Preparation of Dinitrogen Trioxidefor Organic Synthesis: A Phase Equilibrium Approach
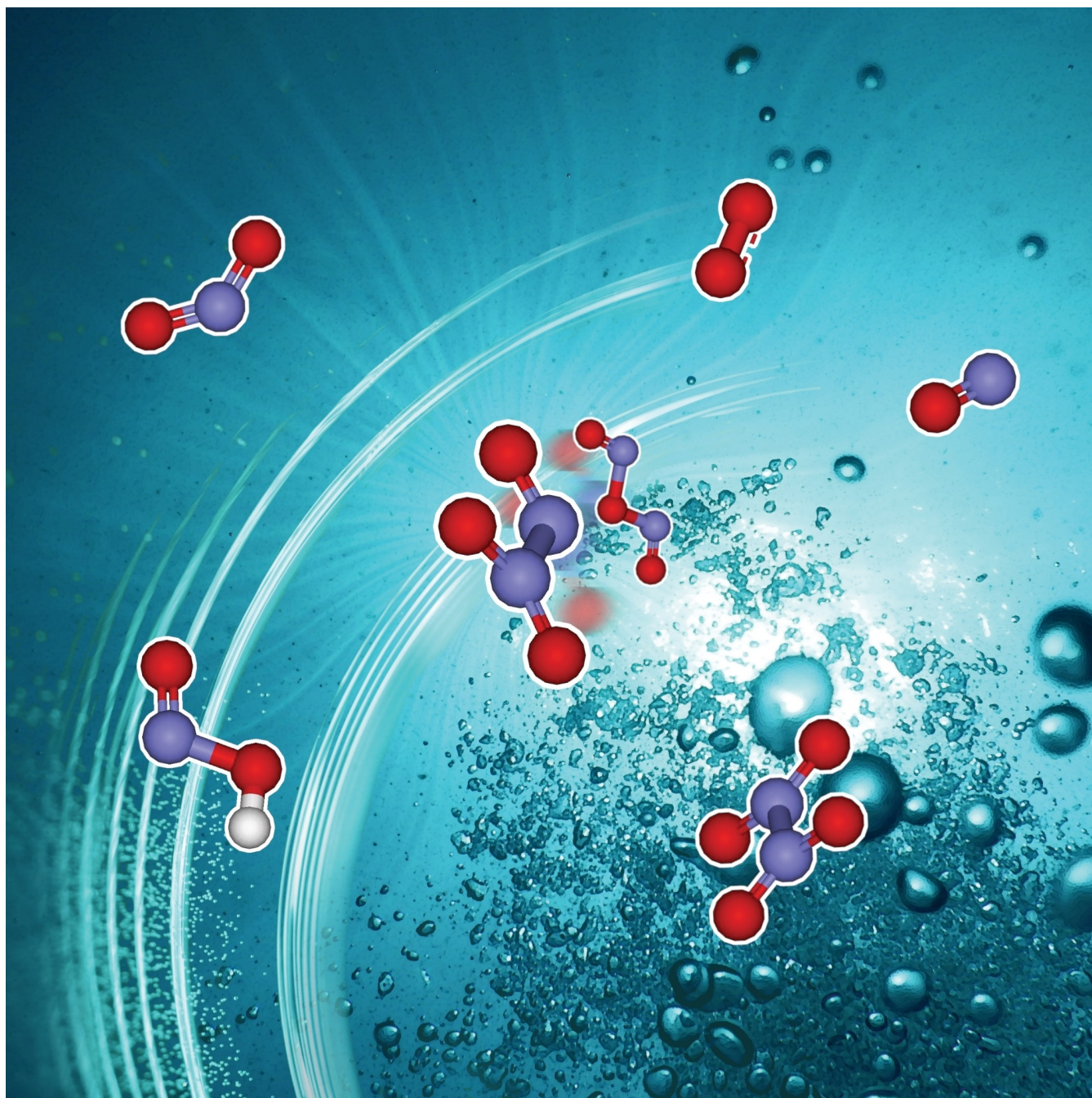
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Dinitrogen trioxide (N$_2$O$_3$) is a potent nitrosating agent featured with high reactivity and appealing atom economy. Because of its instability and the entanglement of chemical and phase equilibria, N$_2$O$_3$ has rarely been utilized in organic synthesis as a stock reagent with well-defined composition. In this review,the preparations of pure N$_2$O$_3$ and its concentrated solution (>0.1 M) are discussed from the aspect of phase equilibrium. Understanding the physical and chemical characteristics of N$_2$O$_3$, along with how reaction parameters (temperature, pressure, molar ratio) interact, plays a crucial role in managing the concentration of N$_2$O$_3$ in the liquid phase. This control holds practical significance in achieving quantitative reactions.

1. Introduction: Dinitrogen Trioxide (N$_2$O$_3$)

Dinitrogen trioxide (N$_2$O$_3$) is an unstable nitroxide, which is formally the anhydride of nitrous acid (HNO$_2$). In the nitrosative transformations using HNO$_2$ generated from nitrite and acid, N$_2$O$_3$ is involved as reactive intermediate.[1,2] Dinitrogen trioxide is a powerful nitrosating agent that outmatches other existing reagents (such as NaNO$_2$,[3] nitrites,[4,5] NOCl,[6] nitrosonium salts[7]) in terms of reactivity and atom economy. Because of the instability of N$_2$O$_3$[8,9] and the consequential difficulties in its preparation with accurate concentrations, pure N$_2$O$_3$[10] and its concentrated solution (>0.1 M)[11] have rarely been used in organic syntheses. An early review on the historical and experimental aspectsof N$_2$O$_3$was published by Beattie.[12]
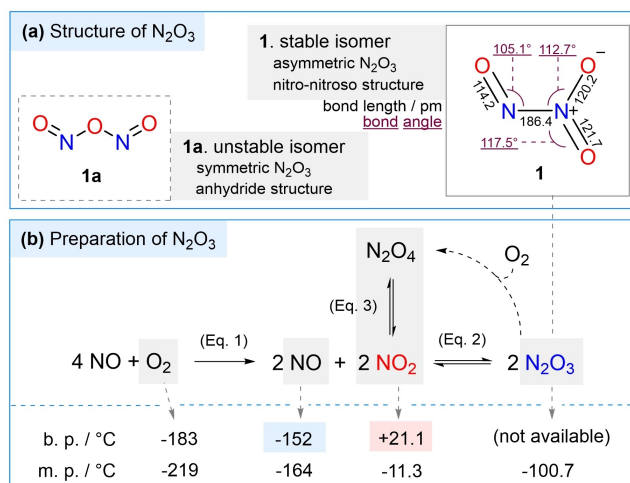
1.1. Structure and Spectroscopic Properties

Dinitrogen trioxide is stable in the nitro-nitroso structure (ON-NO$_2$, **1**)[13] presumably because of its maximized conjugation comparing with other alternative isomers (Scheme 1a).[12,14] The structure of N$_2$O$_3$(**1**) have been demonstrated by ^{14}N-NMR,[15,16,17] Raman spectra,[18,19] microwave,[20,21] and infrared (IR)[22,23] absorption spectra (IR in solid,[24,25] liquid,[26] gas[27] phases, and in solution).[28,29] The anhydride structure (ONONO, **1 a**) isso unstable that can only be detected spectroscopically in solid nitrogen matrices.[30,24] Isomer **1 a** can be enriched by irradiating **1** with 700–900 nm visible light[30] or with laser irradiation.[19,31,32] The absorption around 700 nm (n_N–π^* transition)[33,34] features N$_2$O$_3$ with a characteristic blue color, which is often used for the spectrometric determination of N$_2$O$_3$ concentration in the liquid phase,[35,36] in the gas phase,[37] in aprotic[38,33] and aqueous[39] solutions. At low concentrations in aqueous solution[40] or gas phase,[41] the absorption in the UV region (200–360 nm) has been employed for quantification.

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1.2. Decomposition Equilibrium

Thermodynamic data obtained from barometric experiments,[8,42] spectrometric measurements,[9,35] and statistical mechanical calculations[43] have shown that N$_2$O$_3$ is unstable; it decomposesreversibly to nitric oxide (NO) and nitrogen (IV) oxides (N$_2$O$_4$/NO$_2$) (Scheme 1b).In the gas phase, N$_2$O$_3$ decomposes spontaneouslyat room temperature (rt.),[8] and equilibrates with its decomposition products over a wide range of temperatures (*ca.*-100 °C-rt.) (Scheme 2, blue curve). In the liquid phase, N$_2$O$_3$ is stabilized by solvation, so that only a small fraction dissociates (Scheme 2).[9] The relative stability of N$_2$O$_3$ in the condensed phase[44] allows the preparation of the pure compound[10] and its solution[11] for synthetic applications.

The preparation of N$_2$O$_3$ in $>98\%$ purity relies on the reverse reaction of its decomposition (Scheme 1b, Eq. 2), that will be handled in the following sections. It is noteworthy that these nitroxides have very different boiling points (Scheme 1b) and solubilities. The nitrogen (IV) oxides (N$_2$O$_4$/NO$_2$)[45] are liquid at the temperatures in favor of N$_2$O$_3$ formation; they can be generated *in situ* from the reaction between NO and O$_2$(Eq. 1in Scheme 1b).[46] Nitric oxide (NO) boils below the melting points of N$_2$O$_3$ and of N$_2$O$_4$/NO$_2$, and is poorly soluble in liquid nitroxide mixture NO$_{1.5}$[42] and in common organic solvents;[47] whereas N$_2$O$_3$ and N$_2$O$_4$/NO$_2$ are well-miscible with one another and with organic solvents. The involvement of NO, a low-boiling and low-soluble component, in the dissociation equilibrium of N$_2$O$_3$ requires controlling the compositions of both gas (g) and liquid (l) phases in the preparation of N$_2$O$_3$.
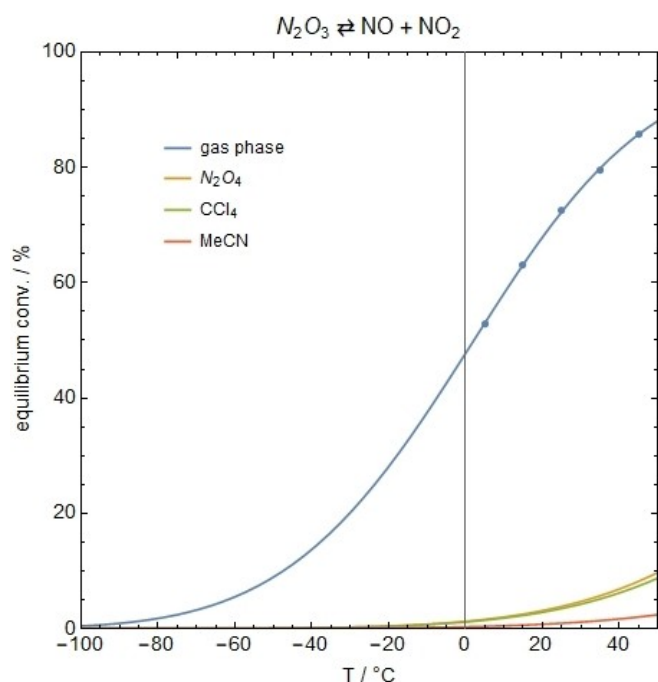

Scheme 1. Dinitrogen trioxide (N$_2$O$_3$): structure[21] and preparation.

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Scheme 2. The decomposition of N_2O_3 in the gas phase[8] and in some aprotic solvents.[9] The equilibrium conversions are calculated from the values of $\Delta_r H_m$ and $\Delta_r S_m$ in the respective references.

2. Properties of Liquid NO_x Mixture

Synthetic organic reactions are often performed in liquid solutions.[48,49] To utilize gases[50,51] or volatile reagents[52,53] for organic synthesis, controlling its concentration in the liquid phase (c_l) is of central importance to the regulation of stoichiometry and reaction rate, which are fundamental to quantitative studies. In the case of liquid N_2O_3, the reversable decomposition to the products having distinct boiling points (NO $-152\,°$C and $N_2O_4/NO_2 + 21.1\,°$C) (Scheme 1b) necessitates the consideration of both chemical and phase equilibria in order to control the liquid phase concentration of N_2O_3 ($c_l(N_2O_3)$) in a predictable manner.

