Methylglutarimide[91]	142–143
3,3-Dimethylglutarimide[91]	147
3,3-Diethylglutarimide[91]	146–147
3-Ethylglutarimide[91, 121]	87
Adipimide[66]	166
Maleimide[244]	93
Dimethylmaleimide[245]	118–119
Diphenylmaleimide[246]	213
3-Ethyl-3-methyl-1,2-cyclopropanedicarboximide[250]	61–63
Cyclobutanedicarboximide[251]	121
Cyclopentane-1,2-dicarboximide[251]	90
Cyclopentane-1,1-diacetic acid imide[89]	153–154
Cyclohexanespirosuccinimide[89, 252]	145
Cyclohexane-1,2-dicarboximide[253]	132
Cyclohexa-2-ene-1,2-dicarboximide[254]	173
trans-Cyclohexa-4-ene-1,2-dicarboximide[254]	232–233
Phthalimide[244]	241
1,2-Naphthalimide[76]	224
2,3-Naphthalimide[34]	275
1,8-Naphthalimide[33]	299–300
4-Nitro-1,8-naphthalimide[33]	289–290
4-Bromo-1,8-naphthalimide[33]	296–297
4-Chloro-1,8-naphthalimide[33]	302–303
4,5-Dichloro-1,8-naphthalimide[33]	372–373
4-Bromo-5-chloro-1,8-naphthalimide[33]	365
4,5-Dibromo-1,8-naphthalimide[33]	343–344
Anthracene-1,9-dicarboximide[248]	293–294
Phenanthrene-8,9-dicarboximide[249]	308–309

Table VI

Melting Points and Boiling Points at Atmospheric Pressure for N-Substituted Imides

Compound	*Mp, °C*	*Bp, °C*
N-Methylsuccinimide[91]	71	226
N-Phenylsuccinimide[244]	158	
N-Benzylsuccinimide[244]	104	
N-Hydroxysuccinimide[255]	175	
N-(Cyanomethyl)succinimide[256]	121	
N-Benzoylsuccinimide[39]	129–130	
(+)-N-Phenyltartrimide[257]	257	
meso-N-Phenyltartrimide[7]	235	
N-Benzyltartrimide[257]	196	327
N-Methyltartrimide[258]	178	327
N-Ethyltartrimide[258]	174	327
N-Methylglutarimide[259]	128	113.5 (20 mm)
N-Ethylglutarimide[239]	179–180	250–260
N-Phenylglutarimide[239]	144–145	
N-Methyladipimide[259]	119	
N-Methylmaleimide[260]	109	
N-Methylmaleimide[261]	90–92	
N-Ethylmaleimide[261]	45.5	
N-Phenylmaleimide[262]	90–91	
N-Methyl-2,3-dimethylglutaconimide[247]	91.5–92.5	
N-Phenylmalonimide[5]	246	
N-Phenylmaleisoimide[263]	60	
N-Phenylphthalisoimide[263]	112	
N-Phenylcyclobutanedicarboximide[264]	89	
N-Methylphthalimide[244]	136	
N-Methylphthalimide[265]	79	
N-Phenylphthalimide[244]	212	
N-Benzylphthalimide[244]	118	
N-Vinylphthalimide[266]	85–86	
N-Hydroxyphthalimide[123]	232–233	
N-Benzyloxynaphthalimide[123]	187–188	
N-Hydroxynaphthalimide[123]	280–281	
N-Phenyldiphenyl-1,1′-dicarboximide[133]	199	
Di-N-phenyl-*cis*-*cis*-1,2,4,5-	98	
cyclohexanetetracarboximide[267]	98	

Table VII

Saturated Vapor Pressure (P, mm) of Imides as a Function of Temperature (°K)[a] [268]

Compound	*a*	*b*
Phthalimide	4326	10.014
3-Dimethylaminophthalimide	4749	10.743
3-Methylaminophthalimide	5480	11.904
3-Acetamidophthalimide	5667	11.855
3-Aminophthalimide	5655	11.865
2-Dimethylamino-5-aminophthalimide	5684	10.756
2,5-Diaminophthalimide	5146	9.731

[a] $\log P = b - (a/T)$.

$$\log P = 5.05 - (1530/T)$$

The heat of vaporization of the N-methyl derivative is the lower by more than one-half owing to the absence of hydrogen bonding through an NH group.[237]

The heats of combustion of a small number of amides have been measured (Table VIII).

B. CRYSTAL STRUCTURES AND DIMENSIONS OF THE IMIDE RING

Succinimide crystals have the form of rhombic bipyramids.[271] There are eight molecules in the unit cell hydrogen bonded in pairs through the N—H and (one) C=O groups. The molecular packing is similar to that for succinic acid except that the N–H group occurs in place of the two O–H groups; however, the detailed molecular symmetry of the two compounds is, of course, not identical in the crystalline state.[272] Mason has reported a three-dimensional least-squares analysis of the crystal structure of succinimide and has calculated bond lengths between the heavy atoms and angles with respective average standard deviations of ±0.011 Å and ±0.6°. The

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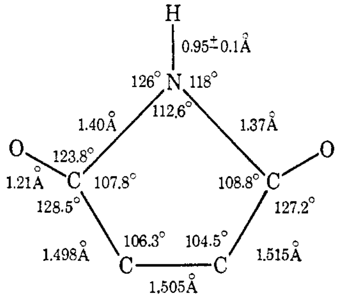

Figure 1. Structural parameters of the imide ring in succinimide in the crystalline state.[273]

Table VIII

Heats of Combustion at Constant Volume (ΔH_v) and Constant Pressure (ΔH_p) for Imides (kcal/mol)[269,270]

Compound	ΔH_v	ΔH_p
Succinimide	479.3	438.1
N-Phenylsuccinimide		1168.5
N-Nitrosuccinimide	436.9	
Phthalimide		850.2
N-Phenylphthalimide		1579.1

values are given in Figure 1.[273] Of particular note is the fact that the ring of heavy atoms is almost completely planar. Strong mesomerism involving the C═O and C—N bond electrons and the unshared electron pair of the nitrogen (*cf.* structure I) holds this ring essentially flat, but not completely so; in particular, the N-hydrogen is about 0.15 Å out of the plane of the ring from which the heavy atoms deviate by no more than an average of 0.02 Å. The C–H bond angles are, of course, approximately tetrahedral. The whole molecule is slightly distorted away from having a plane of symmetry in the solid. However, the distortion of the N–H bond is due to the manner of pairing of molecules by hydrogen bonding in the crystal, and the molecule would be expected to be symmetrical in the nonassociated dissolved state.

Succinimide forms an addition compound with tetraethylammonium bromide, $(C_2H_5)_4NBr–2C_4H_5O_2N$. X-Ray crystallography of this reveals a complicated unit cell containing eight units of the above formula in which the tetraethylammonium ions and bromide ions are in close association, the N–H groups of the succinimide molecules are directed toward the negative bromide ions, and C═O groups are directed toward the positive organic ions.[274] The corresponding chloride forms a similar structure.

N-(*p*-Bromophenyl)succinimide forms orthorhombic crystals of density 1.71 g/cm^3, and its structure has been studied.[275] Here, there are only four molecules per unit cell. The angle between the planes of the phenyl and succinimide rings was found to be 60°, so that at least in the solid there appears to be little conjugation between the unpaired electrons of the nitrogen and the electrons of the benzene ring, which would tend to make the two rings coplanar. Consistently, the N–C bond is at an angle of 15° to the plane of the imide ring and not almost in this plane.

Phthalimide crystallizes in the monoclinic system with the inclined angle close to 90°, namely, 91° 19′.[271,276] The dimensions of the unit cell are $a = 22.7$, $b = 7.61$, and $c = 3.80$ Å, and two flat molecules are accommodated therein.

C. DIPOLE MOMENTS

The dipole moments of a large number of imides have been measured in dioxane as solvent; these are listed in Table IX. As most imides are not very soluble in benzene, the use of dioxane is necessary for dipole moment measurements, and this introduces considerable uncertainty as to the interaction polarization, so that the values given can only be regarded as significant probably to ±0.2 Debye unit.

The smallest moment recorded is for succinimide (1.50), which almost certainly has a flat ring in solution and has strongly polar C═O and C—N bonds due to the mesomerism involving the C═O double bond and the formally unshared electron pair of the nitrogen(IV). It does not seem possible to analyze the resultant moment of succinimide into bond moments because of lack of knowledge of the extent and effect of the mesomerism. What is clear, however, from analytical attempts made,[277] is that the angle between the two C═O bonds is about 154° and that the C═O bond moments are largely opposed, and the two C—N moments are also largely opposed. It appears that the center of positive charge in the ring is slightly further from the nitrogen than is the center of negative charge due to the two oxygens, so that there is a small resultant moment of $\sim$1.5 D in the sense + → − along the formal axis formed by the N–H bond. When the N-hydrogen is substituted by the 4-nitrophenyl radical, for example, its moment of about 4.1 D (judging by nitrobenzene) is added to that of the succinimide ring in the same sense along the formal axis of symmetry to give a total of 5.8 D.

The moment of glutarimide (2.6 D) is higher than that of succinimide and can be explained broadly by the smaller angle of 120° between the C═O groups in the former molecule, so that here the center of negative charge is further along in the N→H direction on the axis of the imide group, and the molecular moment is consequently higher.

