Translated from *Uspekhi Khimii* **58** 1474–1499 (1989) U.D.C. 547.465.5 + 547.414.8

α-Halo-α-nitrocarboxylic acids and their derivatives

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ABSTRACT. The methods for synthesising α-halo-α-nitrocarboxylic acids and their functional derivatives are reviewed. Reference is made to IR, NMR, and Raman spectroscopic data, calculation methods, and X-ray diffraction analysis, and information on the acidity and electron- and proton-donor capacities of the compounds is given. Reactions involving C–H and C–Hal bonds, carboxyl and nitro groups, the mechanisms of the most important reactions, and data on the toxicity and physiological activity are discussed.

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I. Introduction

α-Halo-α-nitrocarboxylic acids and their derivatives are polyfunctional compounds which are interesting from the point of view of studying the relationship between structure and properties. Distinctive (anomalous) behaviour of fluorine, chlorine, and bromine atoms on the carbon atom bonded to the nitro group has been found and elucidated for these compounds. A nontrivial mutual effect between the nitro and carboxyl groups and halogens, which manifests itself in the spectroscopic characteristics, structure, and chemical properties of these compounds, has been demonstrated. They have proved to be successful model compounds for studying the mechanisms of decarboxylation and the formation of halo-oximes, nitroso compounds, and phosphoryloximes. Reactions typical for them are the reductive decarboxylation with elimination of a single oxygen atom from the nitro group, deuterium exchange between cyclic transition states, the formation of heterocycles with complete or partial conversion of functional groups, redox phosphorylation, sulphonation–dehalogenation, etc.

Compounds of this group have become readily available as a result of the development of convenient methods for preparing them from accessible feedstocks. There are extensive possibilities for converting them to various nitro and nitroso compounds, oximes, hydroxylamines, amines, amino acids, and other compounds that have various properties of use for practical application and are difficult to synthesise by other methods. As a result of this, they have attracted the attention of chemists in recent years.

Compounds of this group include fungicides, insecticides, bactericides plant growth regulators, and also compounds that possess anti-choline esterase and hypotensive activity, amine oxidase inhibitors, and certain other physiologically active compounds that have potential for introduction into the national economy. All this is an indication of their important practical significance.

The first examples of this series of compounds were obtained at the beginning of the century. However, a systematic study of them was only carried out during the last 30 years because of the development of practicable synthetic methods. Specific information about α-halo-α-nitrocarboxylic acids and their derivatives is given in monographs[1–4] and review articles.[5–7] However, there are no reviews in the literature specially devoted to such an important group of compounds. The present article is the first attempt to correlate the studies on the preparative methods, properties, and use of α-halo-α-nitrocarboxylic acids and their derivatives. Literature sources from the last 30 years as well as earlier studies are covered here.

II. Synthetic methods

1. Replacement of a hydrogen atom in α-nitrocarboxylic acid derivatives by chlorine

Halogenation of salts of *aci*-nitro compounds is a general method for the preparation of α-halonitrocarboxylic acid derivatives and halonitroalkanes.[4,7,8]

$$O_2NCHY + MOH \rightarrow M^+[O_2N{=}CY]^- \xrightarrow[-MX]{X_2} O_2NCXY,$$

R = H, alkyl, NO_2, halogen; X = F, Cl, Br;
Y = CO_2R, CN, $CONH_2$ etc.; M = Na, K, NH_4, Ag etc.

When salts of *aci*-nitrocarboxylic acid derivatives are treated with bromine or chlorine, bromodinitroacetonitrile,[9] methyl bromonitroacetate,[10] dimethyl and diethyl bromonitromalonates,[11] dibromonitroacetonitrile,[12] ethyl bromo-, chloro-, dibromo-, and bromochloro-nitroacetates, ethyl α-bromo- and α-chloro-α-nitropropionates and -butyrates,[13] dichloronitroacetonitrile,[14,15] and α-bromo- and α-chloro-α-nitropropionamides[16] are obtained. Bromonitromalonamide, *N*-methylbromonitroacetamide, and dibromonitroacetamide were synthesised by treatment with bromine water.[17] It was shown subsequently using IR spectroscopy that *N*,α-dibromonitroacetamide rather than α,α-dibromonitroacetamide is formed under these conditions.[18] Dichloronitroacetamide[19] and ethyl chloronitromalonate[20] are obtained in a similar manner. The bromination of the sodium salt of dinitroacetonitrile was successfully carried out using bromine in a mixture of water and dichloromethane, while chlorination of the same salt could only be achieved using hydrochloric acid and hydrogen peroxide.[21] Treatment of the sodium salts with chlorine led to the synthesis of chloronitromalonamide,

chloronitroacetamide, fluorochloronitroacetamide, and ethyl fluoro-chloronitroacetate.[22] It was possible to obtain methyl α-bromo-α-nitropropionate and methyl α-bromo-α-nitro-β-phenylpropionate as well as ethyl α-bromo-α-nitrobutyrate in methanol solution.[23] When halogenation was carried out in a water–methanol solution, it was possible to increase the yields of ethyl dichloro- and bromo-chloro-nitroacetates.[24] Ethyl bromonitroacetate was synthesised in high yield in an alcohol–ether mixture.[25] Bromination of the potassium salts of dinitrodicarbonitriles in an ether–CCl_4 mixture at 0 °C gave a number of dibromodinitrodinitriles.[26,27]

$$\left[\begin{array}{c} NO_2 \quad NO_2 \\ \| \quad\quad \| \\ NCC(CH_2)_n CCN \end{array}\right]^{2-} 2K^+ \xrightarrow[-2KBr]{2Br_2} NCCBr(NO_2)(CH_2)_n C(NO_2)BrCN,$$
$n = 2, 4, 6$.

The diastereomers were separated by fractional crystallisation from aqueous ethanol. α-Bromo-α-nitrobutyronitrile and α-bromo-α-nitrocapronitrile were obtained in a similar manner. Bromination of the dipotassium salt of α,α′-dinitroadiponitrile in an alkaline medium at the same temperature followed by acidification was accompanied by elimination of one nitrile group and hydrolysis of the other to an amide.[27] The same product is formed by alkaline hydrolysis of α,α′-dibromo-α,α′-dinitroadiponitrile.

$$\left[\begin{array}{c} NO_2 \quad NO_2 \\ \| \quad\quad \| \\ NCC(CH_2)_2 CCN \end{array}\right]^{2-} 2K^+ \xrightarrow[-2KBr]{2Br_2} \begin{array}{c} NO_2 \quad\quad NO_2 \\ | \quad\quad\quad | \\ NCCBr(CH_2)_2 CBrCN \end{array}$$

$$\xrightarrow{1)\ Br_2,\ OH^-,\ 0°;\ 2)\ H^+\ 1)\ KOH\ aq.;\ 2)\ H^+} O_2NCHBr(CH_2)_2 CBr(NO_2)CONH_2$$

The bromination of $K^+[C_2H_5C(NO_2)CONH_2]^-$ and $[CH_2CH_2C(NO_2)CONMe_2]_2^{2-}2K^+$ salts under similar conditions gives the corresponding α-bromo-α-nitroamides, while the potassium salt of *N,N*-dimethylnitroacetamide is converted to a dibromo-substituted product. Formation of the latter is accounted for by the following scheme:[28]

$$K^+[O_2N{=}CHCONMe_2]^- \xrightarrow[-KBr]{Br_2} O_2NCHBrCONMe_2 \xrightarrow[-O_2NCH_2CONMe_2]{K^+[O_2N=CHCONMe_2]^-}$$
$$\rightarrow K^+[O_2N{=}CBrCONMe_2]^- \xrightarrow[-KBr]{Br_2} O_2NCBr_2CONMe_2.$$

Bromination of the sodium salt of ethyl α-nitro-β-hydroxypropionate has been reported.[25]

$$Na^+[O_2N{=}C(CH_2OH)CO_2Et]^- \xrightarrow[-NaBr]{Br_2} O_2NCBr(CH_2OH)CO_2Et.$$

Ethyl dibromonitroacetate was obtained when the mercury salt of ethyl nitroacetate was treated with bromine.[29] Treatment of the Na and K salts of dinitroacetonitrile with equimolar quantities of chlorine fluorosulphate gives chlorodinitroacetonitrile.[30]

$$[NC(NO_2)_2C]^- M^+ + ClOSO_2F \xrightarrow{-MCl} NC(NO_2)_2CCl.$$

When a twofold excess of chlorine fluorosulphate is used, a product derived from addition to the C≡N bond is formed, and this undergoes methanolysis to give methyl chlorodinitroacetate.[30] The fluorinated analogue of a chlorodinitroimidate is obtained by reaction between fluorodinitroacetonitrile and chlorine fluorosulphate.

$$[C(NO_2)_2CN]^- Na^+ + 2\,ClOSO_2F \rightarrow ClC(NO_2)_2C(NCl)OSO_2F \xrightarrow{MeOH}$$
$$\rightarrow ClC(NO_2)_2CO_2Me,$$

$$FC(NO_2)_2CN + ClOSO_2F \rightarrow FC(NO_2)_2C(NCl)OSO_2F.$$

Reaction of chlorine fluorosulphate with ethyl dinitrocyanoacetate leads to replacement of the CN group by Cl:

$$NCC(NO_2)_2CO_2Et + ClOSO_2F \xrightarrow{-20\ to\ -30°} ClC(NO_2)_2CO_2Et.$$

A halogenation method using *N*-chloro- or *N*-bromo-succinimide is also known.[31]

$$O_2NCH(Me)CO_2Et \xrightarrow[dioxan-water]{O,\ argon} O_2NCCl(Me)CO_2Et.$$
70%