2.1. Phase Diagram

The physical properties of neat N_2O_3, or more precisely the nitroxide mixture with average composition $NO_{1.5}$, depend on the contents of its decomposition products (Scheme 1b) in different phases. To envisage the equilibrium behavior involving multiple phases, one has to refer to the phase diagram.[54] Using the liquid/solid (l/s)[55] and gas/liquid (g/l)[42,35] equilibrium data measured by Beattie and Vosper, the isobaric phase diagram of nitroxide mixture (NO_x, $1.5 \leq x \leq 2.0$) can be plotted in Scheme 3. The composition is expressed in the ratio of oxygen (O) and nitrogen (N) atoms (x). In the phase equilibrium above $-100\,°$C, only 4 nitroxides (NO, NO_2, N_2O_3, and N_2O_4) need to be condidered; the molar fraction of a certain phase refers to the reduced formula NO_x (i.e. $N_2O_3 = 2\ NO_{1.5}$, $N_2O_4 = 2\ NO_{2.0}$), which is equal to the fraction of N atoms in the phase of interest.
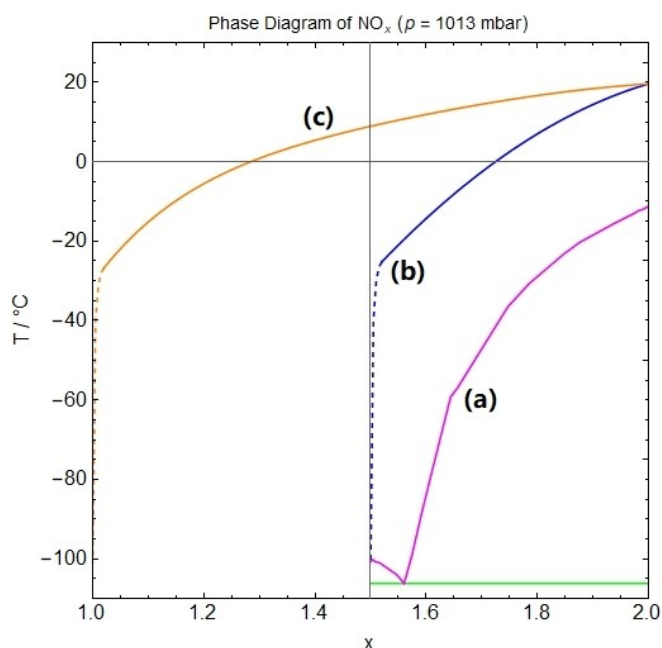
Using the liquid mixture of NO ($NO_{1.0}$) and N_2O_4/NO_2 ($NO_{2.0}$) with known ratio, the freezing point (Scheme 3a) and the vapor pressure were measured in cryoscopic[55] and barometric[42] experiments respectively. The bubble point (Scheme 3b) was calculated from the vapor pressure data; combining with the
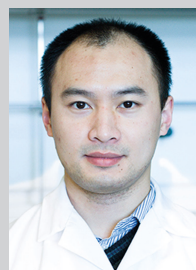
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Jean-Christophe M. Monbaliu is currently Professor of Organic Chemistry at the University of Liège in Belgium. He also serves as an Associate Editor for the Journal of Flow Chemistry. As the head of the Center for Integrated Technology and Organic Synthesis (CiTOS, http://www.citos.uliege.be), he leads the first European Corning® Advanced-Flow™ Reactor Qualified Lab. In 2022, Monbaliu founded FloW4all, a Flow Technology Platform in Wallonia that focuses on training, technology transfer, and services. Additionally, in 2023, he took on the role of Principal Investigator at the WEL Research Institute, where he leads efforts to integrate AI and quantum chemistry for advancements in flow processes. Research interests at CiTOS revolve around synthetic organic chemistry but are multidisciplinary in essence and aim at (a) designing cheaper and more efficient routes for the preparation of high value-added chemicals such as active pharmaceutical ingredients; (b) accelerating the transition from petrobased to biobased strategies and (c) developing efficient processes with a lower environmental impact.

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Scheme 3. Isobaric (T–x) phase diagram of nitroxide mixture NO_x: (a) liquidus line, data from ref. [55]; (b) bubble point line, calculated with the formulae in ref. [42]; (c) dew point line, calculated from the data in ref. [35,42] (For more details, see Supporting Information).

Scheme 4. Gibbs' phase rule and the number of independent intensive variables. Note that volume (V) is an extensive, not an intensive property.

Scheme 5. Lever rule and the molar fractions of equilibrating phases.

equilibrium composition (x_l/x_g) data,[35] the dew point (Scheme 3c) can be calculated.

In order to understand the chemical and phase equilibria of NO_x using phase diagrams, two rules relating thermodynamic variables, namely the Gibbs' phase rule (Section 2.2) and the lever rule (Section 2.3), will be briefly introduced in the two upcoming subsections. The back ground and justifications of these rules have been elucidated in elementary thermodynamics[56] and in physical chemistry.[57] Monographs on phase equilibria[58,59,60] are recommended for detailed applications and more concrete examples.
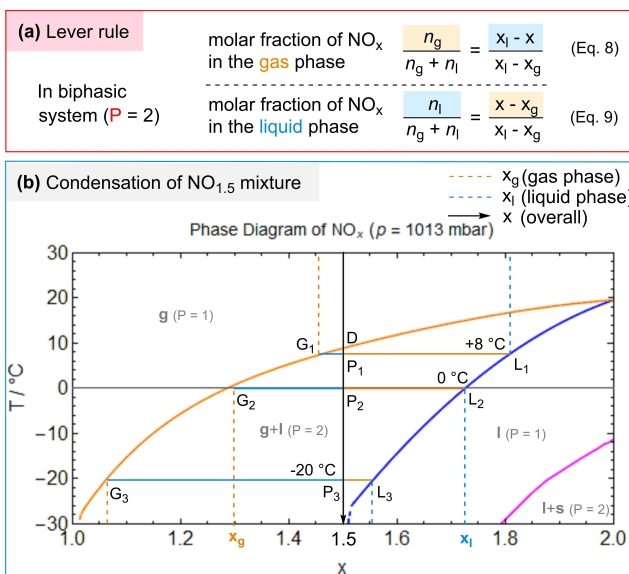
2.2. Gibbs's Phase Rule

The phase rule derived by J. W. Gibbs[61] relates the number independent intensive variables (temperature, pressure, and concentrations) (f) in a closed system with the number of independent components (C) and the number of phases (P) (Scheme 4a). The number of independent components (C)[62] takes the interrelations among the molar fractions (or concentrations) of all ingredients into account, such as linearly independent chemical reactions and stoichiometric constraints (Scheme 4b).[63] The number 2 (Scheme 4a) represents the contribution of temperature (T) and pressure (p) to the degree of freedom (f); when analyzing the phase diagrams under constant pressure (Schemes 3 and 5b) or constant temperature (Scheme 6), this number is reduced by 1.

The solvent-free NO_x ($1.5 < x < 2.0$) mixture in a closed container consists of 4 compounds that are in equilibrium with

each other through 2 chemical reactions (Scheme 4b, Eqs. 5 and 6); such mixture can be regarded as 2 independent components ($C=2$). The mixture of N(IV) oxides ($NO_{2.0}$) does not contain NO and N_2O_3; N_2O_4 and NO_2 equilibrate through 1 reaction (Eq. 6); therefore, the $NO_{2.0}$ mixture is 1 independent component ($C=1$). The $NO_{1.5}$ mixture resembles the case $1.5 < x < 2.0$ (4 compounds, 2 reactions), but it contains 1 stoichiometric constraint (Eq. 7) that makes itself 1 independent component ($C=1$).

The optimization of reaction conditions generally assumes the independence of reaction parameters, such as T, p, and concentrations in different phases (c_g, c_l). In the case of NO_x, the molar concentration (c_l) of NO_x in the liquid phase can be calculated with the density of the liquid mixture.[64] Every factor that influences c_l must not depend on other parameters to be varied (T, p, c_g, etc.) during the optimization; otherwise the individual tuning of each parameter is prohibited by their interrelations.Therefore, the multiphasic reaction system should allow sufficient degrees of freedom (f) not less than the number of intensive parameters to be optimized.

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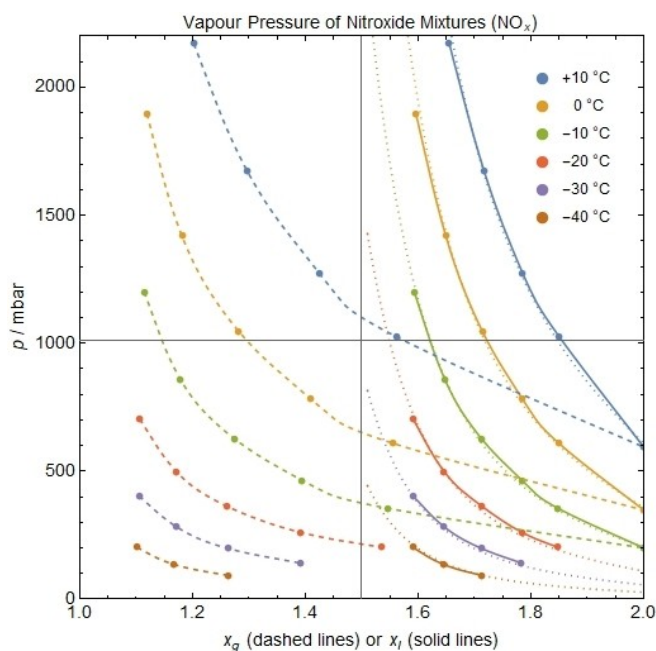
Scheme 6. Isothermal (p–x) phase diagrams of nitroxide mixture NO_x: the liquid phase composition (x_l) and the gas phase composition (x_g) under the same temperature and pressure are in equilibrium (data from ref. [37]); the overall composition (dotted lines), calculated from the data in ref. [42] (For more details, see Supporting Information).

2.3. Lever Rule – the Mass Balance between Two Phases

In a biphasic equilibrium (P = 2), the lever rule can be derived from the mass balance that associates the compositions and the amounts of both phases (Scheme 5a). The amount of one phase is inversely proportional to the difference between its composition and the overall composition.

In the phase diagram of NO_x presenting the composition in terms of the ratio of O- and N-atoms (x) (Scheme 3 and Scheme 5b), the amount of a phase is measured by the number of mole of NO_x (cf. Section 2.1). Under constant pressure (1013 mbar) in a closed container, the mixture of $NO_{1.5}$ (overall composition) falls in the biphasic region at 0 °C (Scheme 5b). The equilibrium compositions of the gas and the liquid phases (x_g and x_l) are given by the intersections of the 0 °C isotherm with the dew point line (G_2) and with the bubble point line (L_2). Taking the overall composition as the fulcrum (P_2), the molar fraction of one phase (g or l) is given by the ratio of the opposite lever arm (P_2L_2 or P_2G_2) and the tie line (G_2L_2).

In the biphasic regions of phase diagrams, the change of the compositions and the amounts of equilibrating phases in response to the changes of T or p can be visualized by moving the fulcrum along the isopleth representing the overall composition, e.g. $x = 1.5$ in Scheme 5b (vide infra).

2.4. Liquid/Solid Equilibrium

Liquid N_2O_3 ($NO_{1.5}$) freezes at −100.7 °C[55] under constant vapor pressure, which is a behavior of a pure compound (C = 1)

according to the phase rule (Scheme 4b) (f = 1−2+1 = 0). Regarding the liquid/solid (l/s) equilibrium data (Scheme 3a),[55] the freezing of the liquid NO_x mixture (1.560 < x < 2.0) starts with the formation of $NO_{2.0}$(s) and is accompanied by the enrichment of low boiling ingredients (NO, $NO_{1.5}$) in the liquid phase; as x_l gets smaller, the equilibrium temperature decreases along the liquidus line (Scheme 3a) (f = 2−2+1 = 1) until reaching the eutectic composition (x = 1.560). Similar analysis can be performed for 1.5 < x < 1.560, where the liquid mixture equilibrates with $NO_{1.5}$ (s). At the eutectic point(1.560, −106.2 °C),[55] the liquid phase and two solid phases ($NO_{1.5}$, $NO_{2.0}$) coexist (P = 3), the liquid freezes at constant temperature and pressure (f = 2−3+1 = 0). At temperatures below −100 °C,[42] some unstable isomers of nitroxides, such as the dimer of NO (ONNO)[65] and the isomer of N_2O_4 ($ONONO_2$),[66] can be enriched in the solid state; the involvement of these species does not change the number of independent components (C).