The general effect of substituents on the moments of the two basic imide rings can be inspected from Table IX. Conjugation effects occur in the case of the aromatic substituents, as is evident from the fact that the moments of molecules bearing aromatic substituents are generally slightly greater than the moments of molecules bearing comparable aliphatic substituents. In the case of N-phenyl-substituted imides, *ortho* substitution on the phenyl groups causes a special effect due to interaction of the *ortho* substituent with one or other of the C═O groups of the imide ring.[278] In the cases of the cyclohexane 1,2- and 1,3-dicarboximides, the five-membered imide ring is almost certainly strongly puckered so that the C═O groups are not almost coplanar as they are in the unsubstituted imide ring; the bond moments in these and related imides have been analyzed in terms of the likely geometry of the various groups present.[277]

Studies have been made of the dipole moments of phthalimide and several of its derivatives in their ground states and first electronic excited states, and the results have been related

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to the observed uv spectra.[279–281] Similarities in the spectra of amino-substituted maleimide and phthalimide have been discussed in this light.[281]

D. MAGNETIC RESONANCE

1. *Nmr of the Imide Hydrogen*

The characterization of imides through the proton resonance of the imide hydrogen is made elusive by the serious broadening effect on the proton resonance caused by interaction with the nuclear quadrupole of the nitrogen, which occurs in the case of all such compounds that have a nonzero electric-field gradient at the nitrogen nucleus owing to the disposition of the bonding electrons around it. In the case of N–H groups in which there is no rapid exchange of the hydrogen with other molecules, the broadening effect is also accentuated by the splitting of the proton resonance into a triplet, through spin–spin interaction of the nitrogen and hydrogen nuclei. Thus, the resonance signal from the N–H proton may be so broad as to be lost in the base line and background noise or be buried under the signals due to other protons. The resonance of the N–H proton in succinimide, for example, cannot be found.[7,285,286] However, broad signals centered at τ 0.8–1.0 have been found for C-phenyl-substituted succinimides, and signals centered at τ 1.3–1.5 occur for the N–H proton in glutarimide and its C-aryl- and C-alkyl-substituted derivatives and in glutaconimides dissolved in deuteriochloroform.[286] The N-hydrogen of the five-membered ring succinimides is more acidic than that of the six-membered ring imides. The N–H proton resonance could not be found for malimide and tartrimide.[7] (The N–H proton resonance for acetamide, for comparison, is a very broad band centered at τ 3.8 and extending from τ 3.3 to 4.3.)

2. *Nmr of the Protons on Carbon*

The methylene protons of succinimide come into resonance at τ 2.74. The methylene protons at the 2 position of glutarimide are at τ 2.58, and those at the 3 position are at τ 1.95. Succinimide derivatives substituted at both 2 positions and glutarimides substituted at both 3 positions possess isolated methylene groups at the 2 positions which, when the substituents are alkyl, have the same chemical shifts even though these molecules have no symmetry. When one of the substituents is phenyl there is a substantial differentiating effect of the diamagnetic anisotropy of this group on the shifts of the two methylene protons; for example, the shift of the methylene protons in 2-methyl-2-phenylsuccinimide are τ 2.87 and 3.12, and the spin–spin coupling constant is 18.5 cps.[286] There appears to be a consistent difference between this coupling constant in the five-membered ring imides and the six-membered ones in which it is about 16.4 cps. This is attributed to a consistent difference in H–C–H bond angle in the two types. In this general connection, the resonance of the protons at the 2 and 3 positions of N-phenyl-2-methoxysuccinimide does show an ABX type of pattern.

Table IX

Dipole Moments of Imides in Dioxane Solution (Debye Units)

Compound	*Temp, °C*	*Moment*
Succinimide[277]	30	1.47
Succinimide[282]	20	1.54
N-Methylsuccinimide[277]	30	1.61
N-Phenylsuccinimide[283]	25	1.68
N-*o*-Tolylsuccinimide[283]	25	1.93
N-Benzoylsuccinimide[277]	30	1.80
N-(2,5-Dimethylphenyl)succinimide[284]	25	1.54
N-(2,6-Dimethylphenyl)succinimide[284]	25	1.87
N-2-Chlorophenylsuccinimide[283]	25	1.78
N-3-Chlorophenylsuccinimide[283]	25	2.92
N-4-Chlorophenylsuccinimide[283]	25	3.30
N-2-Nitrophenylsuccinimide[284]	25	3.55
N-3-Nitrophenylsuccinimide[284]	25	5.11
N-4-Nitrophenylsuccinimide[283]	25	5.77
N-(2-Methyl-4-nitrophenyl)succinimide[284]	25	5.86
N-2-Chlorobenzylsuccinimide[284]	25	2.34
N-4-Chlorobenzylsuccinimide[284]	25	2.69
N-4-Methoxyphenylsuccinimide[283]	25	2.00
N-4-Nitrobenzylsuccinimide[283]	25	5.01
Glutarimide[277]	30	2.58
N-Methylglutarimide[277]	30	2.70
2,4-Methylethylglutarimide[277]	30	2.92
2-Ethyl-2-phenylglutarimide[277]	30	2.83
2-(*p*-Aminophenyl)-2-ethylglutarimide[277]	30	3.64
cis-Cyclohexane-1,2-dicarboximide[277]	30	1.74
Cyclohexane-1,3-dicarboximide[277]	30	2.89
N-Methylcyclohexane-1,3-dicarboximide[277]	30	2.88
3,6-Methanocyclohexane-1,2-dicarboximide[277]	30	2.24
Phthalimide[282]	30	2.10
N-Methylphthalimide[283]	25	2.24
N-Phenylphthalimide[283]	25	2.34
N-*o*-Tolylphthalimide[283]	25	2.47
N-(2,5-Dimethylphenyl)phthalimide[283]	25	2.10
N-(2,6-Dimethylphenyl)phthalimide[283]	25	2.54
N-(2,4,6-Trimethylphenyl)phthalimide[283]	25	2.36
N-(2-Chlorophenyl)phthalimide[283]	25	2.26
N-(3-Chlorophenyl)phthalimide[283]	25	3.47
N-(4-Chlorophenyl)phthalimide[283]	25	3.99
N-(2-Nitrophenyl)phthalimide[283]	25	3.70
N-(3-Nitrophenyl)phthalimide[283]	25	5.70
N-(4-Nitrophenyl)phthalimide[283]	25	6.45
N-(2-Methyl-4-nitrophenyl)-phthalimide[283]	25	6.60
N-(4-Chlorobenzyl)phthalimide[283]	25	3.39
3-Chlorophthalimide[278]	20	2.28
3-Nitro-N-methylphthalimide[278]	20	3.75
3-Chloro-N-methylphthalimide[278]	20	2.45
4-Chlorophthalimide[278]	20	1.43
4-Nitrophthalimide[278]	20	2.60
4-Chloro-N-methylphthalimide[278]	20	1.31
4-Nitro-N-methylphthalimide[278]	20	2.56
4-Nitro-N-phenylphthalimide[278]	20	2.61
3-Dimethylaminophthalimide[280]	20	4.8
2,5-Diaminophthalimide[280]	20	5.4
3-Aminophthalimide[280]	20	4.9
3-Acetamidophthalimide[280]	20	4.5

The glutaconimides show spin–spin coupling between the protons in the 2 position and the N proton, $J_{\mathrm{H_2HN}} = 1.5$ cps.[286]

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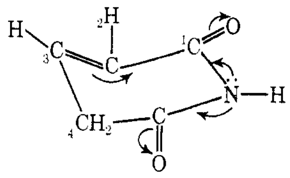
This is typical of protons associated with conjugated systems and constitutes a nice demonstration of the strong mesomerism of the imide group (VII).



VII

In 2-ethyl-2-phenylsuccinimide and 2-ethyl-2-phenylglutarimide the methylene protons of the ethyl group have the same chemical shift even though these molecules have no symmetry. However, in 4-ethyl-4-phenylglutaconimide these two methylene protons curiously have different chemical shifts.[286] The introduction of the double bond in the latter compound compared to the former two may create a dissimilarity in the populations of the rotational conformers of the ethyl group, or possibly the anisotropy of the C=C double bond may be critically important.

The chemical shifts of the protons in the 2 and 3 positions in succinimide and maleimide are about 0.33 ppm to higher field compared to the corresponding anhydrides, and the shifts for the imides are not affected by N substitution by simple alkyl groups. These shifts are lowered by about 0.17 ppm when the N-hydrogen atom is substituted by the allyl group, however.[287] This, again, is clear evidence for conjugation in the imide ring.

The ethylenic protons of N-substituted maleimides show large upfield shifts of almost 1 ppm induced by benzene as solvent compared to the carbon tetrachloride. This results from the diamagnetic anisotropy of the benzene molecule in association with the imide molecule.[288]

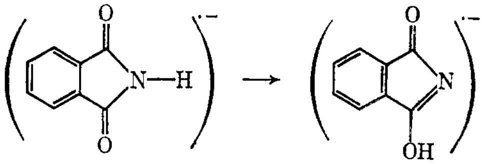
N-Cyclohexylphthalimide has been studied with particular regard to the effects an alkyl substituent on the cyclohexane ring have on the chemical shifts of adjacent axial and equatorial protons.[289]

3. *Miscellaneous Magnetic Resonance Studies*

Elegant studies of the ^{15}N and ^{13}C nmr resonances of phthalimide and N-methylphthalimide containing these nuclides have enabled the following spin–spin coupling constants to be determined: $J_{^{15}\mathrm{N-H}} = 93.0 \pm 8$, $J_{^{13}\mathrm{C-H}} = 141.5 \pm 0.2$, and $J_{^{15}\mathrm{N-C-H}} = 1.4 \pm 0.2$ cps. These and other data were interpreted in terms of Fermi contact coupling mechanics, and empirical relationships were developed which relate the coupling constants to orbital hybridization.[290]

The quadrupole resonances of the halogen nuclei in N-halosuccinimides have been investigated at liquid nitrogen temperatures. The bromine and iodine substituents are polarized positive with respect to the nitrogen as a result of the strong electron-attracting properties of the imide group, but the less polarizable and more strongly electron-attracting N-chloro substituent is negative.