Fluorination of alkali salts of carboxylic acid nitro derivatives has been used less frequently. Fluorodinitroacetate esters are formed when salts of dinitroacetate esters are treated with fluorine over KF. Under the same conditions nitroacetate esters give a mixture of three products.[32]

$$[O_2N{=}CHCO_2Et]^-Na^+ \xrightarrow[-NaF]{F_2} O_2NCF_2CO_2Et + O_2NCHFCO_2Et +$$
$$+ O_2NCH_2CO_2Et.$$

This process results from the intermediate formation of the sodium salt of fluoronitroacetate ester and its reaction with fluorine.

$$[O_2N{=}CHCO_2Et]^-Na^+ + O_2NCHFCO_2Et \rightarrow O_2NCH_2CO_2Et +$$
$$+ [O_2N{=}CFCO_2Et]^-Na^+,$$
$$[O_2N{=}CFCO_2Et]^-Na^+ \xrightarrow[-NaF]{F_2} O_2NCF_2CO_2Et.$$

When similar conditions are used over CaF_2 fluorodinitroacetonitrile is obtained in 70% yield,[33] having been synthesised previously in low yield when an aqueous solution of the potassium salt of dinitroacetonitrile was treated with F_2.[34]

Fluorination of the potassium salt of ethyl dinitroacetate with a mixture of fluorine and nitrogen gave ethyl fluorodinitroacetate with a small amount of fluorodinitromethane.[35]

$$[(O_2N)_2CCO_2Et]^-K^+ \xrightarrow{F_2} (O_2N)_2CFCO_2Et + (O_2N)_2CHF.$$

Fluoronitromalonate ester is obtained by fluorination of the potassium salts of oximes with perchloryl fluoride[36]

$$KON{=}C(CO_2R)_2 + FClO_3 \rightarrow O_2NCF(CO_2R)_2.$$

The ammonium salts of dinotroacetamides are converted to fluorinated products in low yield.[37,38]

$$[(O_2N)_2CCONH_2]^-NH_4^+ \xrightarrow{FClO_3} (O_2N)_2CFCONH_2,$$
5.6%

$$[(O_2N)_2CCONHEt]^-\overset{+}{N}H_3Et \xrightarrow{FClO_3} (O_2N)_2CFCONHEt.$$
14%

Fluorination of dinitronitrile salts in Cellosolve gives a product from fluorination and addition to the C≡N group. It is thought that the process takes place via the formation of dinitrofluoroacetonitrile.[38]

$$[(O_2N)_2CCN]^-Na^+ \xrightarrow{FClO_3} [(O_2N)_2CFCN] \xrightarrow{HOCH_2CH_2OMe}$$
$$\rightarrow (O_2N)_2CFC(NH)OCH_2CH_2OMe.$$

The potassium salts of nitroacetic acid derivatives can be fluorinated with both fluorine and perchloryl fluoride[39]

$$[O_2N{=}CRCO_2R']^-K^+ \xrightarrow{F_2(FClO_3)} O_2NCFRCO_2R',$$
$R = H,\ SAr;\ R' = Et,\ PhCH_2$.

A satisfactory result was obtained when diethyl nitromalonate was fluorinated in DMF in the presence of sodium hydride.[40]

$$O_2NCH(CO_2Et)_2 + NaH + FClO_3 \xrightarrow{DMF} O_2NCF(CO_2Et)_2.$$

2. Nitration of halo-olefins

The synthesis of α-halo-α-nitrocarboxylic acids and their derivatives by nitration of halo-olefins with mixtures of nitric and sulphuric acids is a more versatile and practicable method.

$$X^1X^2C{=}CX^3X^4 \xrightarrow{HNO_3/H_2SO_4} O_2NCX^1X^2C(=O)Y,$$

X^1, X^2, X^3, X^4 = H, F, Cl or Br; Y = F, Cl, Br or OH.

Nitration of a number of halo-olefins with a small excess of a mixture of nitric and sulphuric acids in the molar ratio 1 : 1 at 15–60 °C results in the formation of α-halo-α-nitrocarboxylic acids or their chlorides in 35–85% yield.[41–46] Nitration of trichloroethylene, giving chloronitroacetyl chloride, is accompanied by the formation of chlorocyanogen, dichloroacetyl chloride, and pentachloroethane.[42,43] Fluorochloronitroacetic acid is obtained from symmetrical difluorodichloroethylene.[44] Nitration of $ClF_2CCCl{=}CCl_2$ and $F_3CCCl{=}CCl_2$ gives the acid chlorides $ClF_2CCCl(NO_2)COCl$ and $F_3CCCl(NO_2)COCl$. The accumulation of chlorine atoms at the "allyl" position of 1,1,2-trichloropropylene results in a competing reaction—the formation of trichloroacrylic acid.[45]

$$Cl_2C{=}CClCCl_2F \rightarrow Cl_2C{=}CClCO_2H.$$

For perchloropropylene this reaction becomes the main process. Nitration of tetrafluoroethylene and trifluorochloroethylene leads to difluoronitroacetic acid.[46] Under these conditions perchloroethylene is converted to trichloroacetyl chloride,[46] while 1-fluoro- and 1-bromo-2,2-dichloroethylene are converted to fluoro- and bromonitroacetyl chloride respectively.[47,48] The nitration of vinylidene chloride, which leads to nitroacetyl chloride, requires an excess of the olefin undergoing nitration and cooling to –5 to 0 °C.[49]

The use of a nitric–sulphuric acid mixture comprising 5–10% nitric acid and not containing radical species, according to EPR data, creates favourable conditions for conducting an ionic reaction. It was possible to carry out the nitration of perchloroethylene to dichloronitroacetyl chloride under these conditions and to increase the yield of fluoronitroacetic acid and difluoronitroacetic acid to 85 and 92% respectively.[50] 1,1-Dichloropropene, 1,1-dichloro-3-methylbutene, and 1,1,1-trichloro-3-methylbutene have been nitrated using such a mixture.[51] Pure chloronitroacetyl chloride is obtained from trichloroethylene using a nitration mixture prepared from 60% HNO_3 and oleum.[52]

According to kinetic data, the rate of nitration is affected by the composition of the nitration mixture, the temperature, and the intensity of mixing.[53] A nitric acid content of 10–20% in the nitration mixture achieves the highest rate of reaction. According to the data of vibrational spectroscopy and ^{14}N NMR spectroscopy, at such a proportion HNO_3 is completely converted to a nitronium cation NO_2^+.[50,54–56] The process occurs at the phase boundary and can be given by a first-order equation (with respect to consumption of trichloroethylene and liberation of heat). The high value of the energy of activation (16.7 kcal mol^{-1}) indicates that a process with an ion-molecular mechanism is taking place. The proposed mechanism of ionic nitration appears to be a general one for the nitration of unsaturated compounds and is distinct from the nitration of aromatic compounds, which takes place with zero kinetic order with respect to the contents of the nitration mixture.[57–59] The process can be represented by the following scheme:[41,42,53]

$$ClHC{=}CCl_2 \xrightarrow{NO_2^+} [ClHC{=}CCl_2] \rightarrow [ClHC(NO_2){-}\overset{+}{C}Cl_2] \xrightarrow{H_2SO_4}$$
$$\rightarrow [ClHC(NO_2){-}CCl_2OSO_3H] \xrightarrow{-HOSO_2Cl} O_2NCHClCOCl.$$

The reaction starts with attack by the nitronium cation on the double bond (nitration with nitric acid gives trichloronitroethylene[60]). The carbocation formed is stabilised by the addition of bisulphate anion, and the subsequent elimination of chlorosulphonic acid gives chloronitroacetyl chloride.

3. Preparation of α-nitroperfluorocarboxylic acids from the products of nitration of fluoro-olefins with nitrogen dioxide

The hydrolysis and alcoholysis of 2-nitroperfluoroalkyl nitrites, obtained by nitration of perfluoroalkenes with nitrogen dioxide, is the most studied and most frequently used method for obtaining α-nitroperfluorocarboxylic acids and their derivatives.[6,61–70]

$$F_2C{=}CFX \xrightarrow{N_2O_4} O_2NCF_2CFXONO \rightarrow O_2NCF_2COF \rightarrow$$
$$\xrightarrow[(ROH)]{H_2O} O_2NCF_2COOH\,(R).$$

Difluoronitroacetic acid is formed by nitration of both perfluoroethylene and trifluorochloroethylene.[61] The process is a free-radical one. Reaction of 2-nitroperfluoroethyl nitrite with sulphuric or chlorosulphonic acid gives difluoronitroacetyl fluoride, which is also an intermediate in the hydrolysis and alcoholysis of 2-nitrotrifluoroethyl nitrite.[63]

$$O_2NCF_2CF_2ONO \xrightarrow{H_2SO_4,\ ClSO_3H} [O_2NCF_2CF_2OH] \rightarrow$$
$$\rightarrow O_2NCF_2COF \xrightarrow[(ROH)]{H_2O} O_2NCF_2CO_2H\,(R).$$

Hydrolysis and alcoholysis of nitroperfluoropropyl nitrite does not give the expected α-nitroperfluoropropionic acid or its esters but yields nitroperfluoroacetone hydrate or its hemiketals.[65] Difluoronitrothioacetic acid and difluoronitroacetate thioesters are also obtained when 2-nitrotetrafluoroethyl nitrite is treated with hydrogen sulphide or mercaptans.[68–70]

$$O_2NCF_2CF_2ONO + HSR \rightarrow O_2NCF_2COSR + HF + FNO.$$

Hydrolysis of the reaction products gives difluoronitroacetic acid.