2.5. Gas/Liquid Equilibrium

Because N_2O_3 is unstable in the gas phase (Scheme 2), N_2O_3 could not exist as pure compound near its boiling temperature. The boiling point of N_2O_3, namely the equilibrium temperature under $p(N_2O_3) = 1013$ mbar, does not exist.[44] The g/l equilibrium behavior of $NO_x(1.0 \leq x \leq 2.0)$ resembles that of a two-component mixture made of $NO_{1.0}$ and $NO_{2.0}$. The high-boiling $NO_{2.0}$ is enriched in the liquid phase, whereas the low-boiling NO in the gas phase (cf. Scheme 1b). When the liquid phase composition approaches $x_l = 1.5$, its vapor pressure rises asymptotically[44] (Scheme 6), indicating an extremely low "boiling point" of N_2O_3. Correspondingly, the bubble point (Scheme 3b) and the dew point (Scheme 3c) of the mixture fall asymptotically along the isopleths $x_l = 1.5$ and $x_g = 1.0$, respectively. The vapor above $NO_{1.5}$ (l) is almost pure NO.[35]

While it is permissible to define the equilibrium temperature at which $p(NO) = 1013$ mbar as "boiling point" or "bubble point" according to the phase rule (f = 1−2+1 = 0), such condition is contradicted by the low boiling point of NO (−164 °C) and the low solubility[67] of NO in $NO_{1.5}$(l).[44] The vapor pressure over $NO_{1.5}$(l) could not be reduced to 1013 mbar before it freezes;[54] therefore, the bubble point line (Scheme 3b) does not intersect with isopleths x = 1.5. In the databases and some literature, the "boiling point" of N_2O_3 differs significantly; these values are often provided without specifying measuring methods, that could presumably be the dew point of $NO_{1.5}$(g) (+3 °C)[68,69] or the extrapolation of the vapor pressure curve[42] of NO_x(l)(−27 °C).[70] At the dew point, N_2O_3 is mostly dissociated (Scheme 2); the condensed liquid is rich in $NO_{2.0}$ (L_1 in Scheme 5b). At the temperature obtained by extrapolation, the vapor pressure over $NO_{1.5}$ is still higher than 1013 mbar.[54]

The condensation of gaseous $NO_{1.5}$ mixture for the preparation of N_2O_3 (l) can be visualized by using the isobaric phase diagram (Scheme 5b) and level law (Scheme 5a). In a closed vessel containing $NO_{1.5}$ (g) under constant pressure (1013 mbar), when the temperature becomes lower than the

dew point (D) (e.g.P_1 in Scheme 5b), $NO_{2.0}$-rich liquid (L_1) droplets (G_1P_1) starts to appear. As the condensation proceeds (e.g.P_2), the equilibrium temperature is lowered by the N_2O_3 (l) formed via Eq. 2 (Scheme 1b); the composition of the liquid phase (L_2) approaches $x_l = 1.5$ along the bubble point curve (Scheme 3b), while the gas phase (G_2) along the dew point curve (Scheme 3c) to $x_g = 1.0$. As the formation of N_2O_3 is favored at low temperature (Scheme 2), further refrigeration (e.g. P_3 in Scheme 5b) will collect most (G_3P_3) of the nitroxide in the form of liquid $NO_{\sim1.5}$ (L_3), leaving a small amount (P_3L_3) of $NO_{\sim1.0}$ (G_3) in the gas phase.

At temperatures between the dew point (D) and the freezing point of $NO_{1.5}$, the overall composition $x = 1.5$ falls in the biphasic region (P = 2) (Scheme 3, between curves b and c), the equilibrium composition of the gas phase (x_g) therewith is always dependent on the liquid phase (x_l) (f = 2 − 2 + 1 = 1). Therefore, the stabilization of N_2O_3(l) necessitates the presence of NO in the gas phase. Loosing NO from the gas phase could invoke the decomposition of N_2O_3(l) to maintain the partial pressure of NO ($p(NO)$) above it. Conversely, introducing an excess amount of NO moves the overall composition further into the biphasic region without varying the compositions of both phases (x_g and x_l).

The decomposition of N_2O_3 (Eq. 4 in Scheme 5) increases the amount of gases and is therefore subjected to the influence of pressure. The vapor pressure diagram (Scheme 6) can be regarded as the overlapping of six isothermal (p–x) phase diagrams. Depressurizing $NO_{1.5}$ mixture at constant temperature increases the content of $NO_{2.0}$ in both gas and liquid phases; all liquid is gasified when the pressure is below the intersection of the gas isotherm (dashed line) and isopleths $x = 1.5$ (dew point) at that temperature. In order to prepare N_2O_3(l) with high purity, we expect the liquid isotherm (solid line) could approach $x = 1.5$ as close as possible at atmospheric pressure (1013 mbar); this is only possible at low temperature. Under $p(NO) = 1013$ mbar, N_2O_3(l) will be < 1% dissociated at −40 °C;[44] this temperature can be regarded as the upper limit to prepare and use N_2O_3 as a pure compound.

3. Preparation of N_2O_3

From the discussion in the last section, the preparation of N_2O_3 requires low temperature, excess of NO, and an enclosed reactor. Over the past decades, the preparation and reactions of N_2O_3 were carried out under biphasic conditions (P = 2) in batch reactors (test tubes, flasks, autoclaves etc.), that requires the control of headspace atmosphere to stabilize the liquid phase concentration (c_l). Some researchers have noticed that the c_l of nitroxide is affected by the volume of the headspace.[15,44] Moreover, most nitroxides are toxic and corrosive low-boiling substances[71,72] that require protective measures, special metering devices (gas volumetry),[73] and precautious operation in a well-ventilated environment.[74] For the analytical methods of NO_x in the environment and the hazard of NO_x to human, reports[75,76] from the World Health Organization (WHO) are recommended.

3.1. Preparation of Pure N_2O_3

The preparation of pure N_2O_3 relies on the reaction between NO and N_2O_4/NO_2(Eq. 2 in Scheme 1)at cryogenic conditions (−100 − −40 °C). According to the phase diagram (Scheme 3), N_2O_3(l) reaches an equilibrium with NO(g); the reaction is conducted with a large excess of NO to occupy the headspace and accelerate the reaction at high conversions. At −50 − −80 °C, N_2O_3(l) can be prepared in 1–50 g scale with > 99% purity by the reaction between NO(g) and N_2O_4(s) under agitation.[10] Alternatively, N_2O_4/NO_2 can be generated *in situ* from NO and O_2[77] (Eq. 1 in Scheme 1); slowly passing an 8:1 (v/v) mixture of NO and O_2 through a −60 °C cold trap will condense N_2O_3(l) with > 98% purity.[10]
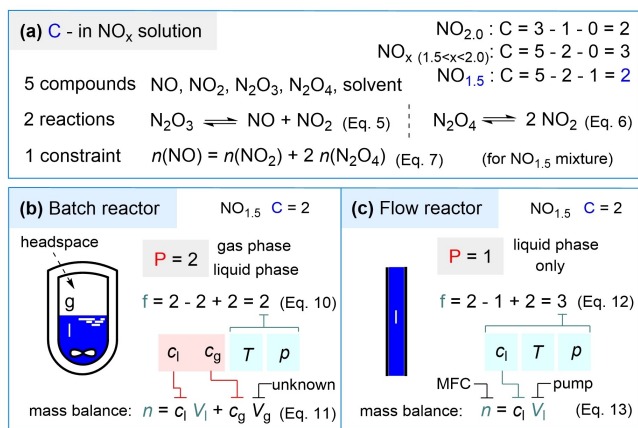
In the preparation of N_2O_3(l), the concentration of NO_x in the liquid phase (c_l) is approximately 10^3 times higher than that in the gas phase (c_g) ($\rho(N_2O_3(l)) = 1.5022$ g mL^{-1} at −57.4 °C,[64] corresponding to $c(NO_x) = 39.53$ M). When the headspace in the reactor is small ($V_g/V_l < 10$), the liquid phase composition (x_l)[37](solid lines in Scheme 6) almost overlaps with the overall composition (x)[42](dotted lines in Scheme 6) in the range without NO excess ($1.5 < x \leq 2.0$). In this case, because of the high concentration of NO_x(l) ($c_l \gg c_g$), the liquid phase composition (x_l) can be approximated by the overall composition (x), which can be adjusted by tuning the ratio of NO and $NO_{2.0}$.

3.2. Preparation of N_2O_3 Solutions

Concentrated solutions (> 0.1 M) of N_2O_3 can be prepared by mixing gases (NO/O_2[11,78] or NO/NO_2)[9] and solvents that do not react with it. These solvents are generally anhydrous non-reductive aprotic solvents; N_2O_3 is more prone to dissociate in apolar solvents than in polar aprotic solvents[9] (e.g. CCl_4 and MeCN in Scheme 2). As N_2O_3 can be stabilized by solvation (Scheme 2), its solutions (up to 1 M N_2O_3) can be stable at 0 °C under $p(NO) \approx 1700$ mbar and used for reactions at room temperature.[11,79,80] Comparing with the preparation of pure N_2O_3 (Section 3.1), the requirement on condition control is attenuated, making N_2O_3 solution relatively accessible for synthetic chemists.

The involvement of solvent has increased the number of independent components (C) by 1 (Scheme 7a), while reducing the NO_x concentration in the liquid phase (c_l). In organic synthesis, c_l between 0.1 and 1 M is of practical significance. However, the liquid phase concentration (c_l) in this range is only 1–10 times of that in the gas phase (c_g), indicating a more pronounced influence of the reactor headspace (V_g). Hence, c_l cannot be approximated by simply neglecting the NO_x in the gas phase(n/V_l).

In batch reactors (Scheme 7b), the headspace always exist (P = 2) with unknown and variable volume (V_g) that prohibits the control of c_l by adjusting the amounts of NO_x (n) and solvent (V_l). The concentrations (c_g and c_l) are not independent variables; their ratio (c_g/c_l) is governed by temperature and pressure. Bohle and coworkers[11] managed to prepare 1 M solution of N_2O_3 by manually injecting NO and O_2 from gas-tight

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Scheme 7. Preparation of N_2O_3 solution: control of reaction parameters.

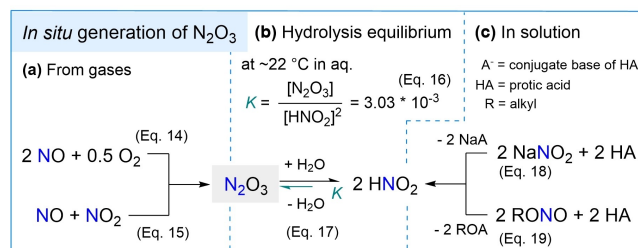**Scheme 8.** The *in situ* generation of N_2O_3 (equilibrium constant from ref. [40]).

syringes into a closed test tube containing organic solvents at $0\,°C$; the concentration of N_2O_3 (c_l) was determined afterwards by a UV-Vis spectrometer. Because of the limited specific g/l interface for the mass transport, the operation is slow and cumbersome. Even though, this method is still handy to prepare a few milliliter of N_2O_3 solution for qualitative experiments.[79,80]

In continuous flow reactors (Scheme 7c), where there is no head space, the gases can be completely dissolved ($V_g = 0$, P = 1) when the ratio of flow rates of NO and O_2 lies between 2 ($NO_{2.0}$) and 4 ($NO_{1.5}$). When the ratio of flow rates $NO/O_2 = 4$, the concentration of N_2O_3 (c_l) in the homogeneous liquid flow is an independent variable that can be precisely controlled by setting the flow rates of the solvent (V_l) and the gases (n) on pumps and mass flow controllers (MFC) respectively. Based on these considerations, Monbaliu and coworkers[28] developed a flow platform for the generation of N_2O_3 solution in accurate and tunable concentrations (up to 1 M). The generated N_2O_3 solution was successfully employed in the quantitative studies of *N*-nitrosative reactions (*vide infra*).

The color of concentrated (> 0.1 M) N_2O_3 solution is intense and varies from dark blue to green depending on the solvent.[11] Generally, polar solvents stabilize N_2O_3 by solvation, exhibiting the blue color of N_2O_3; apolar solvents do not solvate N_2O_3 well, so the solution therein is green, a mixed color of N_2O_3 (blue) and NO_2 (reddish brown).[38] When the substrate is added into N_2O_3 solution, the disappearance of the color could sometimes mark the endpoint of the reaction.[11,81]

3.3. In situ Generation of N_2O_3

Dinitrogen trioxide can be generated *in situ* by passing the 1:1 (v/v) mixture of NO and NO_2 ($NO_{1.5}$(g), so-called "nitrous gas")[82] or the 4:1 (v/v) mixture of NO and O_2[83,84] through the solution of substrates (Scheme 8a). The N_2O_3 collected in the liquid phase reacts with organic substrates immediately before accumulating to high concentrations. The $NO_{1.5}$(g) generated from liquid solutions is sometimes incorrectly referred to as "dinitrogen

trioxide",[85,86,69] although N_2O_3 is dissociated under those conditions (*cf.*Scheme 2).

Dinitrogen trioxide is often involved as a reactive species in the chemistry of HNO_2.[2] The condition for the nitrosation in organic synthesis, *i.e.*, the acidification of nitrites, is sometimes applied to access the reactivity of N_2O_3 (Scheme 8c). In aqueous solutions, HNO_2 equilibrates with a low concentration of N_2O_3 (Scheme 8b);[40,87] that accounts for the light-blue coloration[88,39] and the oxygen exchange between HNO_2 and H_2O (2nd order in HNO_2).[89] In the liquid phase nitrosation at low acidity, the generation of N_2O_3 is often the rate-limiting step, which is characteristic for the second-order kinetics with respect to HNO_2[1,90] (e.g. nitrosation of morpholine,[91] 1-methyl-2-phenylindolizine,[92] and olefins[93]).