Electron spin resonance studies of radical anions of phthalimide and related compounds have been reported.[291] The radical anions were generated by electrolytic reduction of the imide dissolved in dimethylformamide with tetra-*n*-butylammonium iodide as the supporting electrolyte. The initially formed free-radical anion of phthalimide is unstable at room temperature and may undergo an acid-catalyzed rearrangement to an enolic form.[291]



Tables of spin densities and splitting constants were given and discussed theoretically. Radical anions of N-alkylphthalimides have been generated by electrolytic reduction in acrylonitrile solvent, and with less clear results by alkali-metal reduction in tetrahydrofuran.[292] The radicals are stable for some days in solution.

Phthalimide and 1,8-naphthalimide nitroxide radicals can be formed by reduction of the corresponding N-hydroxyimides,[293,294] and the chemistry of such radicals has been explored.[295]

E. INFRARED SPECTRA

1. *Vibrations of the N–H Group*

The frequency of the N–H stretching vibration in the infrared absorption spectra of imides occurs in the range 3000–3500 cm^{-1} and may be confused with bands due to hydroxyl substituents or water. The N–H bands are always of high intensity, however. For imides in dilute solution in carbon tetrachloride relatively sharp bands are obtained for the nonhydrogen-bonded N–H at, for example, 3426 cm^{-1} in the case of succinimide and 3386 cm^{-1} for glutarimide.[296] Apparently two broad N–H stretching bands have been found for succinimide and maleimide in the crystalline state, in which the N–H is hydrogen bonded to a C=O of a twinned molecule.[297] These frequencies are shown in Table X, and they are attributed to the phenomenon of Fermi resonance of the N–H stretching vibration with a combination tone: 1700 plus 1418 in the case of succinimide, and 1700 plus 1375 for maleimide. Broad bands in the range 3000–3300 are quite usual for hydrogen-bonded N–H groups. The N–H bending motion in these five-membered ring compounds is coupled with the antisymmetric stretch-bending vibration of the C–N–C atoms of the imide group; this is a sympathetic motion of the same symmetry as the N–H bending motion, and the frequencies associated with this combination are at about 1400 and 1170 cm^{-1} (Table X). The deformation of the N–H bond out of the plane of the five-membered rings of succinimide and maleimide are assigned to frequencies 849 and 725 cm^{-1}.[297] In these respects, the N–H bond behaves much the same as the O–H bond.

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Table X

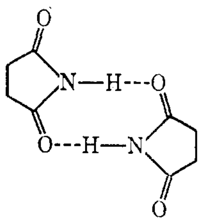
Assignment of Infrared Band Frequencies (cm^{-1})^{a} Characteristic of the Imide Function in the Spectra of Pure Crystalline Maleimide and Succinimide^{297}

Maleimide	*Succinimide*	*Assignment*
3221 s, br	3190 s, br	N—H stretching
3070 sh	3080 s, br	Fermi resonance of N—H stretching
1771 m	1772 m	C=O stretching (free)
1700 vs, b	1700 vs, br	C=O stretching (H-bonded)
1375 m	1418 m	N—H and C—N—C bending (coupled)
1350 s, br	1378 s	Symmetric C—N—C bending
1154 s	1198 s	N—H and C—N—C bending (coupled)
938 s	936 m	Ring vibration
643 m	636 m	C=O in-plane bending
725 m, br	849 s	N—H out-of-plane deformation
550 w	556 w	C=O out-of-plane deformation

^{a} s = strong, m = medium, w = weak, v = very, br = broad, sh = shoulder.

2. *Vibrations of the C=O Group*

The infrared spectra of imides usually exhibit two bands in the carbonyl-stretching region, and these have attracted a great deal of study particularly as the variation of C=O stretching frequencies with ring size and substituents in all classes of compounds has attracted the attention of many academicians. In the solid state (solid imides run as Nujol mulls, for example) one of the carbonyl groups is hydrogen bonded and the other is not, because the imide molecules are twinned (VIII). Hence, the observation of two frequencies for the solid is usually attributed to this. However, quite apart from the phenomenon of hydrogen bonding, the imide group has a formal plane of symmetry, and two frequencies would be expected corresponding to symmetric and antisymmetric vibrations of the two carbonyl groups in phase and out of phase. Thus, in dilute solution in the monomolecular state imides should show two carbonyl stretching bands, which should not be greatly affected by substituents.



VIII

Table XI

Frequencies (cm^{-1}) for C=O Stretching in the Infrared Spectra of Imides

Compound	*Method*	*Frequencies*
Succinimide^{296}	10^{-3} *M* in CCl$_4$	1753, 1727
Succinimide^{244}	10^{-2} *M* in acetonitrile	1769, 1728
Succinimide^{298}	KBr disk	1770, 1698
Succinimide^{297}	Crystal mull	1772, 1700
Succinimide^{296}	Crystal	1771, 1690
Maleimide^{244}	10^{-2} *M* in acetonitrile	1770, 1737
Maleimide^{298}	KBr disk	1770, 1702
Phthalimide^{244}	10^{-2} *M* in benzene	1781, 1747
1-Azabicyclo[3.3.0]-2,8-octanedione^{259}	KBr disk	1765, 1690
Glutarimide^{296}	10^{-3} *M* in CCl$_4$	1742, 1730
Glutarimide^{298}	KBr disk	1703, 1669
Glutarimide^{296}	Crystal mull	1701, 1665
1-Azabicyclo[4.4.0]-2,10-decanedione^{259}	KBr disk	1737, 1657
1,8-Naphthalimide^{299}		1702, 1684

Table XI lists the frequencies observed for the C=O stretching bands of common imides and some bicyclic ones. Although the estimation of the center of these overlapped broad bands is probably subject to an error of at least ±5 cm^{-1} and depends somewhat on the conditions under which the spectrum was obtained, a trend dependent upon ring size is clear. The frequencies for the five-membered ring compounds in the crystalline condition, both mull and KBr disk, appear to be generally higher than those for imides with less strained rings: around 1770 and 1700 cm^{-1} for the former, and lowered toward 1700 and 1660 cm^{-1} for six-membered ring compounds and 1,8-naphthalimide. Bicyclic[3.4.0]imides containing a seven-membered ring do not really show any further lowering of these frequencies.[259] This type of trend is usually explained by a change in hybridization of the C=O σ-bond electrons: the smaller ring has the larger C–C–N bond angles for which the σ bonds have greater p character, in which case the carbonyl groups have greater s character in the σ bond, are stronger consequently, and have higher force constants and higher frequencies of vibration.[296,300]

The existence of a low-energy *cis–trans* isomerism in N-substituted amides and N-substituted noncyclic imides, resulting from partial double bond formation in the C–N bond of the amide group, has been well recognized, and infrared spectra have been interpreted accordingly.[301–303] Although there is no case of isomerism with cyclic imides, this electronic effect is important to the high degree of coupling of the stretching motions of the two carbonyl groups.[304] The mechanical coupling, well recognized by Bellamy and his coworkers,[305] is strongly effective in imides because of the mesomerism in the O=CNC=O bond system, and, as we have seen, the frequency separation is as much as 70 cm^{-1}. For the same reason, the carbonyl stretching frequencies of imides are measurably sensitive to the degree of conjugation of the imide group with N substituents.[306] A large amount of

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data on this point is available and will not be reproduced here.[123,244,278,307] In general, N-substituted succinimides, phthalimides, and maleimides have their two frequencies over the respective ranges 1780–1770 and 1775–1705, 1780–1775 and 1740–1715, and 1780–1770 and 1730–1710 cm^{-1} for dilute solutions.[244] The lower frequency is generally the more affected one. An outstanding example is perhaps N-bromomethylsuccinimide for which 1830 and 1712 cm^{-1} are reported.[307] The range for N-substituted glutarimides appears to be about 1730–1715 and 1690–1665 cm^{-1}.[277] There is naturally some variation of these ranges with the medium for which the spectrum is run. In the case of substituted 1,8-naphthalimides, the two bands ranged from 1720 to 1700 and from 1680 to 1600 cm^{-1}, and a good correlation with the inductive and mesomeric effects of both N substituents and ring substituents was reported.[299] However, in other work no simple correlation of frequencies with the Hammett substituent constants could be found.[244]

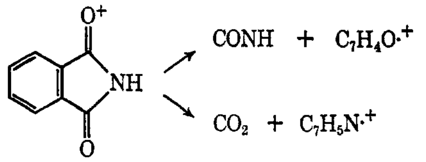
Fayat and Foucard have analyzed quite carefully the effects of N substituents on the two carbonyl frequencies in a set of glutarimide derivatives.[306] The difference between the frequencies of the bands ranged from 40 to 70 cm^{-1}, and the extinction coefficients for the bands of higher and lower frequency were respectively in the ranges 50–300 and 1100–2400 for 10^{-4} *M* solutions in carbon tetrachloride. The ratio of the integrated intensities of the bands was shown to be more sensitive to the substituents than the ratio of extinction coefficients; the ratios of intensities of the low- and high-frequency bands for N-substituted succinimides were in the range 7–32 and increased as the conjugating power of the substituent increased, and for N-substituted glutarimides the ratios were within the range 4–6.[306] These ratios have also been shown to depend on the solvent, and the high intensity of the band at lower frequency attributed to the antisymmetric carbonyl vibration has been considered due to Fermi resonance of this vibration with a combination of skeletal vibrations.[308]