Reaction of 2-nitronitrosotetrafluoroethane with hydroxylamine also gives difluoronitroacetic acid.[71,72] The reaction takes place with evolution of HF and N_2.[72,73]

$$O_2NCF_2CF_2NO + H_2NOH \rightarrow [O_2NCF_2CF_2N(OH)NHOH \xrightarrow{-H_2O}$$
$$\rightarrow O_2NCF_2CF_2N{=}NOH \xrightarrow{-N_2} O_2NCF_2CF_2OH \xrightarrow{-HF}$$
$$\rightarrow O_2NCF_2COF] \xrightarrow[-HF]{H_2O} O_2NCF_2CO_2H.$$

Alkaline hydrolysis of 2-nitronitrosotetrafluoroethane is accompanied by the formation of 1,2-dinitrotetrafluoroethane.[74]

$$O_2NCF_2CF_2NO \xrightarrow{OH^-} O_2NCF_2CO_2H + O_2NCF_2CF_2NO_2 + N_2 + F^-.$$

Difluoronitroacetyl fluoride is formed in small quantities during the nitration of perfluorobutadiene.[74]

$$F_2C{=}CFCF{=}CF_2 \xrightarrow{N_2O_4} O_2NCF_2CF{=}CFCF_2NO_2 \xrightarrow{N_2O_4} O_2NCF_2COF.$$

Difluoronitroacetic acid is isolated in the oxidation of 1,4-dinitro-1,1,4,4-tetrafluoro-2-butene. Addition of alkali gives difluoronitromethane.[76]

$$O_2NCF_2CH{=}CHCF_2NO_2 \xrightarrow[H_2O,\ KMnO_4]{} O_2NCF_2COOH$$
$$O_2NCF_2CH{=}CHCF_2NO_2 \xrightarrow[KOH]{H_2O,\ KMnO_4} O_2NCF_2H$$

Reaction of α-ethoxy-β-nitroperfluoropropane and α-ethoxy-β-nitroperfluoroisobutane with $AlCl_3$ followed by treatment with ethanol gives ethyl α-nitroperfluoropropionate and ethyl α-nitroperfluoroisobutyrate.[77,78]

$$CF_3CX(NO_2)CF_2OEt \xrightarrow{AlCl_3} CF_3CX(NO_2)COX \xrightarrow{EtOH} CF_3CX(NO_2)CO_2Et,$$
$$X = F,\ CF_3.$$

Various esters and amides of α-halo-α-nitrocarboxylic acids are synthesised by esterification or aminolysis of acid halides or esters obtained by nitration of halo-olefins.[1,3,43,44,46–49,51,62–64,67,77–86]

4. Other methods for synthesising functional derivatives of α-halo-α-nitrocarboxylic acids

The prolonged passage of nitryl chloride through a cooled ether solution of ethyl diazoacetate yields ethyl chloronitroacetate.[82]

$$N_2CHCO_2Et + O_2NCl \rightarrow O_2NCHClCO_2Et.$$

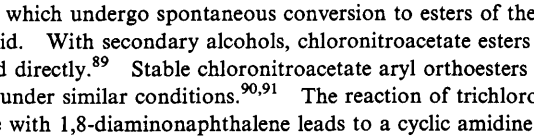
Certain problems have arisen in the preparation of halo-nitroacetate aryl esters. Difluoronitroacetate phenyl esters are not formed from 2-nitrotetrafluoroethyl nitrite and they were obtained from difluoronitroacetyl chloride.[79] Because it was not possible to obtain bromo- and chloro-nitroacetate phenyl esters by esterification of acid chlorides or by transesterification of their alkyl esters, they were synthesised from the corresponding nitroacetate esters, which in turn were obtained by nitration of acetoacetate esters synthesised from phenol and diketene.[87]

$$CH_2{=}C(O){-}CH_2{-}C(=O) + HOPh \rightarrow CH_3COCH_2CO_2Ph \xrightarrow{HNO_2}$$
$$\rightarrow O_2NCH_2CO_2Ph \xrightarrow{X_2} O_2NCHXCO_2Ph$$
$$X = Cl \text{ or } Br.$$

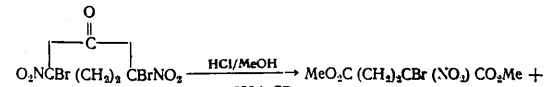
Chlorination of α-nitrocarboxylic acid hydrazides or their derivatives gave chlorodinitroacetyl and α-chloro-α-nitropropionyl chlorides, which were converted to methyl esters.[81]

$$[O_2N{=}CRCONHNH_2]^-H_3^+NNH_2 \xrightarrow{Cl_2} O_2NCClRCOCl \xrightarrow{MeOH} O_2NCClRCO_2Me.$$

The reaction of α-oximinocarboxylate esters with nitrosyl chloride leads to a mixture of chloronitrocarboxylate esters and chloronitroso esters.[88] When ethyl α-chloro-α-nitrosopropionate and ethyl α-chloro-α-nitrosobutyrate are oxidised with peroxytrifluoroacetic acid, the corresponding α-halonitro esters are isolated in good yield.[88] Chloronitroacetamide is obtained by alkaline hydrolysis of chloronitromalonamide, while fluorochloronitroacetamide is obtained by aqueous hydrolysis of the intermediate fluorochloro-nitromalonamide.[22] When trichloronitroethylene is reacted with primary alkoxides, unstable orthoesters of chloronitroacetic acid are formed, which undergo spontaneous conversion to esters of the same acid. With secondary alcohols, chloronitroacetate esters are obtained directly.[89] Stable chloronitroacetate aryl orthoesters are formed under similar conditions.[90,91] The reaction of trichloronitro-ethylene with 1,8-diaminonaphthalene leads to a cyclic amidine.[92]



Treatment of cyclic α,α′-dinitroketone with a methanol solution of hydrogen chloride gives a mixture of dimethyl 2-bromo-2-nitro-glutarate and methyl 2,5-dibromo-2,5-dinitropentanoate.[93] It has been suggested that the first product is formed from the second by a modified Nef reaction.



Reaction of dichloro- and dibromo-nitroacetamides with PCl_5 gives a number of *N*-phosphorylated amides and imidoyl chlorides of dichloro- and dibromo-nitroacetates — $Cl_2C(NO_2)CONHPOCl_2$, $Cl_2C(NO_2)CONHPO(OEt)_2$, $Br_2C(NO_2)CONHPOCl_2$, $Cl_2C(NO_2)CCl{=}NPOCl_2$, and $Br_2C(NO_2)CCl{=}NPOCl_2$.[19]

When difluoronitroacetic acid is treated with SO_3, the mixed anhydride $O_2NCF_2COOSO_3H$ is formed, and it undergoes alcoholysis to give difluoronitroacetate esters.[94,95] The mixed anhydride synthesised by the reaction of 2-nitrotetrafluoroethyl nitrite with glacial acetic acid is converted on treatment with alcohols to acetates and difluoronitroacetic acid.[96,97]

α-Nitroperfluoropropionate esters are synthesised by oxidation of α-nitrosoperfluoropropionate esters.[78]

$$ONCF(CF_3)CO_2Et \xrightarrow{N_2O_4} CF_3CF(NO_2)CO_2Et.$$

Polyfluorinated alcohols deposited as a thin layer on the surface of inert supports (NaF or CaF_2) when treated with dilute fluorine (−15 to −10 °C) form a mixture of aldehydes and esters.[98]

$$O_2NCF_2CH_2OH \xrightarrow{F_2} O_2NCF_2CHO + O_2NCF_2CO_2CH_2CF_2NO_2.$$

Amidines[99] and oximes[100] are obtained by aminolysis of nitroperfluoroalkyl nitrites. Corresponding esters are synthesised when difluoronitroacetic anhydride is treated with dihydric alcohols.[101]

The silver[6] and mercury[102–104] salts of difluoronitroacetic acid are known. The former, in contrast to the latter is unstable on standing and is rapidly decomposed with water.

$$O_2NCF_2COOH + Ag_2CO_3 \rightarrow O_2NCF_2COOAg,$$
$$O_2NCF_2COOH + HgO[(CH_3COO)_2Hg] \rightarrow (O_2NCF_2COO)_2Hg.$$

III. The use of physicochemical methods for studying the structure and properties

1. Vibrational spectroscopy

It is infrared spectroscopy that is usually used to confirm the structure of synthesised α-halo-α-nitrocarboxylic acids and their derivatives.