The reactions using *in situ* generated N_2O_3 are performed at low concentrations (< 0.1 M) of N_2O_3, which could tolerate protic solvents, higher temperature, and no control of head-space atmosphere. Under these conditions, the reaction rate is slower than using concentrated N_2O_3 solution. Regarding the reaction mechanism, the reactivity cannot always be unambiguously attributed to N_2O_3; other reactive species (HNO_2, NO^+, N_2O_4, *etc.*), additives, the solvent, and the atmospheric O_2 may also play a role. In subsequent sections, we will focus on the reactions using pure N_2O_3 and its concentrated solution; the reactions with *in situ* generated N_2O_3 will only be visited when the product stems unequivocally from the participation of N_2O_3.

3.4. Summary of Preparative Methods of N_2O_3

In summary of the discussions in the previous subsections, the key features of the preparative methods of N_2O_3 in different concentrations for chemical synthesis are presented in Table 1. Formulae for the reproduction of phase diagrams (Schemes 3 and 6) are gathered in the Supporting Information.

4. Reactivity of N_2O_3

Molecular orbital calculations[94] have shown that the N—N single bond in N_2O_3 molecule (**1**) is weak; most of the nitrosative reactions of N_2O_3 involves the heterolytic or homolytic fission of this bond. Dinitrogen trioxide is an electrophilic nitrosating agent ($NO^{\delta+}NO_2^{\delta-}$)[95] that transfers a nitroso

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Table 1. Methods for the preparation of N_2O_3 in different concentrations.

	Neat N_2O_3	N_2O_3 solution	*In situ* generated N_2O_3
$c(N_2O_3)/(mol\,L^{-1})$[a]	20	0.1–1	< 0.1
Operation temperature/°C[b]	≤ -40[b]	≤ 0[b] $\leq +25$[c]	$\leq +25$
Solvent	No solvent	Aprotic solvents	Aprotic and protic solvents
Color	Dark blue	Blue to green	Light blue or colorless
NO atmosphere	Required	Required	Not required

[a] $c(NO_x) = 2\ c(N_2O_3)$. [b] Under $p(NO) = 1013$ mbar. [c] In monophasic flow under 6 bar pressure.

group (−NO) to the nucleophilic center of the reaction partner. Reactions arising from the (homolytic) decomposition products of N_2O_3, especially N_2O_4/NO_2,[96] are often encountered at high temperatures and under oxygen-rich conditions.

Dinitrogen trioxide can be oxidized by O_2 to N_2O_4 (Scheme 9a). The oxidation proceeds presumably via NO in the decomposition equilibrium (Eq. 5). In concentrated solutions, the reaction is accompanied with apparent color change from dark blue (N_2O_3) to light yellow (N_2O_4); this feature is used to determine the concentration of N_2O_3 by volumetric methods.[11]
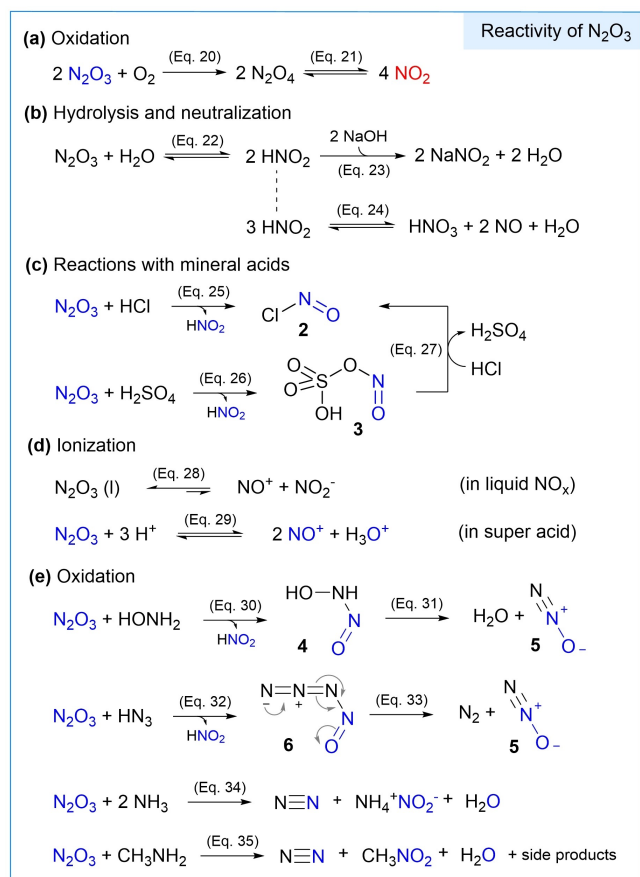
Scheme 9. The reactivity of N_2O_3.

In quantitative experiments with N_2O_3, the dry solvent must be deoxygenated (e.g. by purging with an inert gas)[28] prior use.

As previously mentioned (Scheme 8b), N_2O_3 hydrolyzes in aqueous solution almost completely to HNO_2 (Scheme 9b).[40,88] In the gas phase, the hydrolysis is rather incomplete (*ca.* 20% conversion at 10–50 °C).[97,87,98] The hydrolysis of N_2O_3 (Eq. 22) is involved in the absorption of the mixture of NO and NO_2 with water.[99,100,98,101] The product HNO_2 is an unstable weak acid ($pK_a \approx 3.2$)[102] that can be neutralized with an alkaline into nitrite conjugate base (Eq. 23).[103] Therefore, alkaline solutions are used to absorb and destruct N_2O_3 and other acidic nitroxides.[104,105] In the absence of bases, HNO_2 disproportionates to HNO_3 and NO at room temperature (Eq. 24).[106,39,107] The so-formed HNO_3 could invoke oxidative side reactions[108,109] in the reactions that forms HNO_2 as byproduct.

Mineral acids react with N_2O_3 to give their nitrosyl derivatives (Scheme 9c). Starting from 0.5 M N_2O_3 solutions in organic solvents, Bohle et al. prepared nitrosyl chloride (**2**) and nitrosylsulfuric acid (**3**) as pure compounds from the reactions with the corresponding acids (Eqs. 25–26).[11] Absorbing nitrous gas with H_2SO_4 could also afford **3**, that can subsequently be treated with HCl to generate NOCl (Eq. 27) for the photo-nitrosation of cyclohexane[110] in the manufacturing of carprolactame.[111]

Apart from the homolytic decomposition (Eq. 5), N_2O_3(l) undergoes heterolytic dissociation (Eq. 28) in a very low extent ($K = 2.16 \times 10^{-13}$ at −40 °C).[112] The addition of small amount of N_2O_3 in N_2O_4(l) could significantly increase the conductivity[112] of the latter; this feature could be used to detect NO impurity in N_2O_4(l). In super acids like H_2SeO_4[113] and $H_2S_2O_7$,[114] N_2O_3 could ionize to give nitrosonium ion (NO^+) (Eq. 29), a more potent nitrosating species.[7,115]

Dinitrogen trioxide is an oxidant (Scheme 9e).[116] It appears in the oxidation of hydroxylamine[117] (Eqs. 30–31) and hydrazoic acid[118] (Eqs. 32–33) with HNO_2 as the reactive intermediate under low acidity. Ammonia reacts rapidly with neat N_2O_3, giving N_2 and ammonium nitrite (Eq. 34).[119] An early attempt to prepare diazomethane from methyl amine and N_2O_3 ended up with nitromethane along with side products (Eq. 35);[120] whereas nitrosyl chloride (NOCl)[121] provided 23~25% yield of diazomethane.

As a Lewis acid, N_2O_3 forms adducts with Lewis bases without breaking the N–N bond. Weak Lewis bases like aromatic donors (toluene, *m*-xylene, mesitylene, and anisole)[122] form 1:1 adducts with N_2O_3 in the solid phase; the stoichiometry was identified by the l/s phase diagrams. The adduct with strong Lewis bases like some tertiary amines (DABCO)[79] is stable at room temperature.

5. Reactions with Organic Compounds

Nitrosation is an important protocol for introducing nitrogen atoms onto organic molecules.[123] Nitrosative reactions are predominently carried out with $NaNO_2$ or alkyl nitrites. Although N_2O_3 could accomplish most of the transformations by nitrites in a more efficient and economical way, pure N_2O_3

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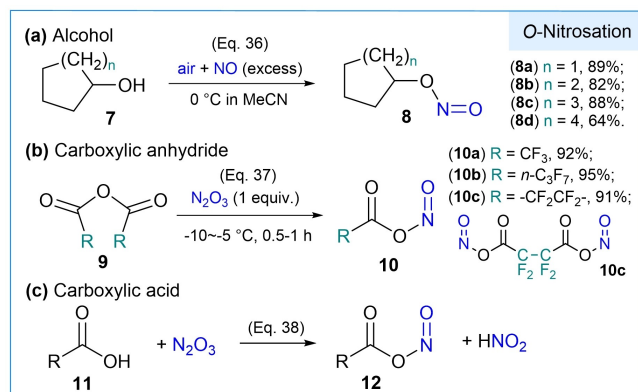**Chemistry Europe**
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and its concentrated (>0.1 M) solutions are much less frequently applied in organic synthesis. In this section, the selected examples focus on the reactions between organic molecules and concentrated N_2O_3 published since 1960s. Using the phase diagrams (Scheme 3 and Scheme 6) in the preceding sections, the readers could confirm the composition of nitroxides in different phases with the reaction parameters (T, p, x) provided in the corresponding references.

5.1. O-Nitrosation

Alcohols react with N_2O_3 to give nitrites. Alkyl nitrites[4] are commercially available nitrosating agents manufactured by the O-nitrosation of alcohols with HNO_2(aq).[124,125] Grossi and co-workers[126] bubbled air and excess NO through the acetonitrile solution of C_5-C_8 cycloalkyl alcohols (**7**) at $0°C$ (Scheme 10a); the nitrosation proceeded via the *in situ* generated N_2O_3 and gave nitrites (**8**) in 64–89% yield (GC-MS) (Eq. 36). After evaporating the solvent, the pure products (**8**) were isolated by distillation under vacuum.

Perfluorocarboxylic anhydride (**9**) reacts with N_2O_3 to afford nitrosyl carboxylate (**10**) (Scheme 10b). Liquid N_2O_3 condensed from the equimolar mixture of NO(g) and NO_2(g)[127] was added slowly with anhydride **9**.[81] The color change of the reaction mixture from blue to amber or yellow indicates the endpoint of the reaction (Eq. 37).[81] Nitrosyl perfluoroacylates (**10**) were isolated by distillation under reduced pressure (**10a-b**) or by evaporation (**10c**).

Carboxylic acid (**11**) can be O-nitrosated by N_2O_3 (Scheme 10c). The introduction of acetate buffer changes the rate laws of diazotization and the oxygen exchange between HNO_2 and H_2O because of the formation of nitrosyl acetate (ONOAc).[128] In the nitrosation of amino acids, the formation of nitrosyl carboxylates (**12**) followed by an intramolecular NO migration is one of the pathways to the formation of N-nitroso product (Scheme 15d).[129] A computational study revealed that the carboxylic groups of aromatic carboxylic acids and N-aryl-α-amino acids (**39**) can be nitrosated by N_2O_3 and HNO_2 in N,N-dimethylformamide (DMF) at $25°C$; the resultant nitrosyl
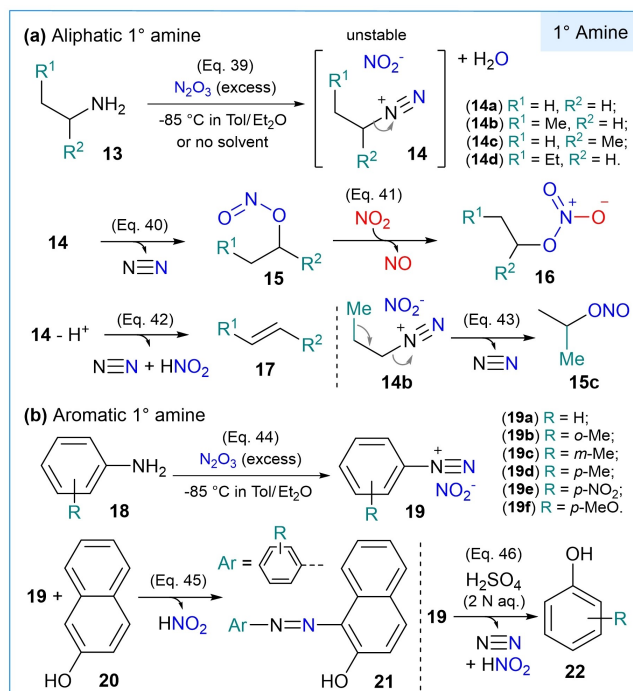
carboxylates (**12**) are not capable of further intermolecular N-nitrosation (e.g. **37v** in Scheme 15b).[28]

5.2. N-Nitrosation

Primary and secondary amines readily react with N_2O_3. The rate determining addition onto N_2O_3 is extremely fast (10^8 M^{-1} s^{-1} at $25°C$) in such extent that the reaction is diffusion controlled.[130] The reaction is highly exothermic that an organic solvent must be used to attenuate the local heating.[119] In cases of bad temperature control and contamination with oxygen, products that stem from the reactions with N_2O_4/NO_2 will be detected.[131] Under neutral conditions, the HNO_2 generated as byproduct can often be neutralized by excess amines.[119]

Primary amines (**13** and **18**) can be diazotized by N_2O_3 (Eq. 39), followed by the reaction of their diazonium salts (Scheme 11). The diazonium salt (**14**) of aliphatic primary amine (**13**) decomposes immediately to several products at low temperature (Scheme 11a); it undergoes nucleophilic substitution with nitrite anion (NO_2^-) (Eq. 40), elimination to alkene (**16**) (Eq. 42), and rearrangement with alkyl migration (Eq. 43), resulting in a complicated mixture.[119] In the treatment with concentrated or neat N_2O_3, alkyl nitrate (**16**) ammonium nitrate (**13**·HNO_3) are isolated in small quantities[119] due to the oxidation[132,133] (Eq. 41) and diazotization[134] with N_2O_4/NO_2 respectively.