We should note that the spectra of succinimide, for example, show anomalous bands in potassium chloride and potassium bromide disks when these are not suitably prepared. This phenomenon is due probably to adsorption of a proportion of the succinimide molecules on the surface of crystals of the salts and can be avoided when the materials or disks are allowed to mature in contact with a certain amount of water vapor which presumably modifies the crystallinity of the alkali halide so as to produce a more homogeneous frozen melt.[309] Succinimide forms a definite addition compound with potassium iodide, so that this material must be avoided.[293,309]

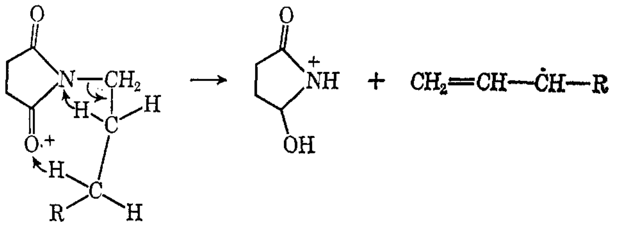
The temperature dependence of band shape and intensity of infrared bands of imides have been studied.[310–312]

F. MASS SPECTRA

The mass spectra of several imide derivatives have been run, and they exhibit the diverse characteristics summarized below, but data appear to be available on only two parent imides. The chief pathways of fragmentation of phthalimide positive ions are as follows.



Maleimide positive ions behave the same way and also readily eliminate CO.[318] The curious elimination of carbon dioxide has been observed also in the cases of N-phenylphthalimide[314] and certain of its derivatives by substitution on the N-phenyl group,[238,314] and also for N-methylphthalimide.[315] This almost certainly does not occur through a preliminary thermal isomerization of imide to isoimide; rather, a transfer of oxygen across the ring is thought to occur in an excited state of the positive ion.[313] This process is not important in the fragmentation of positive ions of those N-substituted imide derivatives that can undergo competitively rapid decomposition through transfer of hydrogen to one of the carbonyl groups, with concomitant elimination of the substituent. Examples are N-2,6-dimethylphenylphthalimide,[313] N-2-phenylphenylphthalimide,[314] N-alkylphthalimide,[316,317] and N-alkylsuccinimides.[318] The chief positive-ion fragmentation paths of the latter have been studied in detail by deuterium labeling in the N-alkyl chain. A certain amount of normal C–C bond cleavage occurs in the side chain, but the most abundant ion fragment in the spectrum of these molecules arises from a double hydrogen atom transfer from the side chain to the polar imide ring and loss of the appropriate hydrocarbon radical as, for example



N-*t*-Butylphthalmide positive ions also show this type of degradation, by the transfer of two hydrogen atoms, and the two main fragmentation paths of the molecular ion appear to be as shown in Scheme VI.

Some further remarks on the mass spectra of this type of compound and also a 1-alkylmaleimide, which shows a remarkably stable molecular ion,[319] are given in a well-known text which, however, only reviews the literature up to 1967.[320] Later studies of methylethylmaleimide, 2-carboxyethylmethylmaleimide (hematinic acid), and its methyl ester each

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(307) L. W. Kisinger and H. C. Ungnade, *J. Org. Chem.*, **23**, 815 (1958).

(308) C. Fayat and M. Guerro, *C. R. Acad. Sci., Paris, Ser. C*, **267**, 1202 (1968).

(309) A. Tolk, *Spectrochim. Acta*, **17**, 511 (1961).

(310) N. A. Borisevich and G. A. Zalesskaya, *Opt. Spektrosk.*, **16**, 772 (1964).

(311) N. N. Khovratovich and N. A. Borisevich, *Opt. Spektrosk. (Akad. Nauk USSR, Otd. Fiz.-Mat. Nauk)*, **3**, 123 (1967).

(312) G. A. Zalesskaya, *ibid.*, **3**, 121 (1967).

(313) T. W. Bentley and R. A. W. Johnstone, *J. Chem. Soc., C*, 2354 (1968).

(314) J. L. Cotter and R. A. Dine-Hart, *Chem. Commun.*, 809 (1966).

(315) R. A. W. Johnstone, B. J. Millard, and D. S. Millington, *ibid.*, 600 (1966).

(316) R. T. Aplin and J. H. Jones, *ibid.*, 263 (1967).

(317) J. Sharvit and A. Mandelbaum, *Israel J. Chem.*, **5**, 33 (1967).

(318) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2913 (1965).

(319) M. Grassl, U. Coy, R. Seyffert, and F. Lynen, *Biochem. Z.*, **338**, 771 (1963).

(320) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, Calif., 1967, Chapter 9-2.

show a quite stable molecular ion; losses occur from side chains, and CO, H, and N are lost from the maleimide ring.[321]

A number of N-oxy derivatives of imides have been studied, and they all exhibit individual characteristics.[322] Loss of CO, rather than CO_2, is the prime decomposition path of N-hydroxysuccinimide positive ions. N-Methoxysuccinimide positive ions readily lose formaldehyde from the methoxyl group, however, to the exclusion of other initial processes. N-Hydroxyphthalimide positive ions, in contrast to their N-alkyl and N-aryl analogs, decompose in a most straightforward manner: first loss of $O\cdot$ or NO occurs and then the latter loss is followed by consecutive losses of 2CO and C_2H_4. N-Carbethoxyphthalimide positive ions (M^+) lose $C_2H_3\cdot$ or $C_2H_5O\cdot$ from the ethoxy substituent, and losses of CO_2 from M^+ and from the ions $M^+ - C_2H_5O\cdot$, $M^+ - C_2H_3\cdot$, and $M^+ - C_2H_5O\cdot$ occur, the latter loss apparently parallelling the elimination of CO_2 from excited states of the N-methyl- and N-phenyl-substituted phthalimides described above. Somewhat similarly, N-acetylphthalimide positive ions decompose by losses of $CH_3\cdot$, CO, $COCH\cdot$, $COCH_2$, and $C_6H_4CO^+$, and loss of CO_2 occurs from the ion $C_6H_4(CO)_2NH^+$.[323] However, surprisingly, N-benzylphthalimide behaves differently: there is no loss of CO_2; there is loss of H_2O, $C_6H_5CNH^+$, and two consecutive losses of CO from the parent ions. Hence, there is no general rule for the decomposition of the positive ion of N-substituted imides; the nature of the substituent directs the main paths of decomposition.

G. ULTRAVIOLET SPECTRA

The ultraviolet absorption spectrum of simple imides like succinimide and glutarimide, in the commonly accessible region available for spectrophotometry in the liquid phase, consists of an intense band near 200 mμ. This is, of course, best detected for the imides in the gas phase, but the band can be seen when solvents that do not absorb prohibitively in this region are used, provided that only thin layers of solution are placed in the spectrophotometer beam. The bands observed in the vacuum ultraviolet spectrum for succinimide and its C-alkyl substituted derivatives are at about 191 mμ,[324] whereas they are displaced to slightly longer wavelengths when ethanol is used as solvent (Table XII). The band for glutarimide is at 198 and 204 mμ under vacuum and ethanol. N-Methyl substitution shifts the λ_{max} slightly to longer wavelengths (bathochromic shift).

The origin of this intense band is not certain, but it is probably a $\pi \rightarrow \pi^*$ transition of the C=O double bond in conjugation with the nonbonded valence-electron pair of the nitrogen. It is unlikely that there should be a high-intensity, low-energy $\pi \rightarrow \pi^*$ transition over the O=CNC=O bond system, because this does not possess the right symmetry. The absorption bands for imides, therefore, must be considered as arising from transitions involving orbitals concerned with individual bonds and unshared electron pairs, and some estimation of what to expect can be obtained by a consideration of the situation for acetone.

Scheme VI

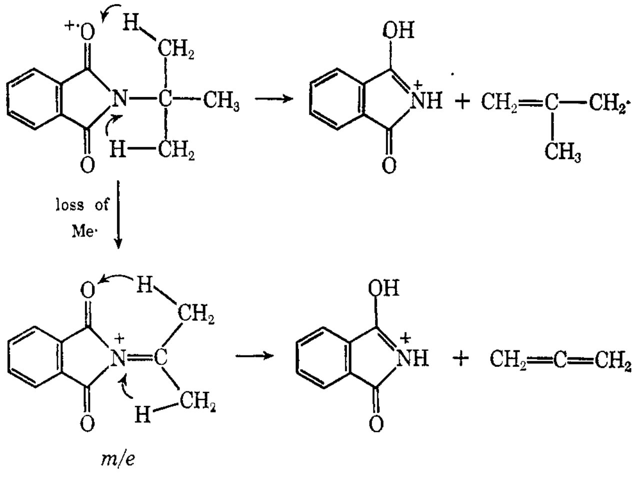

Table XII

Maxima of the Ultraviolet Absorption Spectra of Imides and N-Methylimides in Ethanol