An accumulation of electronegative substituents (NO_2, halogen, CN, COOR) results in a shift of the absorption bands of the nitro group to shorter wavelength. Alkyl substituents give the reverse effect (Table 1). This type of shift is also typical for absorption bands from the carbonyl group. The presence of alkyl groups on the α-carbon atom decreases the difference Δν between the absorption frequencies of asymmetric and symmetric stretching vibrations of the NO_2 group. In the IR spectrum of the mercury salt of difluoronitroacetic acid there are shifts of ν(CO) and $\nu_{as}(NO_2)$ to higher absorption frequency by ~150 and ~40 cm^{-1} respectively compared to the acid and its esters.[64,107] However, the existing data

Table 1. Wavenumbers of stretching vibrations (cm^{-1}) of α-halo-α-nitrocarboxylic acid derivatives.

Compound	NO_2, as	NO_2, s	C=O	Other functional groups	Refs.
$MeO_2C(CH_2)_2CBr(NO_2)CO_2Me$	1560	—	1740, 1725	—	[93]
$O_2NCHBr(CH_2)_2CBr(NO_2)CO_2Me$	1560	—	1740	—	[93]
$O_2NCHBrCONHBr$	1575	—	1695	3155, 3410 (NH)	[18]
$O_2NCHBr(CH_2)_2CBr(NO_2)CONH_2$	—	—	1690	3125, 3360 (NH)	[27]
$NCCBr(NO_2)(CH_2)_4CBr(NO_2)CN$	—	—	—	2220 (CN)	[26]
$(O_2N)_2CBrCN$	1608	—	—	2240 (CN)	[21]
$O_2NCHClCO_2Alk$	1592—1589	1352—1347	1774—1763	740—726 (C—Cl)	[105]
$O_2NCClCO_2R$ $R'CHOH$	~1570	~1360	~1760	3600—3300 (OH)	[106]
$O_2NCDClCO_2Me(Et)$	~1590	~1350	—	~2235 (CD)	[83, 105]
$NH_4^+[O_2N{=}CClCONH_2]$	—	—	~1620	3500—3180 (NH)	[107]
$O_2NCHClCONH_2$	~1560	—	~1680	3360—3160 (NH)	[107]
$O_2NCHClCOCl$	~1575	~1340	~1780	~3000 (CH)	[51]
$O_2NCClCOCl$ $CH(CH_3)_2$	~1570	~1360	~1780	3000—2900 (CH)	[51]
$O_2NCClCO_2Alk$ $CH(CH_3)_2$	1560—1555	1355—1350	1750—1745	2880—2870 (CH)	[51]
$O_2NCF_2CO_2Alk$	1610—1600	1313—1319	1790	~1240, 1190 (CF)	[64]

are not sufficient to make a reliable assessment of the mutual effect from the functional groups. Raevskii et al.[105] undertook such an assessment in the case of a number of chloronitroacetate esters. The absorption region of the "acidic" proton was established (C—H group, 2932—2965 cm^{-1}) from comparative data and the spectrum of the deutero analogue. The strong absorption band in the region 1774—1763 cm^{-1} corresponds to a stretching vibration of the C=O group. Polarised Raman lines correspond to the same regions. The absorption frequencies of $NO_{2,as}$ (1592—1589 cm^{-1}) and $NO_{2,s}$ (1352—1347 cm^{-1}) have been determined. The vibration frequencies of the NO_2 and CO groups differ from those of ethyl nitroacetate (1382, 1562, and 1745 cm^{-1}). The narrow intervals of three absorption bands at 740—726, 670—657, and 580—568 cm^{-1}, the constant ratio of their intensities, and the absence of other bands in these regions can be of use analytically as a spectroscopic characteristic of the chloronitro group (together with asymmetric NO_2).

2. NMR spectroscopy

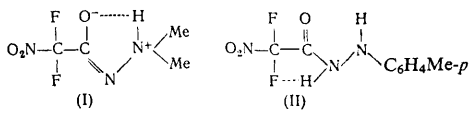
In order to investigate the possibility of self-association and association with an oxygenated solvent, ^1H NMR spectra were obtained for a number of chloronitroacetate esters in a pure form and in solution.[83,108] The signals from the α-CH protons of the pure products appear as singlets downfield (δ 6.36—6.47, HMDS). In the spectra of the same esters in oxygenated solvents—acetone-d_6 and dimethyl sulphoxide-d_6—the "acidic" protons were displaced further downfield the higher the ε value of the solvent, which is related to the formation of hydrogen bonds in which the CH proton and the oxygen atoms of the solvents participate. This is supported by the dependence of the chemical shift on the concentration of solutions. The magnitudes of the chemical shifts of the CH protons give a poor correlation with pK_a values in the series of chloronitroacetate esters.[108] The chemical shifts of the CH protons of chloronitroacetyl chloride (δ 6.67, TMS),[52] chloronitroacetamide (δ 6.56, 50% CD_3CN), and ethyl chloro- and bromo-nitroacetates (δ 6.56 and 6.66 respectively) were determined.[108] The ^{13}C NMR data of chloronitroacetyl chloride are: δ 90.33 p.p.m. (O_2NCHCl) and 161.78 p.p.m. (CO).[52] By studying the ^{13}C and ^{19}F NMR spectra of fluoronitroacetic acid, its propyl ester, and methyl chloronitroacetate, together with other halonitro and halonitroso compounds, it was demonstrated using mathematical calculations that the values of the chemical shifts give an unsatisfactory correlation with the sum of the Swain—Lupton constants (field constants) and correlate well with the charges on the carbon atom, calculated using the RMX [? Ed. of Translation] method (correlation coefficient 0.978). In the case of ^{19}F NMR spectra the paramagnetic contribution to the magnetic shielding constant is important.[109] The signal in the ^{19}F NMR spectrum of the mercury salt of difluoronitroacetic acid is displaced downfield relative to the spectra of other derivatives of this acid. This phenomenon, together with the IR spectroscopy data (see above), indicates that there is a strong donor-acceptor interaction between the Hg atom and the $O_2NCF_2COO_2$ group, with the Hg atom acting as an electron acceptor.[102]

3. Other methods

In order to confirm the structure of chloronitroacetic acid derivatives and to study their reactivity and reaction mechanism, use has been made of mass spectrometry,[52,83,107] EPR specroscopy,[83] calculation methods,[108,111] and electron-diffraction[112] and thermographic[113] methods. X-Ray diffraction analysis was used to study the structure of *aci*-ethyl chloronitroacetate[114] and *aci*-chloronitroacetamide anions.[115] The $O_2^-N{=}CClCOOC_2H_5$ anion is perfectly planar, while the $O_2^-N{=}C^1ClC^2ONH_2$ anion is almost planar. The lengths of the C—Cl bonds (1.711 and 1.713 Å respectively) have values that are intermediate between the bond lengths of C(sp^2)—Cl (1.72 Å) and C(arom)—Cl (1.70 Å).[116] Formally the N=C double bond (1.45 and 1.334 Å) is considerably longer than normal double bonds.[116] The length of the C=O bond in the ester anion is normal while in the amide anion it is extended (1.259 Å). Formally the N—C(2) single bond (1.323 Å) in the amide anion is formally shorter than an N = C double bond. The

C(1)–C(2) (1.465 Å) and N–C(2) bonds are very much shorter compared to single bonds (1.541 and 1.472 Å).[116] The distribution of bond lengths and the planarity of the anions indicate that conjugation occurs in them.

Difluoronitroacetic acid *N,N*-dimethylhydrazide has the zwitterion structure (I). In the case of aryl-substituted hydrazides, a form with a CF–HN hydrogen bond (2) occurs.[80,117]



(I) (II)

4. Acid-base properties

The introduction of chlorine atoms into molecules of nitrocarboxylic acid derivatives gives rise to a significant increase in CH-acidity (Table 2).[108,118–120] The introduction of fluorine atoms, on the other hand, reduces the acidic properties. This phenomenon is due to the destabilising effect of fluorine in the planar anion of the *aci*-form of the nitro compound, which manifests itself as "anticonjugation" (α-effect through the C=N double bond). This effect must assist the carbanion in adopting a pyramidal structure, which would lead to a partial disruption of conjugation, in other words, to destabilisation of the anion.[120] The planar configuration of the anions of ethyl chloronitroacetate and chloronitroacetamide to a certain extent confirms such a hypothesis.[114,115] An X-ray diffraction study of anions of α-fluoronitroalkanes or fluoronitroacetic acid derivatives would help to answer this question.

Table 2. CH-Acidity of α-halonitrocarboxylic acid derivatives (water, 25 °C).