Aromatic primary amine (**18**) is converted to diazonium nitrite (**19**) (Eq. 44). These salts (**19**) are water-soluble solids that precipitate from organic solvents; they are so sensitive to shock and friction that attempts to isolate them by filtration (**19a**[11] and **19e**) resulted in explosion.[119] The so-prepared diazonium

Scheme 10. The O-nitrosation with N_2O_3.

Scheme 11. N-Nitrosation of primary (1°)amines with N_2O_3.

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salts (**19**) undergo azo coupling[135] to azo dyes (**21**) (Eq. 45) and hydrolysis to phenols (**22**) (Eq. 46)[119] likewiseobserved in aqueous solutions.[136,137]

Secondary amines (**23**) are converted to *N*-nitrosoamine (**24**) by N_2O_3 (Scheme 12). Aliphatic secondary amines (**23a–h**) form salts with HNO_2, which is generated as byproduct in *N*-nitrosation (Eq. 47), giving a mixture of *N*-nitrosoamine (**24**) and ammonium salt (**25**) (Scheme 12a).[119] Dimethylamine (**23a**) (~2 wt.% aq.) is converted by diluted nitrous gas (10–11 vol% $NO_{1.5}$ in N_2) to *N*-nitrosodimethylamine (**24a**) and dimethylammonium nitrite (**25a**) (Eq. 48) (addition to N_2O_3 ~10^8 $M^{-1}s^{-1}$ at 37°C);[138] the ammonium salt (**25a**) can be converted to *N*-nitrosoamine (**24a**) upon acidification (Eq. 49), giving 75% yield on **24a**.[139] In the reactions with excess piperidine (**23h**) in 0.1 M NaOH (aq), $NO_{1.5}$(g) gives 100% yield on*N*-nitrosopiperidine (**24h**), whereas N_2O_4 affords 50%**24h** along with *ca.* 15% *N*-nitrocompound (**26h**).[140] Mono- and diaryl secondary amines (**23i-m**) are less basic than their aliphatic counterparts; ammonium nitrite (**25**) is not formed during their nitrosation (Eq. 50) (Scheme 12b).[119]

Amides can be *N*-nitrosated by N_2O_3. Miyahara[141] studied the substituent effect in the nitrosation of 1,3-diaryl ureas (**27**) with N_2O_3, NOCl, and N_2O_4 (Scheme 13a). Using 0.22 M N_2O_3

solution in DMF, the nitrosation at 0°C affords a mixture of 1- and 3-nitrosoureas (**28** and **29**). When the ^{1}H-NMR chemical shift difference of the urea protons in **27** is greater than 0.45 ppm (**27e–f**), only the electron-rich imino group gets nitrosated.
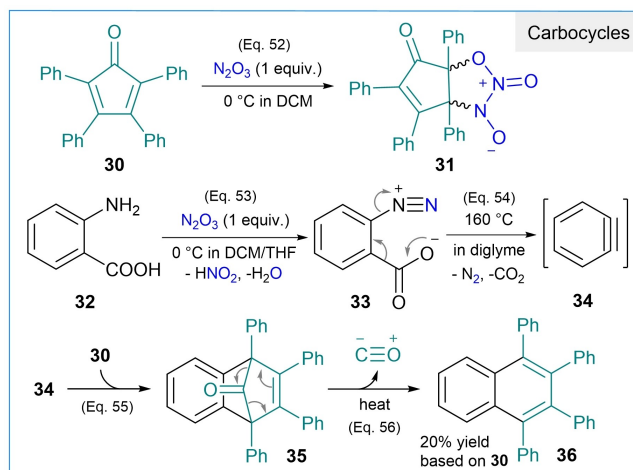
In the synthesis of carbo- and heterocyclic compounds (Schemes 14 and 15), the *N*-nitrosative steps can also be accomplished with N_2O_3. Tetraphenylcyclopentadienone (tetra-
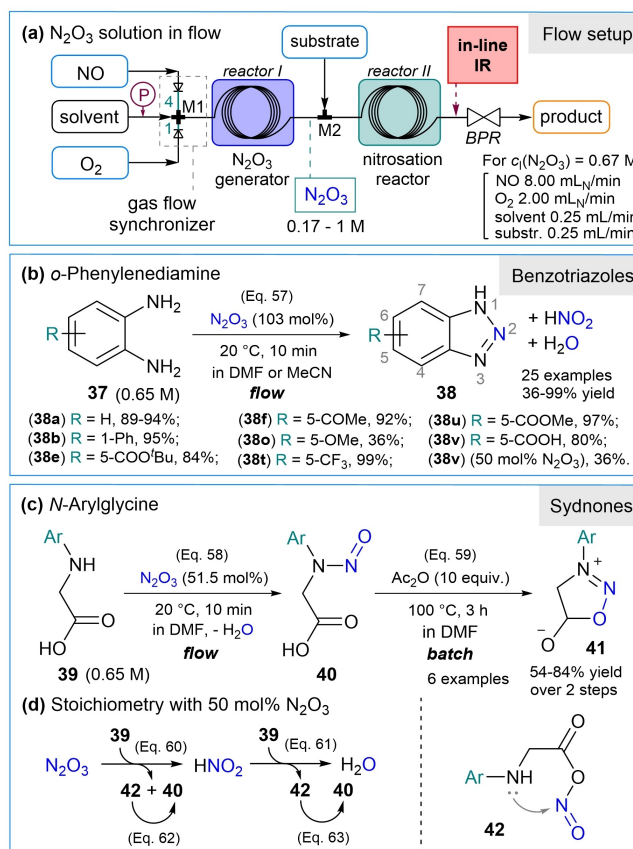

Scheme 14. Synthesis of carbocyclic compounds via *N*-nitrosation with N_2O_3.
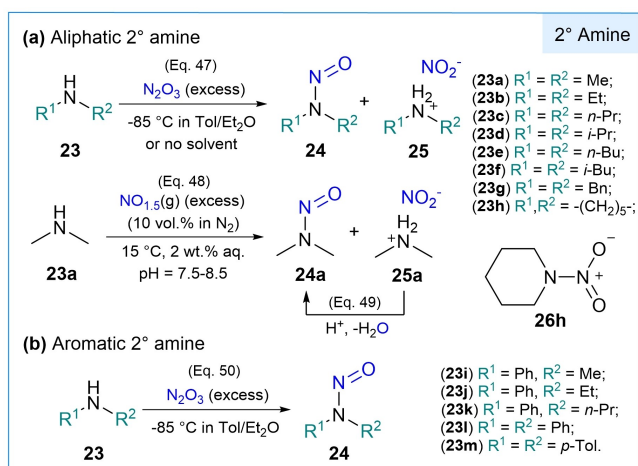
Scheme 12. *N*-Nitrosation of secondary (2°) amines with N_2O_3.
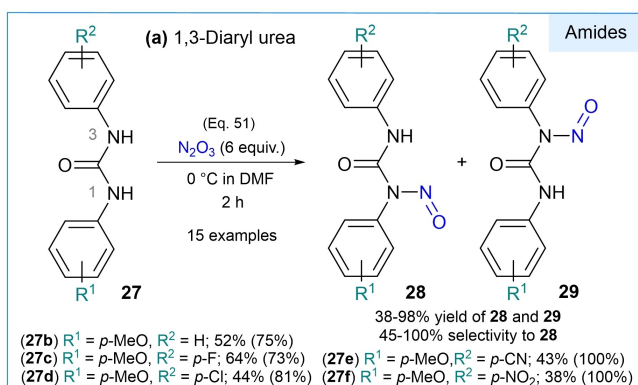
Scheme 13. *N*-Nitrosation of amides with N_2O_3.

Scheme 15. Synthesis of heterocyclic compounds via *N*-nitrosation with N_2O_3.

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cyclone) (**30**)forms an adduct with N_2O_3in DCM solution at 0 °C (Eq. 52 in Scheme 14); the adduct (**31**) can be isolated as non-crystalline solid after evaporating the solvent under rigorously dry condition.[142]

Anthranilic acid(**32**) can be diazotized by the N_2O_3 (Eq. 53) in the solution of **31**; upon heating in diglyme, the diazonium salt (**33**) undergoes elimination (Eq. 54) to benzyne (**34**), which is captured *in situ* by tetracyclone (**30**) via a Diels-Alder reaction (Eq. 55) and decarbonylative aromatization (Eq. 56) to afford tetraphenylnaphthalene (**36**) (20% isolated yield).[143]
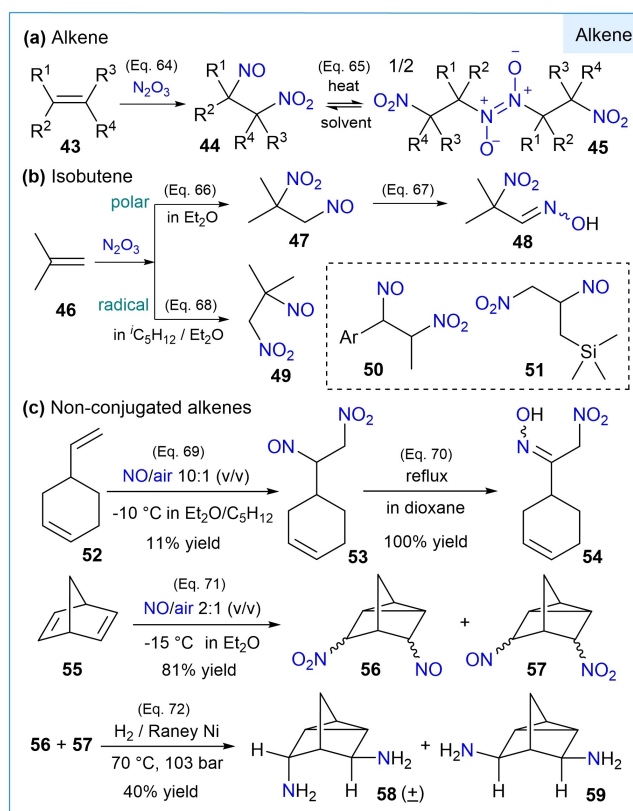
o-Phenylenediamine (**37**) reacts with N_2O_3 (0.67–1 M) to afford benzotriazole (**38**) (Scheme 15b). Under monophasic condition (*vide etiam* Scheme 7c) in a continuous flow reactor (Scheme 15a), 103 mol% N_2O_3 completes the conversion of **37** and its *C*- and *N*-substituted derivatives in 10 min at 20 °C (Eq. 57). Using the same setup, *N*-arylglycine (**39**) can be *N*-nitrosated by 51.5 mol% N_2O_3 (Scheme 15c), giving water as the only byproduct (Eq. 58).This unique stoichiometry (Scheme 15d) is attributed to the *O*-nitrosation of **39**by HNO_2(Eq. 61) after the first turnover (Eq. 60) and the intramolecular nitroso migration (Eq. 63) ofthe nitrosyl carboxylate (**42**) (*vide etiam*Section 5.1). The *N*-nitroso-*N*-arylglycine (**40**) was heated with acetic anhydride in batch for the cyclization to 3-substituted sydnone (**41**) (Eq. 59).

Apart from the applications in chemical synthesis, the *N*-nitrosative reactions with N_2O_3 have also been applied in the fluorescence spectrometric determination[144,145] and sensing[146] of NO under aerobic atmosphere.