Imide	λ_{max}, *mμ* (10^{-3} × ε)		
Succinimide[277]	194 (12.0)		
N-Methylsuccinimide[277]	204 (13.0)	242 (0.110)	
Glutarimide[277]	204 (14.7)		
N-Methylglutarimide[277]	210 (15.6)		
1-Azabicyclo[3.3.0]-2,8-octanedione[259]	232 (1.40)	267 (0.093)	
	243 (0.360)	276 (0.080)	
	253 (0.170)	187 (0.044)	
cis-Cyclohexane-1,2-dicarboximide[277]		255 (0.090)	
cis-Cyclohexane-1,3-dicarboximide[277]	206 (14.0)		
N-Methyl-*cis*-cyclohexane-1,3-dicarboximide[277]	212 (15.0)		
Maleimide	216 (15.2)		
	223 (13.0)		
N-Methylmaleimide	217 (13.6)	231 (5.60)	297 (0.74)
	223 (11.7)		
Phthalimide[325]	217 (40.0)	230 (16.6)	292 (1.90)
		238 (10.7)	298 (1.87)
1,8-Naphthalimide[325]	214 (20.5)	232 (48.1)	333 (12.8)
			342 (12.4)

Apart from the ever-present Rydberg absorption, acetone has a nonionization absorption band at about 150 mμ, a moderately intense band (extinction coefficient (ε ~1000) at 190 mμ, and a low-intensity band (ε ~12) at 277 mμ.[326,327] The origin of the band at 150 mμ need not concern us. The moderately intense band at 190 mμ appears to be due either to the $\pi \rightarrow \pi^*$ transition or a symmetry-allowed $n \rightarrow \pi^*$ transition or both, and the low-intensity 277-mμ band is certainly due to the symmetry-forbidden $n \rightarrow \pi^*$ transition.[328] The latter type of transition depends for its occurrence on vibrational perturbations of the molecule. It is reasonable to assign

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(321) R. K. Ellsworth and S. Aronoff, *Arch. Biochem. Biophys.*, **124**, 358 (1968).

(322) J. H. Bowie, M. T. W. Hearn, and A. D. Ward, *Aust. J. Chem.*, **22**, 181 (1969).

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(324) D. W. Turner in "Determination of Organic Structures by Physical Methods," Vol. 2, F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1962, Chapter 5.

(325) C. M. Lee and W. D. Kumler, *J. Org. Chem.*, **27**, 2055 (1962).

(326) H. L. McMurry, *J. Chem. Phys.*, **9**, 231 (1941).

(327) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy—Chemical Applications," 2nd ed, Butterworth & Co., Ltd., London, 1967.

(328) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, New York, N. Y., 1962, Chapters 5 and 9.

the 190-mμ band to the $\pi \rightarrow \pi^*$ transition because of its expected energy relative to other possible transitions,[328] but its intensity is apparently somewhat unusually low for a transition of this type. However, the high intensity and location of the band at about 200 mμ in imides is entirely consistent with the $\pi \rightarrow \pi^*$ transition in the C=O group (in conjugation with the lone-pair p electrons of the nitrogen). That the whole O=CNC=O system is not involved in this band is evident from the fact that there is very little shift in wavelength of this band between amides and imides, and the intensity difference is approximately a factor of 2; thus, aliphatic amides absorb in the range 180–200 mμ with extinction coefficients in the range 6000–7000, while aliphatic imides have ϵ in the range 10,000–16,000.[324,329] The presence of alkyl substituents at the α carbon in succinimide results in a decrease in the intensity of the band at 190 to 200 mμ, over the ϵ range 15,000–10,000, and the reduction is roughly proportional to the number of methyl substituents introduced, while λ_{max} only varies within ±5 mμ.[329]

Transitions involving the n electrons of either the oxygen or nitrogen in imides depend on individual structures, as would be expected; it is curious that the unsubstituted succinimide and glutarimide show no n bands in ethanol solution, but the N-methyl-substituted derivatives do show weak bands at longer wavelength which should be so assigned. Also, *cis*-cyclohexane-1,2-dicarboximide shows an n band in ethanol solution at 255 mμ. In tetrahydrofuran as solvent, the bicyclic azaimides, which have a different orientation of the O=CNC=O bond system compared to the other common imides, show several low-intensity n bands (Table XII), and interactions of the imide molecules with the solvent also play a part in permitting n-type transitions.[259] The possession of n bands in the uv spectrum is therefore a likely property of all N-substituted imides.

It is worthy of note that the five-membered and six-membered lactams show bands of modest intensity ($\epsilon \backsim 400$) at 214 and 221 mμ.[330] These are probably n bands, from their low intensity, and $\pi \rightarrow \pi^*$ bands of high intensity for these compounds are probably to be found at wavelengths lower than 200 mμ, as for amides.[331]

Some of these matters can certainly not be regarded as settled, and this area deserves further theoretical and experimental research; probably there are other n bands of very low intensity above 210 mμ observable for the simple imides, and they have not been reported because they have not been sought.

In the case of maleimide, high-intensity $\pi \rightarrow \pi^*$ bands from its O=C—C=C and O=C—C=C—C=O conjugated systems would be expected at about 217 and 226 mμ, by analogy with crotonaldehyde and diacetylethylene, for example. Such bands are indeed found and, as with the simple imide group, the parent compound apparently shows no n-type bands of low intensity whereas the N-methyl derivative does.

Phthalimide and naphthalimide show several bands and, of course, the high-intensity bands in the range 200–240 mμ must be regarded as due both to the C=O group and the aromatic system; no doubt many bands are overlapped here. The ultraviolet spectra of a number of phthalimide and N-phenylphthalimide derivatives substituted in the phenyl ring and in the phthalimide ring have been studied and reviewed. It has been shown, for example, that the electron-donating hydroxyl and methoxyl substituents in the *para* position cause bathochromic shifts and intensity increases in bands in the range 215–360 mμ in accord with general observations on $n \rightarrow \pi^*$ bands.[332,333]

H. OPTICAL ROTATORY DISPERSION AND CIRCULAR DICHROISM

The ORD curve of N-((*S*)-α-phenylethyl)phthalimide shows a positive Cotton effect superimposed on a strong negative background. The positive Cotton effect occurs in the same region of the spectrum as the broad absorption band over the range 275–350 mμ which is shown by phthalimide and its N-alkyl derivatives, but not by α-phenylethylamine or its succinyl derivative. The succinyl derivatives show only plain dispersion; hence, this indicates that the phthalimido chromophore is responsible for the Cotton effect. The values of [M]D are given in Table XIII for different substituents. The position of the first extremum appears to be influenced by the polar effects of the substituents.[334] The optical rotatory dispersion of N-((*S*)-α-phenylethyl)phthalimide in methanol, methanol containing HCl, ethanol, propanol, 1-butanol, *t*-butyl alcohol, and a number of other solvents has been studied in order to determine the effect of solvent on the dispersion of rotation. It was suggested that the nature of the rotatory dispersion of such compounds is determined by the effect of the solvent on mesomerism in the amide group.[335]

Table XIII

Dispersion Constant [M] for the ORD of Phthaloyl Derivatives of *para*-Substituted α-Phenylethylamines[334]

para substituent	Trough λ_{max}, *mμ*	Trough *[M]*	Peak λ_{max}, *mμ*	Peak *[M]*
NO	365	−995	335	−150
H	400	−410	340	+190
Cl	390	−590	340	+200
Br	390	−600	340	+170
I	390	−640	340	+100
OCH_3	400	−510	350	+50
NH_2	425	−450	380	−290

The ORD of maleoyl, itaconoyl, and phthaloyl derivatives of (*S*)-(+)-1-phenyl-2-aminopropane, (*R*)-(+)-1-phenylethylamine, and (*S*)-(+)-1,2-diphenylethylamine, and the corresponding cyclohexylamine, have been studied in the range 240–400 mμ together with the ORD spectra of the parent amines.[336] Derivatives of alkylcyclohexylamines give a principal Cotton effect which is positive for the *R* and negative for the *S* configuration. Derivatives of those phenylalkylamines with a phenyl group attached to the asymmetric center give curves

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[329] D. W. Turner, *J. Chem. Soc.*, 4555 (1957).

[330] R. Huisgen, *Angew. Chem.*, **69**, 341 (1957).

[331] H. D. Hunt and W. T. Simpson, *J. Amer. Chem. Soc.*, **75**, 4540 (1953).

[332] A. Arcoria and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **15**, 121 (1957).

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[334] J. H. Brewster and S. F. Osman, *J. Amer. Chem. Soc.*, **82**, 5754 (1960).

[335] V. M. Potapov, V. M. Dem'yanovich, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **35**, 1340 (1965).

[336] A. La Manna, V. Ghislandi, P. Scopes, and R. J. Swan, *Farmaco, Ed. Sci.*, **20**, 842 (1965).

with a Cotton effect of opposite sign to those of the corresponding cyclohexyl analogs of the same absolute configuration. Derivatives of (*S*)-1-phenyl-2-aminopropane in which the phenyl group is remote from the asymmetric center give a negative Cotton effect analogous to the cyclohexyl compounds of the same absolute configuration.[336]

The ORD spectra of (*R*)-tartrimide and (*S*)-maleimide show no peaks above 220 mμ;[7] the curves rise to the Cotton effect in the far-ultraviolet and are positive and negative, respectively, with inflections corresponding to the respective maxima in the CD spectra at 255 and 235 mμ.[10] The circular dichroism of these compounds is interesting in that tartrimide shows a change in the sign of the band at longest wavelength on changing from ethanol to water as solvent, while malimide shows no such change and neither do the N-substituted tartrimides. Perhaps this behavior should be interpreted in terms of the enhancement in ethanol of a band at 257 mμ or its suppression in water. It will be seen that in ethanol, (*S*)-malimide and (*R*)-tartrimide have respective bands at 255 and 257 mμ which are of the same sign. This is awkward for those who like to infer configuration from the sign of a band. Since a DC band is more directly related to a single electronic transition, whereas the ORD curve is derived often from a combination of a number of such transitions, which may not all have the same sign, thus in general one would expect the sign of the CD curve to be a better indication of the chirality of the molecule than the sign of the ORD curve. The above cases show this view to be an over-simplification; however, although the signs of the ORD curves correspond to the generally accepted structural relationship, this must be regarded as largely fortuitous in the absence of detailed knowledge of the contributions which make up the rotatory power.