Compound	pK_a	Refs.	Compound	pK_a	Refs.
$O_2NCH_2CO_2C_2H_5$	5.82	[121]	$O_2NCHClCO_2(CH_2)_2CH_3$	4.21	[108]
$O_2NCHFCO_2C_2H_5$	6.28	[118]	$O_2NCHClCO_2(CH_2)_3CH_3$	4.23	[108]
$O_2NCHClCO_2C_2H_5$	4.16	[118]	$O_2NCHClCO_2CH(CH_3)_2$	4.37	[108]
$O_2NCH_2CONH_2$	5.18	[118]	$O_2NCHClCO_2CH_2C(CH_3)_3$	4.32	[108]
$O_2NCHFCONH_2$	5.89	[118]	$O_2NCHClCO_2CH_2CH(CH_3)_2$	4.21	[108]
$O_2NCHClCONH_2$	3.60	[118]	$O_2NCHClCO_2CH(CH_3)CH_2CH_3$	4.42	[108]
$O_2NCHClCO_2CH_3$	4.02	[108]	$O_2NCHClCO_2CH_2CH_2Cl$	3.92	[108]

The nature of the alkyl substituent in the ester group has a weak effect on the change in CH-acidity in a series of chloronitroacetate esters.[108] A satisfactory relationship has been found between pK_a values and the Taft σ* constants of substituents for eight chloronitroacetate esters $O_2NCHClCOOR$ (R = Me, Et, Pr, Bu, iso-Bu, neopentyl, sec-Bu):[108] $pK_a = 3.98 - 1.94\sigma^*$; n = 8, $r = 0.98$, $s = 0.03$; $F = 143.5$. The acidic properties of α-bromo-α-nitrocarboxylic acid derivatives are not known. Determination of the dissociation constants showed that difluoronitroacetic acid is a stronger acid than trifluoroacetic acid (K_a 9.7 × 10^{-1} and 5 × 10^{-1} respectively).[62]

In terms of proton-donor properties the C–H bond of chloronitroacetate esters considerably surpasses the C–H bond in chloroform, acetylene derivatives, *o*-carborane, and it resembles the N–H bond.[105] Calorimetry was used to establish the proton-donor capacity of ethyl chloronitroacetate, which exceeds that for chloroform by a factor of 1.5. The thermodynamic constants of the hydrogen bond with trimethyl phosphate were determined and the enthalpy and autoassociation constant of this ester in CCl_4 were calculated.[122] The *P*-factor of methyl chloronitroacetate proved to be equal to the *P*-factor of *N*-methylaniline.[105] In the case of the reaction between ethyl chloronitroacetate and phenol in CCl_4 it was shown using IR spectroscopy that the electron-donor capacities of the CO and NO_2 groups were approximately equal and reduced by the mutual effect of the electronegative groups.[105]

IV. Chemical properties

1. Reactions involving the α-CH proton

As aliphatic nitro compounds that contain an active hydrogen atom at the α-position relative to the nitro group, α-halo-α-nitrocarboxylic acid derivatives react with bases to form salts of nitro compounds

$$O_2NCHXCOR \xrightarrow{:B} BH^+O_2^-N{=}CXCOR,$$

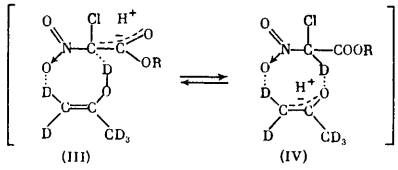
R—residues from alcohols, amines, etc.

Despite the frequent use of these salts in synthesis,[12–14,22,23,25,43,48,106,122] their stability on standing has hardly been discussed at all. Some chloronitroacetic acid derivatives, in particular the salts mentioned above,[114,115] do not decompose over a period of 1–2 months.[107] The sodium salt of benzyl chloronitroacetate[106] (5–10 g) can be stored at room temperature for 2–3 months without decomposition. Other derivatives are stable from several hours up to several days. On the whole, compounds such as salts of aliphatic nitro compounds cannot be stored for a long period because of their tendency to undergo spontaneous decomposition.

Bromo- and chloro-nitroacetate esters readily undergo the Henry reaction with aldehydes in the presence of calcium hydroxide[43] or potash.[48] The use of sodium acetate as a catalyst increased the yield of α-chloro-α-nitro-β-hydroxycarboxylic acids.[106]

$$O_2NCHXCO_2R \xrightarrow{R^1CHO} O_2NCXCO_2R,$$
$$\quad\quad\quad

suggested that deuterium exchange takes place via the highly unstable eight-membered transition states (III) and (IV).



(III) (IV)

Deuterium exchange takes place by a mechanism involving the concerted "departure" of a proton via the COOR group of (III) or the CO group of acetone in (IV) and arrival of a deuterium ion via the NO_2 group,[108] which is borne out to a certain extent by the approximately equal electron-donor capacities of the CO and NO_2 groups in chloronitroacetate esters.[105] Since a correlation exists between $T_{1/2}$ and the Taft σ^* constants of unbranched substituents, this type of deuterium exchange can serve as a method for measuring the relative mobility of protons in CH-acids.

The involvement of calculation methods for determining the charge distribution in anions that are formed by deprotonation of chloronitroacetate esters made it possible to propose an almost planar structure for the anion,[108] which was subsequently confirmed by X-ray diffraction analysis.[114]

2. Reactions involving the C—Hal bond

The presence of a nitro group at the α-position relative to a bromine atom activates the latter in a reaction with aqueous hydrazine. Diethyl bromonitromalonate is reduced more rapidly than diethyl bromomalonate.[123]

$$O_2NCBr(CO_2Et)_2 + H_2NNH_2 \rightarrow O_2NCH(CO_2Et)_2 + N_2 + HBr,$$
$$BrCH(CO_2Et)_2 + H_2NNH_2 \rightarrow CH_2(CO_2Et)_2 + N_2 + HBr.$$

The nitro group has a lesser effect on the mobility of halogen atoms in this reaction than keto or carbethoxy groups, as can be seen from the examples of the reduction of hydrazine hydrate given below.[13]

Halogen is reduced	Halogen is not reduced
$RCOCHClCO_2Et$, $RCOCRClCO_2Et$, $RCOCCl_2CO_2Et$, $CHCl(CO_2Et)_2$, $RCCl(CO_2Et)_2$, $CCl_2(CO_2Et)_2$	$O_2NCHClCO_2Et$, $O_2NCRClCO_2Et$, $O_2NCCl_2CO_2Et$

This is also confirmed by the ready reduction of ethyl bromonitroacetate, in contrast to bromonitroethane.

Bromonitrocarboxylate esters are reduced more readily than their chlorine analogues. Thus, ethyl α-chloro-α-nitropropionate and ethyl α-chloro-α-nitrobutyrate are not reduced, in contrast to their bromine analogues.

Esters of chloro-, bromochloro- and fluorochloro-nitroacetic acids when reacted with triphenylphosphine in benzene—methanol solution replace a bromine or chlorine atom with a hydrogen atom.[24] A change to a benzene medium reduced the yield of ethyl nitroacetate from ethyl chloronitroacetate from 71 to 20%.

$$O_2NCX_2COOR \xrightarrow[\text{benzene}]{Ph_3P,\ MeOH} O_2NCHXCOOR + Ph_3PO + Ph_3PO\cdot HX,\ X = H,\ Cl \text{ or } Br.$$

Hydrodechlorination of bromo- and chloro-nitroacetate esters can take place when sodium dithionite is used in aqueous alcohol.[86]

$$O_2NCHXCOOR \xrightarrow{Na_2S_2O_4} O_2NCH_2COOR.$$

3. Reactions involving the carboxyl group

Fluoronitroacetic,[50] difluoronitroacetic,[61,62] and fluorochloronitroacetic[44] acids have been obtained in a pure form. Difluoronitroacetic acid is stable in aqueous solution.[61,62] The remaining α-halo-α-nitrocarboxylic acids have only been determined as derivatives: esters, amides, acid chloride, etc. Bromo- and chloro-nitroacetic acids were determined in ether solution using IR spectroscopy.[86]

Table 3. Decarboxylation of α-halo-α-nitrocarboxylic acids and their chlorides to nitroso compounds or oximes.

Acid (chloride)	Reaction conditions	Reaction product	Yield, %	Refs.
$O_2NCHClCOCl$	conc. HCl, 20 °C	$HON{=}CCl_2$	10	[124]
$O_2NCHClCOCl$	$AlCl_3$ or AlF_3, 20–30 °C	$HON{=}CCl_2$	42 or 48	[125]
$O_2NCHClCOCl$	urea, carbonyl and other compounds, 20–35 °C	$HON{=}CCl_2$	60—75	[52]
O_2NCCl_2COCl	$AlCl_3$, 20–30 °C	$ONCCl_3$	50	[125]
$O_2NCFClCOOH$	21% aq. HCl, 100 °C	$ONCFCl_2$	60	[124]
$O_2NCFClCOOH$	KCl	$ONCFCl_2$	13	[126]
$O_2NCFClCOOH$	90% HNO_3	$O_2NCFClNO$	52	[128, 129]
$O_2NCFClCOOH$	60% HNO_3	$O_2NCFClNO$ + $+O_2NCFCl_2$	—	[128]
$O_2NCFClCOOH$	aq. HBr	$ONCFClBr$	—	[128]
$O_2NCHFCOOH$	conc. HCl, 70 °C	$HON{=}CFCl$	23	[130]
O_2NCF_2COOH	conc. HCl, 100 °C	$ONCF_2Cl$	60	[66, 131]

Table 4. Decarboxylation of α-halo-α-nitrocarboxylic acids and their chlorides to halonitroalkanes.