Scheme 16. Addition of N_2O_3 to C=C double bonds.

5.3. C-Nitrosation

Alkenes (**43**) can react with N_2O_3 to give pseudonitrosites (**44**, *i.e.*the nitroso nitro compounds),[147] which could dimerize[148] like other *C*-nitroso compounds[149] (Scheme 16a). The mechanism and the orientation of such addition depend strongly on the substrate structureand reaction conditions (specially the nature of solvent). Molecular N_2O_3 is an electrophilic nitrosating agent ($NO^{\delta+}NO_2^{\delta-}$) that can be added to alkenes via a polar or ionic mechanism.[150] However, because some decomposition products (NO, NO_2) of N_2O_3 are radicals, they can be added stepwise to afford the N_2O_3-adduct with opposite regioselectivity (*vide infra*). When an α-proton is available to *C*-nitroso group (**44** with $R^1/R^2 =$ H), the dimer (**45**) of pseudonitrosite dissociates and isomerizes to nitroxime[151] upon standing over long time[150] or heating.[84]

Isobutene (**46**) reacts with N_2O_3througha polar (Eq. 66) or radical (Eq. 68) mechanism (Scheme 16b). In ethereal solution at ice-salt batch temperature, Williams et al.[150] found that the NO_x(l) condensed from nitrous gas behaves like an electrophilic reagent ($NO^+NO_2^-$) (Eq. 66); the product **47** isomerizes to oxime **48** when heated (Eq. 67). The same regioselectivity was observed in the addition with N_2O_4 at ≤-78 °C.[73] However, when Pfab[152] added the cold (−70 °C) ether/isopentane solution of N_2O_3 into the pentane solution of **46**at−20 °C (Eq. 68), the product of radical addition (**49**) was obtained, whereas neither oxime (**48**) nor nitrosonitrites was formed. The

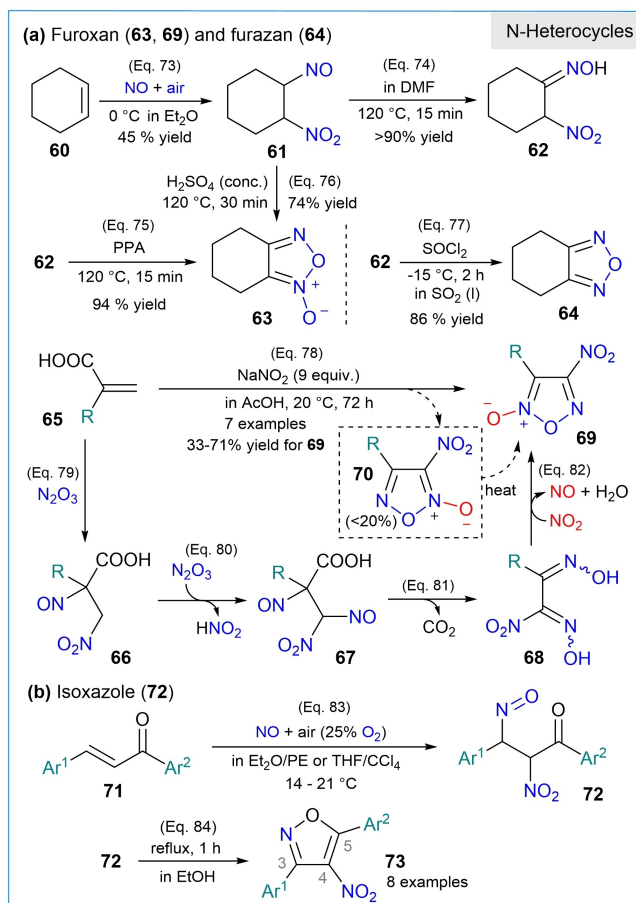additions to 2,5-dimethoxypropenylbenzene (**50**),[153] cinnamyl acetate (**86**),[154] allyltrimethylsilane (**51**),[155] and many other alkenes[149] exhibits the selectivity of radical mechanism.[156] Generally, a polar reaction (e.g.Eq. 66) takes place under conditions disfavoring the dissociation of N_2O_3 (low temperature, weakly basic solvent). In this regard, Willams et al.[150] might have performed their reactions undertemperatures much lower than−20 °C; but unfortunately, the temperatures of the cold finger and the reaction mixture are unknown.

Non-conjugated alkene (**52**) reacts with N_2O_3preferentially at the less substituted double bond (Scheme 16c). Scheinbaum[157] treated the ether/pentane solution of **52** with the mixture of NO and air at−10 °C, the pseudonitroside (**53**) precipitates (Eq. 69) and therefore inhibits the nitrosation of the second double bond. The reaction is believed to be a free radical process. Under similar reaction condition, the skeletal rearrangement has been observed in the nitrosation of norbornadiene (**55**)[157] (Eq. 71) and norbornene.[158]
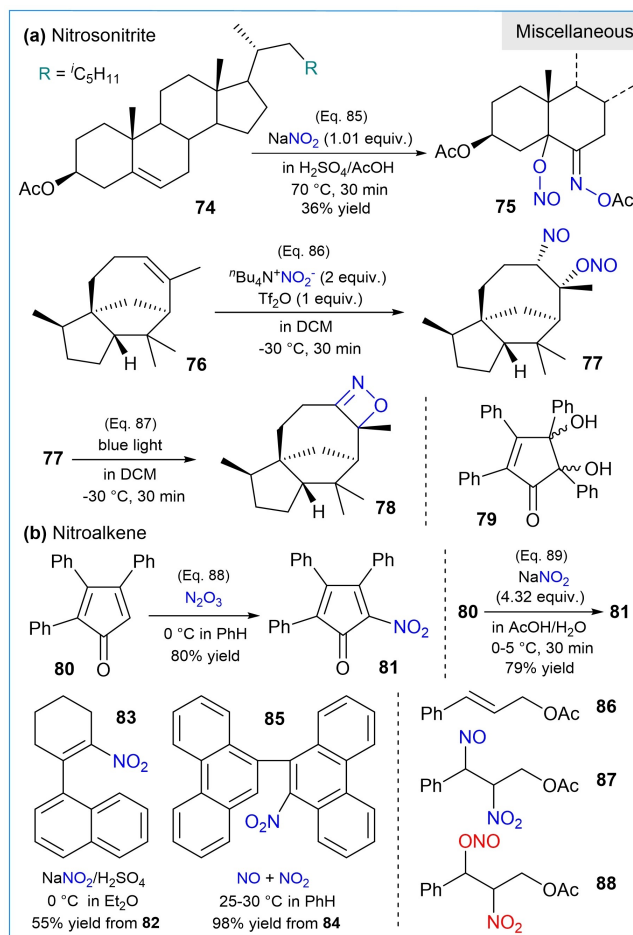
When both *C*-nitro and *C*-nitroso groupsin pseudonitrosite (**61**) could access α-protons (**44**, $R^1/R^2 =$ H and $R^3/R^4 =$ H) (Scheme 17a), the corresponding nitroxime (**62**) undergoes dehydrative cyclization (Eq. 75) to give furoxan (**63**) upon heating with a strong acid (H_2SO_4 or polyphosphoric acid (PPA)).[84] The addition of **60** (Eq. 73) used N_2O_3 formed *in situ* from NO and air;[84] this step has also been performed in aqueous solution with $NaNO_2$ and formic acid (HCOOH).[159] The rearrangement of **61** (Eq. 74) and the cyclization (Eq. 75) can be

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Scheme 17. Synthesis of heterocycles via C-nitrosation with N_2O_3.

Scheme 18. The C-nitrosation with N_2O_3 that gives products other than pseudonitrosite and its derivatives.

combined in one operation (Eq. 76). The nitroxime (**62**) is converted to furazan (**64**) by the treatment with thionyl chloride ($SOCl_2$) in liquid sulfur dioxide (SO_2) (Eq. 77).[84]

Makhova and co-workers[160] nitrosated 2-substituted acrylic acid (**65**) with large excess (9 equiv.) of $NaNO_2$ in acetic acid (AcOH) for the synthesis of 3-substituted-4-nitrofuroxan (**69**) (Eq. 78); this one-pot reaction involves (a) the addition with *in situ* generated N_2O_3 (Eq. 79), (b) the nitrosation of the α-position of the nitro group (Eq. 80), (c) decarboxylation (Eq. 81), and (d) the oxidative condensation between two nitroso groups (Eq. 82, not mentioned in the manuscript). A similar decarboxylative oximization was observed in the reaction of Cephalosporin with N_2O_3 in DCM.[161] In the explored conditions, isomer **70** was formed in low yields ($< 20\%$); it can be converted to **69** by refluxing in toluene. The nitroso (or oxime) moiety may also condensates with neighboring functional groups other than nitro. In the reaction between α,β-unsaturated ketone (**71**) and N_2O_3 (Scheme 17b), the resultant pseudonitroside (**72**) cyclizes to 4-nitro isoxazole (**73**) (Eq. 84) via the condensation of the nitroso and carbonyl groups.[83]

Double bonds having three or four substituents also react with N_2O_3 to afford nitrosonitrites (Scheme 18) in the orientation of polar addition (cf. Eq. 66). A concerted mechanism via a transition state resembling the N_2O_3-adduct (**31**) is likely involved. Onda and Azuma[162] heated 3β-acetoxycholest-4-ene (**74**) with $NaNO_2/H_2SO_4$ in AcOH at 70 °C to give acetoxime nitrite (**75**) (Eq. 85). Reddy et al.[163] found that α-cedrene (**76**) reacts with the N_2O_3 generated from tetrabutylammonium nitrite ($^nBu_4N^+NO_2^-$)/ triflic anhydride (Tf_2O) to give nitrosonitrite (**77**) (Eq. 86), which cyclizes to 1,2-oxazetes (**78**) upon blue light irradiation(Eq. 87). The authors[164] had also performed the same transformation with the yellow liquid ($-78 °C$) condensed from the gaseous products of the reaction between $^nBu_4N^+NO_2^-$ and Tf_2O;regarding the color, the IR absorption, and the phase diagram (Scheme 3), the so-prepared liquid should bemainly N_2O_4, not N_2O_3 (**1**, dark blue color) nor ONONO (**1a**, not stable under those temperatures).

Tetracyclone (**30**) in cold (0 °C) aqueous acids (AcOH or H_2SO_4) can be transformed by the benzene solution of N_2O_3or by $NaNO_2$ to the cis-dihydroxylation product (**79**).[142] The N_2O_3 adduct (**31**) was believed to be the intermediate.[143] Under the same conditions, 3,4,5-triphenylcyclopentadien-1-one (tricyclone) (**80**) was nitrated at its 2-position (Eq. 88–89). Similarly, 1-(naphth-1-yl)cyclohexene (**82**)[165] and 9,9′-biphenanthyl (**84**)[166] can be nitrated to the corresponding nitro alkenes (**83** and **85**).

The formation of 1-nitro alkene could be attributed to the stability of ring double bonds, which allows the elimination of

NO^+ under less acidic conditions. This reactivity is not unique for N_2O_3 adducts; N_2O_4[167] and the mixed anhydride $CF_3SO_2ONO_2$ (generated from $^nBu_4N^+NO_3^-/Tf_2O$)[168] can do the same job. In the study of the *C*-nitrosation of cinnamyl acetate (**86**), Seifert[154] found that the type and volume of the solvent and the reaction temperature both have a significant impact on the ratio of products (**87** and **88**). The nitronitrate (**88**), which is the adduct with N_2O_4, eliminates HNO_2 to give the nitro alkene.[169]

Enolizable carbonyl compounds can be *C*-nitrosated by N_2O_3. Williams et al.[170] discovered that the ketones are nitrosated in aqueous solution via their enol tautomers. Acetone and butan-2-one are nitrosated by N_2O_3 in the absence of nucleophilic additives (Cl^-, Br^-, SCN^-). Less basic 1,3-dichloroacetone and β-dicarbonyl compounds are less reactive; their nitrosation is rate-limiting[171] and requires stronger nitrosating species (NO^+).[7]

6. Conclusions

The preparation of dinitrogen trioxide (N_2O_3) as a pure compound and in concentrated (> 0.1 M) solution requires precautious control of reaction conditions (temperature, stoichiometry, volume ratio of gas and liquid phases). Molecular N_2O_3 is unstable in the gas phase, but relatively stable as liquid or in solution; it is prepared via a reversible reaction between nitric oxide (NO) and nitrogen (IV) oxides (N_2O_4/NO_2) (externally added or *in situ* generated) at low temperature. Because the decomposition products (NO, N_2O_4/NO_2) having very different boiling points are enriched in different phases, the coupled chemical and phase equilibria necessitate equilibrium data (phase diagrams) to determine the composition in each phase. From the analysis of the phase diagrams of nitroxides (NO_x), low temperature, excess of NO, small or zero headspace (V_g) are generally preferred to achieve an accurate liquid phase concentration (c_l) of N_2O_3 for quantitative reactions.