I. FLUORESCENCE SPECTRA OF IMIDES

1. Introduction

The fluorescence spectra of the aromatic imides have been much studied, mainly in the USSR. They form a class of chemically stable, strongly fluorescing substances which are useful as optical bleaches. Many aromatic imides fluoresce in the blue-green region. Optical bleaches or brightening agents absorb light in the ultraviolet region and emit blue light, which compensates for the absorption of blue light by aged or soiled textile materials. In this way the material appears to be whiter than would otherwise be the case. It is, however, necessary that the compound used should not absorb in the visible region, and in general the aromatic imides are satisfactory in this respect. Of particular importance to their suitability as fluorescent agents, phthalimide derivatives possess the molecular rigidity that is required to retain electronic excitation energy sufficiently long in the molecule for it to be released as radiation rather than its being lost through vibrational degeneration and interaction with surroundings. A substantial amount of work has been reported on details of the fluorescence spectra, and the general trends of the work are reviewed below.

2. Behavior of Fluorescence Spectra

The work has been concentrated on phthalimide and naphthalimide substituted by the amino group and its derivatives. Intensity measurements on the fluorescence spectra of N-substituted 4-amino-, 4-acetamido-, 4,5-diamino-, and 4,5-diacetamido-1,8-naphthalimide have shown that the fluorescence yield is increased by greater electron-releasing characteristics in the substituents.[337,338] Detailed behavior of the spectra of many phthalimide derivatives has been determined with respect to variation in environment. The shifts in the fluorescence spectra brought about by the association of such imides with solvent molecules such as benzene, ethyl acetate, isoamyl alcohol, acetone, anisole, carbon tetrachloride, pyridine, toluene, and dioxane have been investigated from a comparison of the spectra run in single solvents with spectra run in mixed solvents.[339] The sensitivity of a spectrum to the nature of the solvent (and increase in temperature) decreases with the following order of substituents: 3-amino, 2-amino, 2-methylamino, 2,5-diamino, 2,5-di(dimethylamino), and 2,5-di(acetylamino).[339] Change of solvent usually shifts the absorption and fluorescence spectra in the same direction, but with some imides, such as 2-acetamido- and 2,5-diacetamidophthalimide, the shifts are in opposite directions.[340] In all solvents, increase of temperature generally causes a hypsochromic shift of the spectra, broadening of the bands, and a strong decrease in the quantum yield.[339] The shift of the maxima of both absorption and fluorescence spectra to shorter wavelengths with increasing temperature has been observed with other solvents up to 150°.[341] The lowering of the temperature toward −196° also causes the maxima of the fluorescence bands to move closer together. Suitable Frank–Condon models of potential curves of the ground and excited states can provide satisfactory explanations of such observations.[341] Transitions from the dissolved state to the vapor are generally accompanied by a displacement of the spectra to shorter wavelengths, and by little other change.[268,342] Spectra in the vapor phase were observed to be essentially independent of temperature over the range 150–250°.[268]

3. Polarization of Fluorescence

While the above details of the fluorescence spectra of phthalimide derivatives have been fairly extensively studied for some time, the study of the polarization of the fluorescent radiation has only been undertaken more recently, mainly by Gurinovich, Sarzhevskii, and Sevchenko, jointly and severally, and also by Klochov and Neporent. The assessment of results in this field is somewhat difficult since these main groups of workers appear to disagree both on experimental technique and the interpretation of their results. The polarization spectra and the spectral dependence of the dichroism of a series of phthalimide derivatives were examined by Sarzhevskii, and he proposed a scheme for the distribution of the absorption and emission oscillators in the phthalimide molecule. The shorter wavelength absorption oscillators are assumed to be aligned along the transverse axis of the molecule while the longer wavelength emission and absorption oscillators were directed along the longitudinal axis of the mole-

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(337) K. Yasuda, *J. Chem. Soc. Jap.*, **80**, 960 (1959).

(338) K. Yasuda, *ibid.*, **79**, 897 (1958).

(339) N. G. Bakhshiev and I. V. Piterskaya, *Opt. Spektrosk.*, **19**, 698 (1965).

(340) T. Rudy, *Tr. Inst. Fiz. Mat. Akad. Nauk Beloruss. SSR*, No. 3, 167 (1959).

(341) L. G. Pikulik and M. A. Solomakho, *Izv. Akad. Nauk SSSR, Ser. Fiz.*, **22**, 1391 (1958).

(342) B. S. Neporent, V. V. Zelinskii, and V. P. Klochkov, *Dokl. Akad. Nauk SSSR*, **92**, 927 (1953).

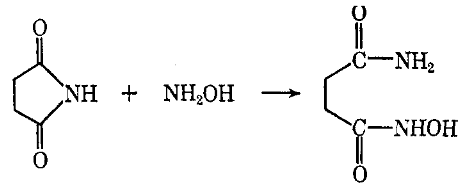
cule.[343] In the case of the molecular fluorescence of solid solutions of phthalimide derivatives in poly(methyl methacrylate), the degree of polarization approached the theoretical limit of 50% and was found to depend on the difference between the frequency of excitation and that of the fluorescent light.[344] The effects of temperature and viscosity on the polarization of fluorescence in phthalimide derivatives were studied in ethylene glycol, cyclohexanol, glycerol, 2-butanol, and several other solvents, over the temperature range 20–90°. The various factors were related by the Levshin–Perrin equation

$$\frac{1}{P} = \frac{1}{P_0} + \left(\frac{1}{P_0} - \frac{1}{3}\right)\frac{kT}{v\eta\tau}$$

Here, τ is the lifetime of the excited state, T the absolute temperature, η the viscosity of the medium, v the effective volume of the molecule, P the polarization, and P_0 the polarization limit. Within the range of temperature used, it was established that $(1/P) \propto (T/\eta)$ for all the phthalimides investigated. The molecular volumes (v) were larger in the dissolved state than in the solid state, and this difference was treated as due to solvation. The degree of solvation of three-substituted derivatives, as expressed by the molecular volume, was greater than that of 2-substituted derivatives. The presence of a methyl group on the nitrogen of the imide group lowered the solvation in comparison with the unsubstituted compound. A higher degree of solvation resulted from the replacement of the hydrogen of the imide group by phenyl than by methyl. Among the solvents studied, ethylene glycol increased the molar volume of the phthalimide derivatives the most, and cyclohexanol and glycerol the least.[345]

V. Detection of Imides

Both amides and imides may be converted by reaction with hydroxylamine to hydroxamic acids, which form colored complexes with ferric chloride. This can serve as the basis of a method for the detection of imides, and the characteristic rates at which individual imides react with hydroxylamine can be of diagnostic value.[346] However, the method cannot generally serve to distinguish imides from amides. A similar method has been developed previously for the estimation of esters and anhydrides.[347]



The reaction in which a pink or violet color is developed between pyrrole and *p*-dimethylaminobenzaldehyde in 20% trichloroacetic acid–benzene has been used to detect succinimide in amounts as little as 2.5 μg in a spot test; it is necessary to convert the succinimide first to pyrrole by a zinc-dust distillation step.[348] Succinimide has also been characterized by its thermal behavior. The differential thermal analysis curve for a heating rate of 9°/min has an endothermic peak over the range 120–135°, corresponding to the melting point of succinimide at 125°, and two exothermic peaks occur in the range 300–325°, corresponding to thermal decomposition.[349] In a somewhat gross way, this method can be claimed to distinguish imides from one another and from other substances.

Phthalimide, in alcoholic 0.05 *N* sodium hydroxide solution as the supporting electrolyte, gives a well-defined polarographic wave at −1.425 V. Phthalimide may be distinguished from certain of its products by this method and estimated in a more precise, more selective, and faster manner than through the determination of the imide nitrogen by the Kjeldahl method.[350]

Imides may be detected through the characteristic absorption bands in the carbonyl region of their infrared spectra (section IV.E.2), and imides may also be distinguished from isoimides by this method (section VIII).

VI. Uses of Imides

A. QUALITATIVE ANALYSIS

A saturated solution of imide dioximes in alcohol reacts with an aqueous solution of a metal cation with the development of characteristic color (Table XIV).[351] The range of detectability for Mn^{2+} with succinimide dioxime is 0.01 ppm, for example, while for UO_2^{2+} it is 1 ppm.