Acid (chloride)	Reaction conditions	Reaction product	Yield, %	Refs.
$O_2NCHClCOCl$	H_2O, 20° C	O_2NCH_2Cl	—	[132]
$O_2NCFClCOOH$	H_2O, 25—30° C	$O_2NCHFCl$	35	[44, 127]
$O_2NCFClCOOH$	KF	$O_2NCHFCl$	28	[126, 127]
$O_2NCFClCOOH$	KCl	$O_2NCHFCl$	24	[126]
$O_2NCFClCOOH$	N_2O_4	$(O_2N)_2CFCl$	—	[128]
$O_2NCFClCOOH$	Br_2+H_2O	$O_2NCFClBr$	—	[128]
$O_2NCFClCOOH$	90% HNO_3	$(O_2N)_2CFCl$	3—5	[128]
O_2NCCl_2COCl	H_2O, 20° C	O_2NCHCl_2	37	[132]
O_2NCF_2COOH	KF	O_2NCHF_2	26	[126, 127]
O_2NCF_2COOH	aq. K_2CO_3, 100 °C	O_2NCHF_2	46	[66]
$O_2NCCl(CF_2Cl)COCl$	H_2O, 45—50° C	O_2NCH_2Cl	61	[127]
$O_2NCCl(CF_3)COCl$	H_2O, 50° C	$O_2NCHClCF_3$	55	[127]

A large number of studies have been devoted to the decarboxylation of α-halo-α-nitrocarboxylic acids as a method for obtaining various halonitro-, halonitroso-, and halonitronitrosoalkanes.[44,52,66,124–132] Depending on the nature of the acid and reagents and the temperature of the medium, α-halo-α-nitrocarboxylic acids (or their acid chlorides) form halonitro, halonitroso, or halonitronitroso compounds (Tables 3 and 4). The conversion of α-nitro-α,β-dichloro-β,β-difluoropropionyl chloride to chloronitromethane when treated with water[124] is accounted for by the following reaction scheme:

$$ClCF_2CCl(NO_2)COCl \rightarrow ClCF_2CClNO_2^- \xrightarrow[-Cl^-]{} CF_2{=}CClNO_2 \xrightarrow{H_2O} \rightarrow HOCF_2CHClNO_2 \xrightarrow[-HF]{} FCOCHClNO_2 \xrightarrow[-HF]{H_2O} \rightarrow O_2NCHClCOOH \xrightarrow[-CO_2]{} O_2NCH_2Cl.$$

There is no common view on the mechanism of decarboxylation of α-nitrocarboxylic acids and their derivatives.[52,124,125] Evidently the solvating capacity and polarity of the reaction medium as well as the nature of the nitrocarboxylic acid and other reactants affect the course of the reaction and the nature of the products.

In effectively solvating polar media, *aci*-nitrocarboxylic acid is formed, undergoing decarboxylation.

$$HO_2N{=}CRCOOH \xrightarrow[-CO_2]{} HO_2N{=}CHR \rightarrow O_2NCH_2R.$$

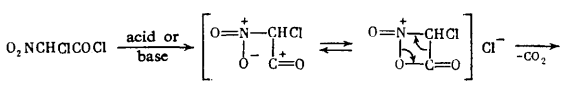
Depending on the nature of the radical R, the decarboxylation product can be converted to a nitro compound or, after protonation, dehydration, and addition of an anion, to a nitroso compound (or oxime).

$$HO_2N{=}CRR' \rightleftharpoons O_2NCHRR' \xrightarrow{HCl} HO(HO)\overset{+}{N}{=}CRR'Cl^- \xrightarrow[-H_2O]{} O{=}NCClRR'$$

The course of the reaction will most likely be mainly affected by the lifetime of the *aci*-nitro compound and its concentration. The amount of *aci*-form is known[133] to vary according to the series (%): CH_3NO_2 (0.000011) < $C_2H_5NO_2$ (0.0085) < iso-$C_3H_7NO_2$ (0.275).

The presence of the electronegative substituents COOH, COOR, or halogens at the α-position of nitroalkanes evidently substantially reduces the percentage of the *aci*-form. This can explain the conversion of salts of 2-nitropropane, nitrocyclohexane,[131] and ethyl nitroacetate[134] to the corresponding chloronitroso compounds on treatment with anhydrous HCl in ether and the absence of such a reaction for diethyl nitromalonate, nitroform,[131] and ethyl chloronitroacetate.[52]

In weakly solvating nonpolar media, where the probability of a sufficiently long lasting protonated nitro group is low, an intermolecular redox decarboxylation can take place.[52,125]



$$\longrightarrow ONCHCl_2 \longrightarrow HON{=}CCl_2.$$

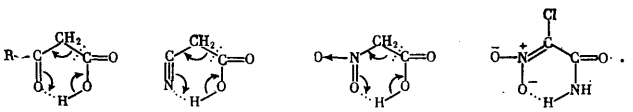
The course of the reaction is evidently also affected by the temperature, phase state, and steric and other factors. For example, difluoronitroacetic acid, as one of the strongest organic acids, can act as a base towards stronger acidic reagents.

Esters are apparently decarboxylated in the same way as acids. Thus, ethyl esters of chloro- and dichloro-nitroacetic acid,[132] and also of difluoronitroacetic acid[131] when reacted with hydrochloric acid form the corresponding halonitromethanes. Ethyl perfluoronitropropionate is converted under similar conditions to α-chloroperfluoronitrosoethane.[78]

$$O_2NCF(CF_3)CO_2C_2H_5 \xrightarrow{HCl} ONCFClCF_3 + EtOH + CO_2 + H_2O.$$

Since the values of the dissociation constants of trifluoro- and trichloro-nitroacetic acids are comparable and the stability of the former is higher, the greater stability of difluoronitroacetic acid compared to other α-nitrocarboxylic acids can be accounted for by the electron-donor properties of fluorine atoms. A series of acid stabilities has been put forward:[135] O_2NCF_2COOH > $O_2NCFClCOOH$ > $O_2NCHFCOOH$ > O_2NCH_2COOH > $O_2NCHClCOOH$.

Decarboxylation of α-substituted carboxylic acids results from the formation of six-membered transition states (V)–(VII) [136]



(V) (VI) (VII) (VIII)

The stability functions of such transition states will be mainly the planarity and solvation. In the case of fluorinated nitroacetic acids, there is evidently an affect from the same factors that determine CH-acidity, that is, repulsion beween the *p*-orbitals of the fluorine atom and the π-systems involving the central carbon atom, nitro group, and carboxyl group (covalent radii F 0.64, Cl 0.99, Br 1.14 Å). In other words, the fluorine atoms inhibit the formation of a planar six-membered transition state and thus inhibit the decarboxylation of fluoronitroacetic acids. It appears that proton solvents can form such a transition state through hydrogen bonding, as a result of which fluoro- and fluorochloro-nitroacetic acids, which are stable in a pure form, are readily decarboxylated in water. As was mentioned above, anions of chloronitroacetic acid derivatives are planar,[114,115] and evidently as a result of this, chloronitroacetic acid is readily decarboxylated. The anion of chloronitroacetamide (VIII) has a structure which resembles the hypothetical transition states (V)–(VII), which to a certain extent is an argument in favour of their possible formation.

Esterification of α-halo-α-nitrocarboxylic acid chlorides with aliphatic alcohols occurs in the normal way. However, it is better to obtain benzyl chloronitroacetate[83] by using sodium benzylate in benzyl alcohol in order to avoid decomposition of benzyl chloronitroacetate with HCl that is formed during the reaction.

$$O_2NCHClCO_2CH_2Ph \xrightarrow{HCl} O_2NCHClCOOH \xrightarrow[-CO_2]{} O_2NCH_2Cl.$$

By reacting chloronitroacetyl chloride with benzenediazonium chloride, the α-chloro derivative of nitroformaldehyde phenylhydrazone is formed in high yield[137]

$$O_2NCHClCOCl \xrightarrow{NaHCO_3,\ H_2O,\ PhN_2^+Cl^-} O_2NCCl{=}NNHPh.$$

However, there is no conclusive evidence in this study that benzenediazonium chloride reacts with disodium chloronitroacetate $2Na^+[O_2N{=}CClCOO]^{2-}$ rather than the sodium salt of chloronitromethane $Na^+[O_2N{=}CClH]^-$ which is formed from it by decarboxylation.

Difluoronitroacetyl fluoride and chloride form various products with trimethylsilane.[138]

$$O_2NCF_2COF + HSiMe_3 \rightarrow O_2NCF_2CO_2CH_2CF_2NO_2 + FSiMe_3,$$
$$O_2NCF_2COCl + HSiMe_3 \rightarrow O_2NCF_2CH_2OSiMe_3 + ClSiMe_3.$$

Treatment of difluoronitroacetyl fluoride with methyltrichlorosilane gives difluoronitroacetyl chloride.[138]

$$O_2NCF_2COF + MeSiCl_3 \rightarrow O_2NCF_2COCl + MeSiFCl_2.$$

An attempt to obtain the mercury salt from fluorochloronitroacetic acid and mercuric oxide gave di(fluorochloronitromethyl)-mercury.[139,140] It was suggested that the reaction takes place via the mercury salt of fluorochloronitroacetic acid, which is unstable to decarboxylation, in contrast to the mercury salt of difluoronitroacetic acid.[102,104]

Alkyl difluoronitroacetates and difluoronitroacetyl halides undergo aminolysis with ammonia and aniline without complications, giving amides and anilidies.[62,77,78] Derivatives of other α-halo-α-nitrocarboxylic acids react in more than one way. On treatment with ammonia, ethyl perfluoronitropropionate decomposes to α-hydroperfluoronitroethane and urethane.[77,78]

$$O_2NCF(CF_3)COOEt \xrightarrow{NH_3} CF_3CHFNO_2 + H_2NCOOEt.$$

Reaction of ammonia with methyl α-chloro-α-nitrotrifluoropropionate at −30 °C gives an amide which is unstable at room temperature.[141] The presence of methyl carbamate in the reaction mixture is an indication that a haloform decomposition is taking place at the same time.