Reactions with neat N_2O_3 are highly exothermic and have to be performed at cryogenic temperatures. Protocols for the preparation and reaction of pure N_2O_3 in large (> 50 g) quantities are still underdeveloped. Concentrated (0.1–1 M) solution of N_2O_3 is a safe and handy form of N_2O_3 for the nitrosation in anhydrous media. Continuous flow protocols for the generation of N_2O_3 solution in accurate concentrations have been established for the quantitative reactions in both flow and batch. Dinitrogen trioxide can be generated *in situ* from gases (NO and O_2) or from nitrite and acid. The *in situ* generated N_2O_3 in low (< 0.1 M) concentrations can tolerate aqueous solution and uncontrolled headspace atmosphere, but other coexisting species (HNO_2, NO^+, N_2O_4, *etc.*) may also participate the reaction.

The synthetic application of pure and concentrated N_2O_3 has been intensively but not thoroughly explored between 1960s and 1990s. A large number of the experiments in that era were performed without precise control of liquid phase composition (c_l) and stoichiometry. Despite of the gaseous feedstock (NO and O_2), the high reactivity and the attractive atom economy have made N_2O_3 a promising strong nitrosating agent for organic synthesis in lab and industry scales. Equipped with the continuous flow setup for the generation and reaction of N_2O_3 under zero-headspace conditions, the reactivity of N_2O_3 can be quantitatively investigated at accurate high (> 0.1 M) concentrations with in-line analytical technologies.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

[1] T. A. Turney, G. A. Wright, *Chem. Rev.* **1959**, *59*, 497–513.
[2] D. L. H. Williams, *Nitrosation Reactions and the Chemistry of Nitric Oxide*, Elsevier, Amsterdam, **2004**.
[3] S. Mukhopadhyay, S. Batra, *Eur. J. Org. Chem.* **2019**, 6424–6451.
[4] P. Li, X. Jia, *Synthesis* **2018**, *50*, 711–722.
[5] A. Dahiya, A. K. Sahoo, T. Alam, B. K. Patel, *Chem. Asian J.* **2019**, *14*, 4454–4492.
[6] L. J. Beckham, W. A. Fessler, M. A. Kise, *Chem. Rev.* **1951**, *48*, 319–396.
[7] L. Bering, A. P. Antonchick, *Tetrahedron* **2019**, *75*, 1131–1143.
[8] I. R. Beattie, S. W. Bell, *J. Chem. Soc.* **1957**, 1681–1686.
[9] A. W. Shaw, A. J. Vosper, *J. Chem. Soc. A Inorg. Phys. Theor.* **1971**, 1592–1595.
[10] A. W. Shaw, A. J. Vosper, *J. Chem. Soc. A Inorg. Phys. Theor.* **1970**, 2193–2195.
[11] K. A. Rosadiuk, D. S. Bohle, *Eur. J. Inorg. Chem.* **2017**, 5461–5465.
[12] I. R. Beattie, in *Prog. Inorg. Chem. Vol. 5* (Ed.: F. A. Cotton), John Wiley & Sons, Inc., **1963**, pp. 1–26.
[13] J. Demaison, M. Herman, J. Liévin, L. Margulès, H. Møllendal, *J. Mol. Spectrosc.* **2007**, *244*, 160–169.
[14] I. Hermans, J. Henrique, T. Richard, P. N. Plessow, *Top. Catal.* **2014**, *57*, 1256–1264.
[15] L.-O. Anderson, J. Mason, *Chem. Commun.* **1968**, *1968*, 99–101.
[16] L. O. Andersson, J. Mason, W. van Bronswijk, *J. Chem. Soc. A Inorganic, Phys. Theor. Chem.* **1970**, *1970*, 296–299.
[17] J. Mason, W. van Bronswijk, *J. Chem. Soc. A Inorganic, Phys. Theor. Chem.* **1970**, *1970*, 1763–1767.
[18] I. C. Hisatstune, J. P. Devlin, *Spectrochim. Acta* **1960**, *16*, 401–406.
[19] E. M. Nour, L. H. Chen, J. Laane, *J. Phys. Chem.* **1983**, *87*, 1113–1120.
[20] R. L. Kuczkowski, *J. Am. Chem. Soc.* **1965**, *87*, 5259–5260.
[21] A. H. Brittain, A. P. Cox, R. L. Kuczkowski, *Trans. Faraday Soc.* **1969**, *65*, 1963–1974.
[22] F. Mélen, M. Herman, *J. Phys. Chem. Ref. Data* **1992**, *21*, 831–881.

Chem. Eur. J. **2024**, e202303516 (13 of 15)

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Chemistry–A European Journal

Review

doi.org/10.1002/chem.202303516

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Societies Publishing

[23] J. Laane, J. R. Ohlsen, in *Prog. Inorg. Chem.* (Ed.: S. J. Lippard), New York, **1980**, pp. 456–513.

[24] W. G. Fateley, H. A. Bent, B. Crawford, *J. Chem. Phys.* **1959**, *31*, 204–217.

[25] I. C. Hisatsune, J. P. Devlin, Y. Wada, *J. Chem. Phys.* **1960**, *33*, 714–719.

[26] G. M. Bradley, W. Siddall, H. L. Strauss, E. L. Varetti, *J. Phys. Chem.* **1975**, *79*, 1949–1953.

[27] I. W. M. Smith, G. Yarwood, *Chem. Phys. Lett.* **1986**, *130*, 24–28.

[28] Y. Chen, S. Renson, J. C. M. Monbaliu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210146.

[29] R. F. Holland, W. B. Maier, *J. Chem. Phys.* **1983**, *78*, 2928–2941.

[30] E. L. Varetti, G. C. Pimentel, *J. Chem. Phys.* **1971**, *55*, 3813–3821.

[31] X. Wang, Q. Z. Qin, *J. Photochem. Photobiol. A* **1999**, *122*, 1–5.

[32] X. Wang, Q. Z. Qin, *Spectrochim. Acta Part A* **1998**, *54*, 575–580.

[33] J. Mason, *J. Chem. Soc.* **1959**, *1959*, 1288–1295.

[34] J. Mason, *J. Chem. Soc. Dalton Trans.* **1975**, *1975*, 19–22.

[35] I. R. Beattie, A. J. Vosper, *J. Chem. Soc.* **1961**, *1961*, 2106–2109.

[36] C. M. Wright, A. A. Orr, *Anal. Chem.* **1968**, *40*, 29–33.

[37] A. J. Vosper, *J. Chem. Soc. A Inorg. Phys. Theor.* **1971**, *1971*, 1589–1592.

[38] A. W. Shaw, A. J. Vosper, *J. Chem. Soc. Dalton Trans.* **1972**, *1972*, 961–963.

[39] A. M. M. Dohertyt, N. Haine, E. Jonesb, G. Stedman, *J. Chem. Soc.-Perkin Trans.* **1996**, *2*, 2055–2058.

[40] G. Y. Markowits, S. E. Schwartz, L. Newman, *Inorg. Chem.* **1981**, *20*, 445–450.

[41] W. R. Stockwell, J. G. Calvert, *J. Photochem.* **1978**, *8*, 193–203.

[42] I. R. Beattie, A. J. Vosper, *J. Chem. Soc. A* **1960**, *1960*, 4799–4802.

[43] J. Chao, R. C. Wilhoit, B. J. Zwolinski, *Thermochim. Acta* **1974**, *10*, 359–371.

[44] A. J. Vosper, *J. Chem. Soc. A Inorg. Phys. Theor.* **1966**, *1966*, 1759–1762.

[45] C. C. Addison, *Chem. Rev.* **1980**, *80*, 21–39.

[46] H. Gershinowitz, H. Eyring, *J. Am. Chem. Soc.* **1935**, *57*, 985–991.

[47] A. W. Shaw, *J. Chem. Soc. Faraday Trans. 1* **1977**, *73*, 1239–1244.

[48] M. Besson, P. Gallezot, *Catal. Today* **2003**, *81*, 547–559.

[49] I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519–552.

[50] C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360.

[51] M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362.

[52] D. Dallinger, B. Gutmann, C. O. Kappe, *Acc. Chem. Res.* **2020**, *53*, 1330–1341.

[53] H. Ding, S. Sadeghi, G. J. Shah, S. Chen, P. Y. Keng, C. J. Kim, R. M. Van Dam, *Lab Chip* **2012**, *12*, 3331–3340.

[54] R. H. Purcell, G. H. Cheesman, *J. Chem. Soc.* **1932**, *1932*, 826–834.

[55] I. R. Beattie, S. W. Bell, A. J. Vosper, *J. Chem. Soc.* **1960**, *1960*, 4796–4799.

[56] D. Kondepudi, I. Prigogine, *Modern Thermodynamics: From Heat Engines to Dissipative Structures*, Wiley, Chichester, **2015**.

[57] P. Atkins, J. de Paola, J. Keeler, *Atkins' Physical Chemistry*, Oxford University Press, Oxford, **2022**.

[58] B. Predel, M. Hoch, M. Pool, *Phase Diagrams and Heterogeneous Equilibria*, Springer, **2004**.

[59] B. Predel, *Heterogene Gleichgewichte*, Dr. Dietrich Steinkopff Verlag, GmbH & Co. KG, Darmstadt, **1982**.

[60] J. J. Moore, *Chemical Metallurgy*, Butterworth-Heinemann, Oxford, **1990**.

[61] J. W. Gibbs, *Trans. Conn. Acad. Arts Sci.* **1878**, *3*, 343–525.

[62] M. Zhao, Z. Wang, L. Xiao, *J. Chem. Educ.* **1992**, *69*, 539–542.

[63] W. B. Jensen, *J. Chem. Educ.* **2001**, *78*, 1369–1370.

[64] A. W. Shaw, A. J. Vosper, *J. Chem. Soc. A* **1971**, *1971*, 2708–2710.

[65] W. J. Dulmage, E. A. Meyers, W. N. Lipscomb, *Acta Crystallogr.* **1953**, *6*, 760–764.

[66] J. Maurais, C. Wespiser, H. Kang, P. Ayotte, *J. Phys. Chem. A* **2022**, *126*, 2353–2360.

[67] E. T. Chang, N. A. Gokcen, C. D. Robison, *Solubilities of O2, NO, and N2O3 in Liquid N2O4*, Los Angeles, California, **1965**, AD0466369.

[68] D. R. Lide, Ed., *CRC Handbook of Chemistry and Physics*, CRC Press, **1999**.

[69] B. C. Challis, S. A. Kyrtopoulos, *J. Chem. Soc.-Perkin Trans. 1* **1979**, 299–304.

[70] G. Baume, M. Robert, *Comptes rendus l'Académie des Sci.* **1919**, *169*, 968–970.

[71] R. Morley, S. J. Silk, *Ann. Occup. Hyg.* **1970**, *13*, 101–107.

[72] P. E. Morrow, *J. Toxicol. Environ. Health* **1984**, *13*, 205–227.

[73] L. Parts, J. T. Miller, *J. Phys. Chem.* **1969**, *73*, 3088–3097.

[74] A. T. Austin, *Br. J. Anaesth.* **1967**, *39*, 345–350.

[75] J. A. Graham, L. D. Grant, L. J. Folinsbee, D. J. Kotchmar, J. H. B. Garner, *Nitrogen Oxides*, World Health Organization, **1997**.

[76] World Health Organization, *Environmental Health Criteria 4. Oxides of Nitrogen*, World Health Organization, Geneva, **1977**, pp. 79.

[77] J. D. Greig, P. G. Hall, *Trans. Faraday Soc.* **1966**, *62*, 652–658.

[78] K. A. Rosadiuk, *The Chemistry of Solvated Nitric Oxide: As the Free Radical and as Super-Saturated Dinitrogen Trioxide Solutions*, McGill University, **2015**.

[79] K. A. Rosadiuk, D. Scott Bohle, *Eur. J. Inorg. Chem.* **2018**, *2018*, 4543–4549.

[80] K. A. Rosadiuk, R. S. Stein, D. S. Bohle, *Eur. J. Inorg. Chem.* **2018**, 659–665.

[81] D. E. Rice, G. H. Crawford, *J. Org. Chem.* **1963**, *28*, 872–873.

[82] P. Angibeaud, C. Bosso, J. Defaye, D. Horton, C. Cohen-Addad, M. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1979**, *1979*, 1583–1592.

[83] J.-P. Hauff, J. Tuaillon, R. Perrot, *Helv. Chim. Acta* **1978**, *61*, 1207–1212.

[84] D. Klamann, W. Koser, P. Weyerstahl, M. Fligge, *Chem. Ber.* **1965**, *98*, 1831–1836.