Table XIV

Color Reactions of Metal Cations with Imide Dioximes[351]

Cation	*Phthalimide dioxime*	*Glutarimide dioxime*	*Succinimide dioxime*
Mn^{2+}	Pink-red	Purple	Brown
Co^{2+}	Red		Red
Fe^{3+}	Yellow	Maroon	Red-violet
UO_2^{2+}	Deep red		Orange
Pd^{2+}	Yellow-orange		Yellow
Ni^{2+}	Yellow		
Ce^{3+}		Reddish brown	
Au^{3+}		Dark green	

Potassium naphthalimide reacts spontaneously with a solution of a primary alkyl halide in dimethylformamide, but more slowly with solutions of secondary halides, while tertiary halides do not react. The formation of crystalline N-alkyl derivatives of naphthalimide can therefore be used in the distinguishing and the identification of alkyl halides.[352]

N-Phenylmaleimide is useful in the analysis of cysteine by paper chromatography, because an addition compound is formed which travels as a compact spot on the chromatogram.[353]

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B. INDUSTRIAL USES

1. Synthetic Polymers

N-Vinylphthalimide and N-vinylsuccinimide can be copolymerized with ethylene to give polymers in the form of white plastic or clear tough film.[354] Polymers containing lactam rings in the polymer chain have been prepared by polymerization of mixtures of maleic anhydride and N-vinylphthalimide and treatment of the product with alkali and hydrazine.[355]

The synthetic fibers prepared from polymers containing 40–100% of N-methyl-2-methylglutarimide units are reported to be resistant to acids, dilute alkalies, and dry cleaning solvents. They have good hydrophilic properties and thermal stability, and are used for the preparation of acid-resistant filter cloths, protective clothing, tarpaulins, and umbrellas.[356]

Heat-resistant thermoplastic polymers are obtained by treating N,N′-bimaleimides with substituted thiophene dioxides.[357] Heat-resistant glass fiber laminates may be made from an unsaturated polyester, triallyl cyanurate, and maleimide.[358] Polymers used as mouldings and protective coatings are obtained by copolymerization of various ethylenic compounds with N-carbaminylmaleimide, or various of its derivatives, in the presence of a free-radical catalyst.[359] A polymer obtained from N-allyloxymethylmaleimide is used as an insulating coating in electrical equipment.[360] Ion-exchange resins of high capacity can be prepared by the copolymerization of N-vinylsuccinimide, N-vinylphthalimide, or N-vinylmaleimide with divinyl crosslinking agents and styrene in a suitable solvent.[361] Wool has been treated with N-carbamoylmaleimide and with N-ethylmaleimide to modify its properties.[362,363]

2. Activators and Stabilizers

Adipimide is used as activator for the alkali-catalyzed polymerization of 2-pyrrolidone.[364] 4,5-Epoxycyclohexane-1,2-dicarboximide is used as a plasticizer and stabilizer for vinyl resins.[365] Succinimide improves the storage and cross-linking characteristics of diisocyanate-modified polyesters, polyesteramides, and polyethers.[366] Cellulose compounds plasticized with alkenylsuccinimides are supposed to be relatively age-resistant and retain flexibility and toughness.[367] N-(3,5-Di-*t*-butyl-2,5-cyclohexadien-4-one-1-ylidenemethyl)maleimide can be used to stabilize polyvinyl chloride against heat.[368] N-(4-Anilinophenyl)maleimide is a rubber antioxidant.[369] Succinimide, among other compounds, prevents the decomposition of the insecticide Thiodan during its storage.[370]

3. Vulcanizing Agents

N,N′-Bismaleimides and N,N′-biscitraconimides are used for the vulcanization of natural rubber and diene elastomers in place of sulfur.[371] N-Substituted derivatives of maleimide and methylmaleimide are also used as vulcanizing agents for natural rubbers, diene elastomers, and polyurethan elastomers.[372] Another typical example of a maleimide derivative useful as a vulcanizing agent is 2,6-di-*t*-butyl-4-(N-maleimidomethyl)-phenol. This compound also has fungicidal properties and may be copolymerized with ethylene.[373]

4. Lubricant Additives

The reaction product of phthalimide with formaldehyde and a reduced hexose amine is reported among several useful surface active compounds.[374] Bivalent-metal alkenylsuccinimides and -glutarimides are water-stable, oil-soluble detergents and antisludge additives which may be used at 0.5–3% concentration in crank-case oil for automobile, diesel, and aeroplane engines.[375] Certain maleimide copolymers are detergent and antiwear additives for engine lubricants.[376]

5. Dyes and Optical Brightening Agents

3-Amino or 3-alkylamino derivatives of naphthalimide and N-alkylnaphthalimides are useful as intermediates for the synthesis of dyes.[377] Monoazo compounds of 2-amino- and 3-aminonaphthalimide, and the corresponding aryl derivatives, are recently developed dyes, and the 4-amino derivatives are intensely colored.[378] Succinimide gives imidomethyl derivatives of phthalocyanins which are resistant to crystallization and flocculation and are valuable intermediates in the preparation of oil- and spirit-soluble colorants.[379] N-(*p*-Phenylazophenyl)maleimide is a chemically bonded fast dye for wool.[380]

1,8-Naphthalimide and substituted imides containing alkoxy groups absorb in the ultraviolet region of the spectrum

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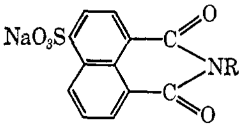
and emit blue light. These compounds are therefore used as whitening agents for natural and synthetic fibres and other polymeric products, particularly as the imides possess adequate thermal and photochemical stability. Typical examples of optical bleaching agents have the general formula IX.[381]



IX

6. Photographic and Printing Aids

N-(*p*-Aminophenyl)phthalimides are useful as color developers in photography.[382] Certain bismaleimides added to gelatin–silver halide emulsions give coatings which are resistant to swelling or melting in hot water.[383] Arylene and alkylene dimaleimides and their derivatives harden gelatin and are used in many photographic emulsions.[384]

Dicarboxylic acid imides serve as developers for stable textile printing. The usual use of steam and acid in the development of azo dyes from diazo compounds can be replaced by pastes of a coupling anilide and a dicarboxylic acid imide, which gives an odorless and more convenient developer. Succinimide, for example, forms a stable paste and yields the same color as the acid development.[385]

7. Solvent Uses

Succinimide and its N-acyl and N-alkyl derivatives can be used as solvents and gelatinizing agents for polyacrylonitrile.[386]

C. BIOLOGICAL USES OF IMIDES

1. Physiological Rate Regulators

Compounds like 4-succinimide-2,6-dimethylpyrimidine modify the growth of plants.[387] Certain aromatic derivatives of succinimide stimulate the growth of wheat and radish seedlings.[385]

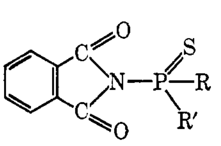
Inhibition of growth and carotenogenesis has been shown by adipimide.[388] N-Phenyl-, N-(*o*-, *m*-, or *p*-chlorophenyl)-, N-(2,4-dichlorophenyl)-, N-(2,5-dichlorophenyl)-, and N-(2,4-dichlorobenzoyl)maleimides, when spread on the surface of the leaves, cause complete defoliation of peach branches within 3 days. These compounds are antiauxins. Saturation of the double bond in the imide causes inactivation.[389] (Maleic hydrazide is a well-known herbicide.[390])

Phenylmercurisuccinimide and phenylmercuriphthalimide inhibit cytochrome oxidase, succinoxidase, and succinic dehydrogenase. In this particular case the imide is probably best regarded as a vehicle for the mercury, which probably acts as the phenylmercury ion.[391]

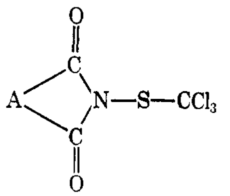
N-Ethylmaleimide inhibits the reductive acetylation of lipoic acid that is catalyzed by pyruvic dehydrogenase from *B. tuberculosis*.[392] N-Ethylmaleimide also inhibits the glucose permeability of erythrocytes in human beings.[393]

2. Fungicides and Bacteriocides

N-(4-Iodophenyl)naphthalimide and related compounds are fungicidal,[394] and naphthalimide itself is fungistatic and bacteriostatic.[395] 2-Chlorophenyl-3-chlorosuccinimide is useful as a specific fungicide against *Alternaria solani* on plant foilage and seeds.[396] N-(Trichloromethylthio)-2,2-pentamethylenesuccinimide is a broad-spectrum fungicide.[397] Phthalimidophosphonothionates (X) have high fungicidal activity and low toxicity to mammals.[398]



X



XI

N-Phenylmaleimides and related compounds have been examined as soil fungicides; among these N-(2,6-dimethylphenyl)maleimide was found to have the greatest fungicidal effect in the disease known as "damping-off" of peas.[399] N-Trichloromethylthiomaleimide mixed with cycloheximide is also used as a fungicide.[400]

The unsaturated imides have high activity against Gram-negative bacteria. Addition of thioacetic acid destroys the antimitotic activity of N-ethylmaleimide and maleimide.[401]

3. Insecticides

N-(Trichloromethylmercapto)imides of dicarboxylic acids of all types (XI) are useful as fungicidal, insecticidal, and germicidal agents in seed and plant protection. Many phthalimide and succinimide derivatives are fungicides and good insecticides acting in the stomach; they are nonphytotoxic and may be used as dusts, soils, and water emulsions for the

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protection of leather, woods, wool, and fabrics.[402] For example, N-(dichlorofluoromethylthio)maleimide is a systemic and contact miticidal agent.[403] N-Substituted 4-cyclohexene-1,2-dicarboximides and their 4-chloro derivatives are effective as synergistic insecticides.[404] The isopropoxymethyl ether of N-(β-hydroxyethyl)succinimide is claimed as an active contact insecticide.[405] N-(Trialkylammonium methyl)succinimide chloride is also recommended as an antiseptic fungicidal agent and pesticide for use on young plants.[406]

N-Amylsuccinimide is active against *pediculus humanis corporis* (the human body louse). Suitable treatment with a 1% solution of N-ethyl-2-phenylsuccinimide in acetone effectively controls the lice for up to a month, and the solution can be impregnated into fabrics.[407]

Aliphatic N-substituted imides of maleic acid are toxic to rats.[408] N-Propylchloromaleimide is effective against the oriental cockroach, for further example.[409] N-Ethylmaleimide has been used as a molluscicide.[410]

Tolylmaleimides are used as mosquito repellents, the *ortho* isomer being the most active.[411] N-Amylsuccinimide acts as a tetse fly repellent, though it is only active for 2 hr after application.