$$O_2NCCl(CF_3)COOMe + NH_3 \rightarrow O_2NCCl(CF_3)CONH_2 + H_2NCOOMe.$$

At room temperature haloform decomposition is the main process.

$$O_2NCFClCOOMe + Et_2NH \rightarrow CHFClNO_2 + Et_2NCOOMe,$$
$$O_2NCCl(CF_3)COOPr\text{-}n + NH_4OH \rightarrow H_2NCOOPr\text{-}n.$$

Reaction of ethyl bromo- and chloro-nitroacetates with aqueous ammonia at 50−60 °C leads to the ammonium salts, which are acidified to give the amides. Hydrazinolysis can be achieved over a period of days at room temperature.[107]

$$O_2NCHXCOOEt + H_2NR \rightarrow H_3\overset{+}{N}R[O_2N{=}CXCONHR]^- \xrightarrow{H^+} O_2NCHXCONHR,$$
$$X = Br,\ Cl;\ R = H,\ Me,\ NH_2.$$

When the temperature is increased to 80−100 °C, decomposition of the initial esters occurs with formation of ammonium halides. When bromo- and chloro-nitroacetate esters are treated with aqueous solutions of sterically hindered amines and also alcohol and ether solutions of ammonia or amines, ammonium salts are also formed. This occurs because of the instability of the ammonium salts of the nitro compounds formed, as a result of their insufficient solvation, and leads to elimination of halogen and subsequent decomposition of the nitroester.[107]

Reaction of methyl difluoronitroacetate with sodium borohydride gives a mixture of difluoronitroacetaldehyde and its hemiacetal.[142]

$$O_2NCF_2COOMe + NaBH_4 \rightarrow [O_2NCF_2CH\overset{O^-}{\overset{|}{O}}Me(BH_3Na)^+] \rightarrow$$
$$\xrightarrow{H_2O} O_2NCF_2CH(OH)OMe + O_2NCF_2CHO.$$

When diethyl fluoronitromalonate is treated with alcoholic alkali and subsequently acidified, fluoronitromethane is obtained.[40] It has been suggested that the disodium salt of fluoronitromalonic acid is formed as an intermediate.

$$O_2NCF(COOEt)_2 \xrightarrow{EtOH,\ NaOH} [O_2NCF(COONa)_2] \xrightarrow[H_2O]{ClCH_2COOH} O_2NCH_2F.$$

In contrast, for example, to nitroacetic acid, difluoronitroacetic acid is not fluorinated on treatment with SF_4, which is due to a combination of the electron-acceptor effect of the fluorine atoms on fluorination and the ease of undergoing decarboxylation.[143]

$$O_2NCF_2COOH \xrightarrow[130°C]{SF_4} O_2NCF_2CF_3,$$
$$O_2NCH_2CO_2H \xrightarrow{SF_4} O_2NCH_2CF_3.$$

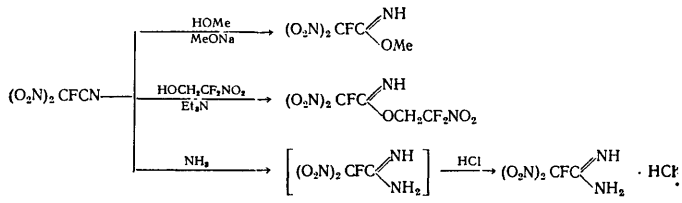
The reaction of chlorine fluorosulphate with ethyl chlorodinitroacetic acid is accompanied by displacement of the carbethoxyl group.[30]

$$(O_2N)_2CClCOOEt + ClOSO_2F \rightarrow (O_2N)_2CCl_2.$$

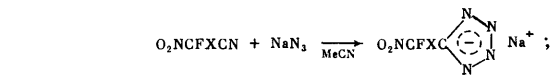
The reaction of difluoronitroacetyl fluoride with acetone and methyl ethyl ketone results in the formation of 1,1-difluoro-1-nitropentane-2,4-dione and 1,1-difluoro-1-nitro-3-methylpentane-2,4-dione.

$$O_2NCF_2COF + RCH_2COCH_3 \rightarrow O_2NCF_2COCHRCOCH_3.$$
R=H, CH_3.

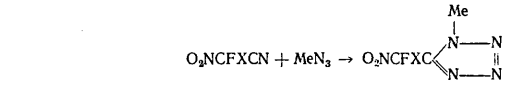
The presence of two nitro groups in fluorodinitroacetonitrile increases the electrophilic nature of the nitrile group. Reaction of this compound with alcohols gives imidates,[33,145] while with ammonia an amidine is formed.[33]



The reaction of difluoronitro- and fluorodinitro-acetonitrile with sodium azide is not so vigorous as for CF_3CN. This is because the nitro group shields the carbon atom of the nitrile group and hinders attack by azide ion.[146]



1,5-Disubstituted tetrazoles are synthesised by a reaction with methyl azide.[146] Reactions of trifluoroacetonitrile and chlorinated acetonitriles with MeN_3 take place with considerably greater difficulty, which is related to the strong electron-acceptor effect of the NO_2 group, which assists 1,3-cycloaddition.



By studying the kinetics of the addition of the radical $CH_3^{\cdot}$ to a number of perfluorocarbonitriles and α-nitroperfluorocarbonitriles in relation to the rate of elimination of H from iso-octane it was established that fluoronitronitriles are more reactive. Thus, O_2NCF_2CN adds on a methyl radical four times as fast, and $(O_2N)_2CFCN$ ten times as fast, as does CF_3CN. This phenomenon is due to the increased electrophilicity of the carbon atom of the nitrile group as a result of the strong electron-acceptor effect of the fluoronitro groups. The linear correlation of the ratio k_2/k_1 and σ^* indicates that the inductive effect mainly contributes to the reactivity of nitriles of this series towards a methyl radical.[147]

The mercury salt of difluoronitroacetic acid decarboxylates in the presence of strong bases.[102]

$$(O_2NCF_2COO)Hg \xrightarrow[or\ NaOH,\ H_2O]{Na_2CO_3,\ H_2O} O_2NCF_2H.$$

In ether it readily reacts with alkyl iodides and lower alkyl bromines.[102,103]

$$(O_2NCF_2COO)_2Hg + RX \xrightarrow[-HgCl_2]{ether} O_2NCF_2COOR + O_2NCF_2COOEt + ROEt,$$
$$R = Me,\ Et,\ Pr\text{-}n,\ Bu\text{-}n;\ X = Br,\ I.$$

The formation of ethyl esters as by-products, in quantities which increase as the activity of the alkyl halides decreases, occurs because

the salt undergoes reaction in solvated forms. With benzyl bromide and benzyl chloride the reaction takes place without by-products.

$$(O_2NCF_2COO)_2Hg + PhCH_2X \xrightarrow[-HgX_2]{ether} O_2NCF_2COOCH_2Ph.$$

In acetonitrile alkylation is also unaccompanied by side-reactions. The reaction in THF mainly leads to ring-opening.[103,104] The quantity of decomposition products from THF rises as the strength of the acid increases.[103]

$$(RCOO)_2Hg + MeI \xrightarrow[-HgI_2]{THF} RCOOMe + RCOO(CH_2)_4OMe,$$
$$R=O_2NCF_2,\ CF_3,\ Me,\ 2,4,6\text{-}Cl_3C_6H_2OCH_2.$$

The explanation that side-reactions occur because of solvation is not entirely convincing. The overall logic of these studies[102–104] indicates that two independent processes are taking place under these conditions — alkylation of the salts with alkyl halides and decomposition of ether or THF by difluoronitroacetic acid derivatives formed during reaction.

4. Reaction of α-halo-α-nitrocarboxylic esters with trivalent phosphorus compounds

The reaction of α-halonitrocarboxylic acids with trivalent phosphorus compounds, as a special case of the reaction of aliphatic and alicyclic α-halo-α-nitro compounds with phosphines and phosphites, is the most characteristic feature of these compounds.[23,24,148–154] The reaction has been studied in the case of α-bromo- and α-chloro-nitro compounds. The products of the reaction between α-halonitro compounds and triphenylphosphine and triphenyl phosphite, as a rule, are of differing types.