[85] H. Heaney, A. J. Jones, I. T. Millar, *J. Chem. Soc.* **1965**, *1965*, 2587–2594.

[86] H. D. Ross, J. Henion, J. G. Babish, J. H. Hotchkiss, *Food Chem.* **1987**, *23*, 207–222.

[87] R. Varma, R. F. Curl, *J. Phys. Chem.* **1976**, *80*, 402–409.

[88] T. A. Turney, *J. Chem. Soc.* **1960**, *1960*, 4263–4265.

[89] C. A. Bunton, D. R. Llewellyn, G. Stedman, *J. Chem. Soc.* **1959**, *1959*, 568–573.

[90] D. L. H. Williams, *Adv. Phys. Org. Chem.* **1983**, *19*, 381–428.

[91] J. Casado, A. Castro, M. A. López Quintela, M. Mosquera, M. F. Rodríguez Prieto, *Monatsh. Chem.* **1983**, *114*, 647–660.

[92] A. Wicaksana, T. Rachman, *J. Chem. Soc. Perkin Trans.* **1979**, *1979*, 312–316.

[93] J. R. Park, D. L. H. Williams, *J. Chem. Soc.-Perkin Trans. 2* **1972**, 2158–2163.

[94] I. J. Doonan, R. G. A. R. Maclagan, *Aust. J. Chem.* **1977**, *30*, 2613–2619.

[95] I. I. Zakharov, O. I. Zakharova, *J. Struct. Chem.* **2009**, *50*, 212–218.

[96] A. B. Ray, *Inorg. Chem.* **1967**, *6*, 110–113.

[97] A. J. Vosper, *J. Chem. Soc. Dalton Trans.* **1976**, *1976*, 135–138.

[98] P. G. Ashmore, B. J. Tyler, *J. Chem. Soc.* **1961**, *1961*, 1017–1021.

[99] B. J. Tyler, S. Street, M. Manchester, *J. Chem. Soc. Faraday Trans. 1* **1972**, *68*, 683–688.

[100] H. Komiyama, H. Inoue, *Chem. Eng. Sci.* **1980**, *35*, 154–161.

[101] E. J. Koval, M. S. Peters, *Ind. Eng. Chem.* **1960**, *52*, 1011–1014.

[102] D. D. Perrin, *Pure Appl. Chem.* **1969**, *20*, 113–236.

[103] G. Carta, *Ind. Eng. Chem. Fundam.* **1984**, *23*, 260–264.

[104] J. L. de Paiva, G. C. Kachan, *Chem. Eng. Process. Process Intensif.* **2004**, *43*, 941–948.

[105] M. P. Pradhan, J. B. Joshi, *AIChE J.* **1999**, *45*, 38–50.

[106] D. Axente, O. Piringer, M. Abrudean, N. Bâldea, N. Palibroda, *J. Radioanal. Chem.* **1976**, *30*, 233–244.

[107] J. B. Joshi, V. V. Mahajani, V. A. Juvekar, *Chem. Eng. Commun.* **1985**, *33*, 1–92.

[108] Y. Ogata, in *Oxid. Org. Chem. Part C* (Ed.: W. S. Trahanovski), Ames Iowa, **1978**, pp. 295–342.

[109] Y. Ogata, H. Tezuka, *J. Am. Chem. Soc.* **1967**, *89*, 5428–5432.

[110] R. Lebl, D. Cantillo, C. O. Kappe, *React. Chem. Eng.* **2019**, *4*, 738–746.

[111] Y. Ito, *New Chem. Process. Monomers he Unied States Japan* **1969**, *147*, 618–624.

[112] A. W. Shaw, A. J. Vosper, M. Pritchard, *J. Chem. Soc. Dalton Trans.* **1974**, *1974*, 2172–2176.

[113] M. M. Nour, S. Wasif, *J. Chem. Soc. A Inorganic, Phys. Theor. Chem.* **1969**, *1969*, 474–476.

[114] R. C. Paul, V. P. Kapila, J. K. Puri, K. C. Malhotra, *J. Chem. Soc. A Inorg. Phys. Theor.* **1971**, *1971*, 2127–2131.

[115] B. C. Challis, R. J. Higgins, A. J. Lawson, *J. Chem. Soc.-Perkin Trans. 2* **1972**, 1831–1836.

[116] W. L. Lindsay, M. Sadiq, L. K. Porter, *Soil Sci. Soc. Am. J.* **1981**, *45*, 61–66.

[117] M. N. Hughes, G. Stedman, *J. Chem. Soc.* **1963**, *1963*, 2824–2830.

[118] G. Stedman, *J. Chem. Soc.* **1960**, *1960*, 1702–1709.

[119] D. J. Lovejoy, A. J. Vosper, *J. Chem. Soc. A* **1968**, *1968*, 2325–2328.

[120] F. Klages, J. Dasch, *Ber. Dtsch. Chem. Ges.* **1955**, *88*, 379–384.

[121] E. Müller, W. Rundel, *Ber. Dtsch. Chem. Ges.* **1958**, *91*, 466–468.

[122] E. Niciecki, A. J. Vosper, *J. Chem. Soc. Dalton Trans.* **1978**, *1978*, 1721–1723.

[123] A. T. Austin, *Sci. Prog.* **1961**, *49*, 619–640.

[124] A. Publication, *Org. Synth.* **1936**, *16*, 7.

[125] J. C. M. Monbaliu, J. Jorda, B. Chevalier, C. V. Stevens, B. Morvan, *Chim. Oggi* **2011**, *29*, 50–52.

[126] L. Grossi, S. Strazzari, *J. Org. Chem.* **1999**, *64*, 8076–8079.

Chemistry–A European Journal

Review

doi.org/10.1002/chem.202303516

Chemistry Europe
European Chemical
Societies Publishing

[127] R. Gibbs, R. N. Haszeldine, R. F. Simmons, *J. Chem. Soc. Perkin Trans. 2* **1972**, *1972*, 773–778.

[128] C. A. Bunton, M. Masui, *J. Chem. Soc.* **1960**, *1960*, 304–308.

[129] R. Gil, J. Casado, C. Izquierdo, *Int. J. Chem. Kinet.* **1997**, *29*, 495–504.

[130] J. Casado, A. Castro, J. R. Leis, M. A. López Quintela, M. Mosquera, *Monatsh. Chem.* **1983**, *114*, 639–646.

[131] M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Tetrahedron* **2010**, *66*, 9077–9106.

[132] T. G. Bonner, R. A. Hancock, *J. Chem. Soc. B Phys. Org.* **1970**, 519–524.

[133] B. G. Gowenlock, J. Pfab, V. M. Young, *J. Chem. Soc.-Perkin Trans. 2* **1997**, 1793–1798.

[134] B. Houston, T. B. Johnson, *J. Am. Chem. Soc.* **1925**, *47*, 3011–3018.

[135] H. U. R. Shah, K. Ahmad, H. A. Naseem, S. Parveen, M. Ashfaq, T. Aziz, S. Shaheen, A. Babras, A. Shahzad, *J. Mol. Struct.* **2021**, *1244*, 131181.

[136] F. Mo, D. Qiu, L. Zhang, J. Wang, *Chem. Rev.* **2021**, *121*, 5741–5829.

[137] B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298–2308.

[138] J. Casado, M. A. Lopez Quintela, *Z. Phys. Chem.* **1981**, *127*, 179–192.

[139] B. M. Laskin, O. N. Voznyuk, I. A. Blinov, *Russ. J. Appl. Chem.* **2018**, *91*, 996–1001.

[140] B. C. Challis, S. A. Kyrtopoulos, *J. Chem. Soc. Perkin Trans. 2* **1978**, 1296–1302.

[141] M. Miyahara, S. Kamiya, M. Nakadate, *Chem. Pharm. Bull.* **1983**, *30*, 41–44.

[142] S. Ranganathan, S. K. Kar, *J. Org. Chem.* **1970**, *35*, 3962–3964.

[143] S. Ranganathan, S. K. Kar, *Tetrahedron* **1975**, *31*, 1391–1398.

[144] A. M. Miles, Y. Chen, M. W. Owens, M. B. Grisham, *Methods* **1995**, *7*, 40–41.

[145] A. M. Miles, David A. Wink, J. C. Cook, M. B. Grisham, *Methods Enzymol.* **1996**, *268*, 105–120.

[146] P. R. Escamilla, Y. Shen, Q. Zhang, D. S. Hernandez, C. J. Howard, X. Qian, D. Y. Filonov, A. V. Kinev, J. B. Shear, E. V. Anslyn, Y. Yang, *Chem. Sci.* **2020**, *11*, 1394–1403.

[147] J. R. Park, D. L. H. Williams, *Chem. Commun.* **1969**, *1969*, 332–333.

[148] A. Mackor, T. A. J. W. Wajer, T. J. de Boer, *Tetrahedron Lett.* **1967**, *8*, 2757–2761.

[149] B. G. Gowenlock, G. B. Richter-Addo, *Chem. Rev.* **2004**, *104*, 3315–3340.

[150] J. R. Park, D. L. H. Williams, *J. Chem. Soc.-Perkin Trans.* **1976**, *2*, 828–832.

[151] A. Shaabani, H. R. Bijanzadeh, A. R. Karimi, M. B. Teimouri, K. Soleimani, *Can. J. Chem.* **2008**, *86*, 248–252.

[152] J. Pfab, *J. Chem. Soc. Chem. Commun.* **1977**, *6*, 766–767.

[153] T. R. Govindachari, B. R. Pai, *J. Org. Chem.* **1953**, *18*, 1253–1262.

[154] Y. Kurihara, K. Yamagishi, *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1327–1330.

[155] H. Jolibois, A. Doucet, R. Perrot, *Helv. Chim. Acta* **1976**, *59*, 1352–1356.

[156] A. I. Titov, *Tetrahedron* **1963**, *19*, 557–580.

[157] Monte L. Scheinbaum, *J. Org. Chem.* **1970**, *35*, 2785–2790.

[158] M. L. Scheinbaum, *J. Org. Chem.* **1968**, *33*, 2586–2587.

[159] H. C. Hamann, D. Swerna, *J. Am. Chem. Soc.* **1958**, *90*, 6481–6486.

[160] L. L. Fershtat, M. I. Struchkova, A. S. Goloveshkin, I. S. Bushmarinov, N. N. Makhova, *Heteroat. Chem.* **2014**, *25*, 226–237.

[161] M. M. Campbell, B. P. Connarty, J. Kemp, S. J. Ray, *J. Chem. Soc. Chem. Commun.* **1982**, *1982*, 748–749.

[162] M. Onda, A. Azuma, *Chem. Pharm. Bull.* **1972**, *20*, 1467–1472.

[163] G. S. Reddy, E. J. Corey, *Org. Lett.* **2023**, *25*, 236–239.

[164] G. S. Reddy, E. J. Suh, E. J. Corey, *Org. Lett.* **2022**, *24*, 4202–4206.

[165] V. Kesavan, V. C. Devanathan, N. Arumugam, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 3008–3011.

[166] M. A. Ali, J. G. Carey, D. Cohen, A. J. Jones, I. T. Millar, K. V. Wilso, *J. Chem. Soc.* **1964**, *1964*, 387–396.

[167] W. K. Seifert, *J. Org. Chem.* **1963**, *28*, 125–129.

[168] G. S. Reddy, E. J. Corey, *Org. Lett.* **2021**, *23*, 3399–3402.

[169] H. Shechter, F. Conrad, *J. Am. Chem. Soc.* **1953**, *75*, 5610–5613.

[170] J. Ramón Leis, M. E. Peña, D. L. H. Williams, S. D. Mawson, *J. Chem. Soc.-Perkin Trans.* **1988**, *2*, 157–162.

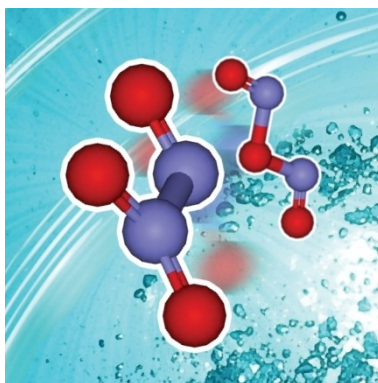[171] E. Iglesias, *J. Chem. Soc.-Perkin Trans.* **1997**, *2*, 431–439.

REVIEW

Dinitrogen trioxide (N₂O₃) is a potent and atom economic nitrosating agent. The preparation of N₂O₃ is difficult due to its instability and entangled chemical and phase equilibria. This review reexamines the preparative methods of pure N₂O₃ and its concentrated (> 0.1 M) solutions via a phase equilibrium approach in combination with worked examples in organic synthesis.

Dr. Y. Chen, Prof. Dr. J.-C. M. Monbaliu*

Preparation of Dinitrogen Trioxide for Organic Synthesis: A Phase Equilibrium Approach