D. PHARMACOLOGICAL USES OF IMIDES

1. *Sedatives, Hypnotics, and Anticonvulsants*

N-Methyl-3-alkoxyglutaconimides variously substituted at the 2 and 4 positions have sedative, hypnotic, and anticonvulsant properties.[412] 3-Methyl-3-ethylglutarimide (Bemegride) and several related 3,3-substituted glutarimides have an analeptic effect.[413] A large number of 2-phenyl-substituted succinimide derivatives were tested for anticonvulsant activity.[414] The 3-methyl- and 3-ethyl-substituted compounds were more effective against metrazole convulsions than against electrostatic convulsions. Methylation of the heterocyclic nitrogen of most of these compounds increased the antimetrazole activity. This enhancing effect is reduced with increasing length and branching of the chain. Dimethylsuccinimides were more effective in suppressing electrostatic convulsions than metrazole-induced convulsions. Methylation of the heterocyclic nitrogen of these compounds diminished the activity against electrostatic convulsions. N-Substituted succinimides and N-substituted 2-phenylsuccinimides were active against metrazole and electrically induced convulsions, and several were also effective in petit mal epilepsy.[415] 3-Phenyl-2,3-dimethylsuccinimide and its N-methyl derivative are anticonvulsant, particularly against the petit mal type of epileptic seizure, and give no hypnotic side effects.[416] N-Ethyl-2,2-dimethylsuccinimide and N-propyl-2,3-dimethylsuccinimide are also useful for petit mal epilepsy.[417]

Many aryl-substituted succinimide derivatives were tested for activity and toxicity.[418] *p*-Xylylsuccinimide is the most promising anticonvulsant in the group, but is inferior to Milontin (see below). 2-Ethyl-3-methyl-3-phenylsuccinimide is a sedative, anticonvulsant, and anesthetic in the mouse.[419] *dl*-2-Phthalimidosuccinimide and 2-phalimido-3-methylsuccinimide are sedatives and anticonvulsants and have tetragenic properties.[420] Further examples of nontoxic and highly active anticonvulsants for the petit mal type seizures are N-methyl-2-phenyl-2-ethylsuccinimide and N-methyl-2-phenyl-3-methylsuccinimide.[421] Milontin (N-methyl-2-phenylsuccinimide) is an antiepileptic and is used as a standard for comparison of anticonvulsant activity.[422]

2. *Hypotensive Agents and Diuretics*

The maleimide adduct of levopimaric acid and derivatives are hypotensive agents and possess coronary dilatory activity.[423] Substituted phthalimides are antihypotensive agents.[424]

The 3-succinimidomercuri-2-methoxypropyl derivative of urea and related compounds have diuretic properties.[425] The *in vitro* inhibition of renal glutaminase and the *in vivo* diuretic activity in rats have been determined for glutarimide, among a number of compounds. Weak diuretic activity was reported in the case of glutarimide.[426] N-Substituted 3-chloro-4-sulfamoylphthalimides show diuretic activity.[424] The reduction of the CO group in the *para* position to the sulfamoyl group in the phthalimide produces a much more active compound.[427]

3. *Antitubercular Agents and Carcinostatics*

Alkyl-substituted succinimides and their N-substituted derivatives were tested against the tuberculum bacillus.[428] N-

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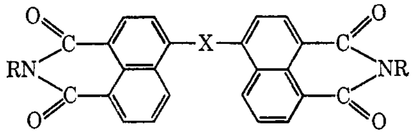
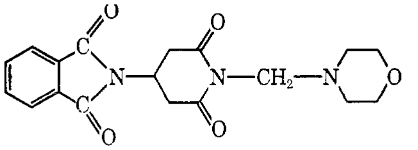
Isonicotinamido-2-methyl-3-dodecylsuccinimide is an antitubercular substance.[429] N-Alkylated 4,4′-bis-1,8-naphthalimides (XII) and related compounds are effective against tubercular bacillus, amoebae, and nematodes, and also have laxative action.[430]

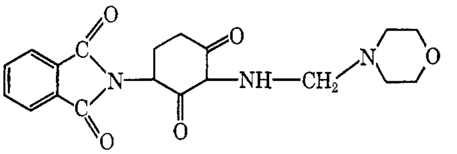

XII

$X = CO, CH_2,$ or $p\text{-}COC_6H_4CO$

$R = Me_2NCH_2CH_2,$ etc.

Compounds XIII and XIV have proved superior to Thalidomide (N-(2,6-dioxo-3-piperidyl)phthalimide) in the treatment of cancer in laboratory test animals.[431] Tumor-inhibiting activity has been found in other N-substituted derivatives of imides.[432]


XIII


XIV

4. Barbiturate Antagonists

3-Methyl-3-ethylglutarimides and related compounds are useful antagonists for the treatment of barbiturate poisoning.[433] The alkali metal salts of 3,3-dialkyl-substituted glutarimide are used in admixture with barbiturates for inducing anesthesia by injection. This use shortens by about 50% the recovery time from barbiturate anesthesia in both humans and animals. Some protection against barbiturate overdose is also claimed for these compounds.[434] 3-Methyl-3-isopropylglutarimide and some of its salts are mild central-nervous-system stimulants and barbiturate antidotes.[435]

5. Antimitotic Agents

The antimitotic activities of maleimide, citraconimide, N-ethylmaleimide, and succinimide have been tested in tissue cultures of chick fibroblasts. The unsaturated imides were active in a concentration of about 10^{-6} *M*. The highest activity is shown by N-ethylmaleimide.[436]

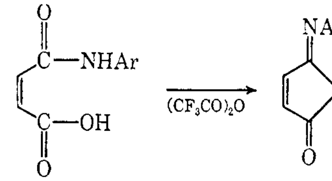
6. Miscellaneous Pharmacological Uses

Sodium succinimide aurate has been used in the treatment of arthritis. Phthalimide derivatives inhibit the growth of the polio virus.[437] Succinimide raises the antibiotic activity of the culture of Actinomyces streptomycin.[438] Phthalimide is useful in the fermentation of wine and is favorable for the definition of the organoleptic characteristic of wine.[439] Glutarimide derivatives were found to reduce the growth of cartilage in mice; those tested were Thalidomide, Gentemide, and Bemegride.[440] N-(2-Diethylaminoethyl)diphenylmaleimide and related compounds are good local anesthetics of low toxicity and of particular use in corneal anesthesia.[441]

VIII. Isoimides

The synthesis of isoimides (II) requires a nucleophilic displacement by a neighboring amide group upon an activated carboxyl function. Thus, N-substituted maleamic acids react with triethylamine followed by ethyl chloroformate at 0–50° to yield the corresponding isoimides. N-(5-Chloro-2-methoxyphenyl)maleamic acid and its analogs react when warmed with acetic anhydride in the presence of sodium acetate to give N-(5-chloro-2-methoxyphenyl)maleimide in more than 80% yields, but if the reaction is carried out at room temperature or with only mild heating, the N-arylisomalemides are formed. For example, when N-(*p*-methoxyphenyl)maleamic acid and sodium acetate are kept in acetic anhydride for 30 hr, an 84% yield of N-(*p*-methoxyphenyl)isomaleimide results.

Another method for the preparation of isoimides, which is useful for obtaining unsaturated imides, is the dehydration of N-substituted amic acids by trifluoroacetic anhydride.[442]



The double bond here facilitates the cyclization, and the reaction works well with N-substituted maleamic and phthalamic acids. Succinamic acid cannot be cyclized by this method, perhaps because it has unfavorable conformation, but N-substituted camphoramic acid derivatives do cyclize readily to the isoimides because of their favorable rigid conformation.

The isoimides are generally unstable with respect to the corresponding imides.[443-446] Fusion or prolonged heating

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in an inert solvent like chlorobenzene, dioxane, nitrobenzene, nitromethane, or dimethylformamide generally converts cyclic isoimides into their imide isomers. It has been suggested that nucleophilic catalysis for the isoimide–imide transformation may involve attack at the activated carbonyl group of the isoimide to give an activated intermediate which undergoes ring closure to the imide.[443] Isomaleimide derivatives may be converted to the corresponding maleimide derivatives when the former are heated with an equimolecular amount of sodium acetate and an excess of acetic anhydride or trifluoroacetic anhydride on the steam bath for 0.5 hr.[444]

The pH–rate profile for the hydrolysis of N-phenylphthalisoimide over the pH range 0–11 in water at 30° shows acid and base catalysis and also an uncatalyzed hydrolytic reaction. A kinetic study of the reaction of nucleophiles with these isoimides has revealed that they may react with either the neutral or protonated isoimide to give the rearranged N-phenylphthalimide.[263] The hydrolysis of maleimides and isomaleimides with hot 1 *N* sodium hydroxide solution for about 15 min gives the same product, maleamic acid.[444]

N-Arylphthalisoimides and N-arylmaleisoimides all show infrared absorption bands in the 5.54-μ (C=O stretching) and 5.88-μ (C=N stretching) regions, the exact frequency depending somewhat on the nature of the N substituent. Imides also have a band near 5.9 μ, but imides can be distinguished from isoimides in that this band has an extinction coefficient in the range 850–1300 for imides (C=O stretching) and only 200–400 for isoimides.[442] A further suggestion for the distinguishing of isoimides from imides, when both are available, involves the higher yield of carbon dioxide eliminated from the molecular positive ion of the former on electron bombardment.[318]