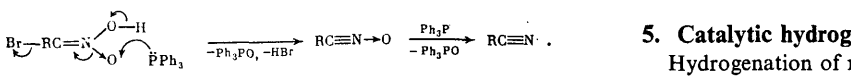
In a study of the reaction of triphenylphosphine with a number of α-bromonitro compounds it was found[148,149] that bromonitromethane and 1-bromo-1-nitroethane form quaternary salts which do not react with a further portion of triphenylphosphine.

$$Ph_3P + BrCRHNO_2 \rightarrow Ph_3\overset{+}{P}\text{—}CR{=}NO_2H\ Br^-.$$

At the same time, 1-bromo-1-nitropropane, ethyl bromonitroacetate, 1-bromo-1-nitro-octane, and bromonitrophenylmethane with twice the amount of triphenylphosphine give nitriles with yields of 63, 50, 72, and 75% respectively.

$$2Ph_3P + BrCRHNO_2 \rightarrow RC{\equiv}N.$$

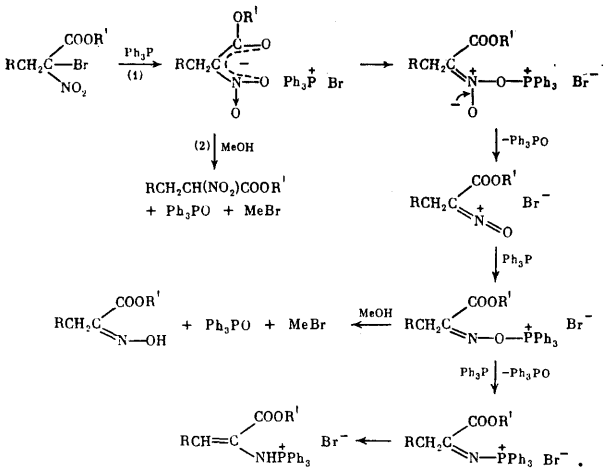
In the opinion of Trippet and Walker,[149] in the latter cases attack by Ph_3P occurs on the oxygen atom of the nitrile group.



Subsequently, reaction of 1-bromo-1-nitroalkanes with twice the amount of Ph_3P gave salts of phosphonium-substituted oximes, whose structure was confirmed by elemental analysis and IR and ^1H NMR spectroscopy.[150]

$$2\,Ph_3P + BrCRHNO_2 \rightarrow Ph_3\overset{+}{P}CR{=}NOH\ Br^- + Ph_3PO,$$
$$R=H,\ Me,\ Et..$$

The various stages were studied in the case of the reaction of a number of α-bromo-α-nitrocarboxylate esters with triphenylphosphine, with determination of the intermediate and final products, which to a considerable extent clarified the reaction route.[23]



Chloro-, fluorochloro-, and dichloro-nitroacetate esters react with triphenylphosphine in a similar manner according to reactions (1) and (2).[24]

The reaction of bromo-, chloro- and fluorochloro-nitroacetic acids and α-chloro-α-nitrotrifluoropropionic acid with triethyl phosphite gives phosphorylated oximes.[151,153]

$$O_2NCRXCOOR' + (EtO)_3P \rightarrow (EtO)_2\overset{O}{\overset{\|}{P}}\text{—}O\text{—}N{=}CRCOOR'.$$

The same products are obtained by counter synthesis from the ammonium salts of *aci*-nitrocarboxylate esters and diethyl phosphorochloridite.[152]

$$(EtO)_2PCl + NH_4^+[O_2N{=}CXCOOR]^- \rightarrow (EtO)_2\overset{O}{\overset{\|}{P}}\text{—}O\text{—}N{=}CXCOOR,$$
$$X=H,\ Cl,\ Br.$$

Phosphoryloximes were obtained for the first time by Allen[154] in the reaction of triethyl phosphite with 2-chloro-2-nitropropane and 2-chloro-2-nitrosopropane.

Methyl diphenylphosphinite also reacts to form a phosphorylated oxime.[23] This reaction, in principle, is a link that connects the reactions of α-halo-α-nitro compounds with triphenylphosphine and trialkyl phosphites into a single whole.

5. Catalytic hydrogenation

Hydrogenation of methyl and ethyl chloronitroacetates over palladium catalysts gives glycine ester hydrochlorides.[86,113]

$$O_2NCHClCOOR + H_2 \xrightarrow[EtOH]{Pd} HCl \cdot H_2NCH_2COOR.$$

A study of the kinetics of the process using thermography showed[113] that the main quantity of hydrogen is absorbed at the initial stage. It is possible to conclude from the decrease in reaction heat effect and small absorption of hydrogen at high degrees of conversion that at 40–50 °C decarboxylation starts to play a significant role. This conclusion is also supported by the fact that carbon dioxide has been detected in excess hydrogen removed from the reaction. Decarboxylation may take place because of the accumulation of water and hydrogen chloride during reduction, which increases the probability of hydrolysis of the initial ester to chloronitroacetic acid. This is one of the possible reasons for the low yields of final products (up to 65%).

V. Physiological activity

Bromine- and chlorine-containing α-halonitroacetate esters acquire a yellow colour and sharp odour on standing as a result of partial decomposition. Methyl bromonitroacetate has an irritating effect on the eyes and cause irritation on skin contact.[10] According to the WHO classification, chloronitroacetate esters are classed as compounds with moderate and low hazards. For peroral administration to mice, the acute toxicity amounted to 830 to 2300 mg kg^{-1} (2.3–9.1 mmol kg^{-1}) and for skin application it was 6000–8100 mg kg^{-1}.[85,155] Introduction of additional halogen atoms into the different parts of the molecules of these compounds increases the toxicity by a factor of 3–10.[85] The toxicity of fluorochloronitroacetate esters is higher than for esters of chloro-, dichloro-, and bromochloro-nitroacetic acids.[156] In working with difluoronitroacetic acid and its derivatives it is recommended to use care because of the known toxicity of these compounds.[62,66]

Chloronitroacetate esters at concentrations of 0.5–3 μM increase the ionic permeability of mitochondria, in other words, they act as decouplers of oxidative phosphorylation. Their effective concentrations are 10–15 times higher than for the traditional decoupler—2,4-dinitrophenol.[155] At minimum concentrations they inhibit the activity of mitochondrial succinate oxidase.[155]

Propyl and butyl chloronitroacetates have insecticidal activity.[85] Various esters of the same acid have suppressed the growth of bacteria of fungal mycelia and also the development of plant diseases.[85] Growth-regulating activity has been found in them, according to the results of initial experiments.[85]

Fluorochloronitroacetate esters have an anti-choline esterase action.[84,156–158] The most active is the butyl ester. The bimolecular constants for irreversible inhibition (k_2) of acetyl- and butyryl-choline esterase are $(3 \pm 0.7) \times 10^{-4}$ and $(5.1 \pm 0.5) \times 10^{-5}$ litres mol^{-1} min^{-1} respectively.

The effect of chlorine- and fluorine-containing nitroacetate esters on the morphology of mouse liver has been studied.[159] α-Fluoro-nitrocarboxylic acid hydrazides inhibit monoamine oxidase and have hypotensive properties.[160]

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During preparation of the manuscript for printing, a number of publications whose contents considerably complement the present review have appeared.

The bromination of nitroacetonitrile with bromine has been carried out without using bases.[161] Dinitroacetonitrile anion is almost quantitatively chlorinated on platinum, graphite, and ruthenium oxide-titanium anodes.[162] α-Fluoro-α-nitrocarboxylate esters can serve as initial reactants for the synthesis of various fluorine-containing synthons.[163] Nitration of symmetric difluoro-dichloroethylene and fluoro-1,2-dichloroethylene with a nitration mixture containing added SO_3 gives fluorochloro- and chloro-nitroacetyl fluorides respectively.[164] 1,1-Dichlorodifluoro-1,2-dinitroethane, in addition to difluoronitroacetyl chloride, is found amongst the products from the gas-phase nitration of 1,1-difluorodichloroethylene.[165] The conversions of alkyl fluoronitroacetates have been studied in Henry and bromination reactions.[166] Treatment of diethyl 2,5-dinitroadipate with excess aqueous KOBr gives diethyl 2,5-dibromo-2,5-dinitroadipate.[167] When treated with xenon difluoride, difluoro- and fluorochloro-nitroacetic acids can undergo halo- and nitro-decarboxylation.[168,169] The same system can be used for the halonitromethylation of benzene derivatives.[170–172] Primary and secondary amines can aminolyse methyl difluoro- and fluorochloro-nitroacetates.[173,174] Chloronitroacetic acid derivatives readily undergo sulphonation and dehalogenation with sodium sulphite, hydrosulphite, and dithionite.[175–178] Replacement of the chlorine atom is accompanied by oxidation of S(IV) to S(VI). Treatment of anhydrous ammonium salts of halonitroacetic acid derivatives with thionyl chloride gives the corresponding halo-oximinoacetic acid derivatives.[178,179] Chloronitroacetic acid derivatives coordinate with Cu(II) and Ni(II) ions.[180,181] The minimum negative charge on the chlorine atom in chloronitroacetic acid derivatives has been established using ^{35}Cl NQR and quantum-chemical calculations. The composition and molecular structures of chloronitroacetanilide,[183] dichloronitroacetamide,[184] bis(chloronitro-acetamidato)tetra-amminecopper(II),[185] and the hydrazine salt of 1-difluoronitroacetyl-2-acetylhydrazide[186] have been studied using X-ray diffraction analysis. On changing from esters to thioesters of fluorochloronitroacetic acid, their anti-choline esterase activity is markedly reduced.[187] Chloronitroacetamide has a retardant effect on wheat plants.[188] Detailed information on the synthesis and relationship between the hypotensive and anti-monoamine oxidase activities of difluoronitroacetic acid hydrazides has been published.[189–191] The synthesis of chiral α-substituted fluoronitro-acetates has been carried out and the racemates have been separated.[192–194] The absolute configuration of their optical isomers has been established by X-ray diffraction analysis.[195] The formation of isoxazoline-*N*-oxide from dibromonitroacetonitrile and tetramethylethylene has been reported.[196]

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