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Formation of 3,4-Diazabicyclo[4,3,0]non-2-ene and N,N′-Azo-3-azabicyclo[3,3,0]octane by Oxidation of an Alicyclic Hydrazine. Influence of *pH* on the Diazene Rearrangement

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Summary. 3,4-Diazabicyclo[4,3,0]non-2-ene and N,N′-azo-3-azabicyclo[3,3,0]octane are the main products of the oxidation of N-amino-3-azabicyclo[3,3,0]octane by chloramine. The reaction leads to the transient formation of a saturated bicyclic aminonitrene (diazene). At $pH > 13$, the diazene undergoes an intramolecular rearrangement to afford a hydrazone. At $pH < 9$, a white solid is formed resulting from the dimerization of the molecular and protonated forms of the aminonitrene. At intermediate *pH*-values, a mixture of both species is obtained. They have been isolated and characterized by UV, GC/MS, IR, and $^1H/^{13}C$ NMR. A reaction mechanism is proposed.

Keywords. Synthesis; 3,4-Diazabicyclo[4,3,0]non-2-ene; N,N′-Azo-3-azabicyclo[3,3,0]octane; Diazene; Hydrazine; NMR.

Bildung von 3,4-Diazabicyclo[4,3,0]non-2-en und N,N′-Azo-3-azabicyclo[3,3,0]oktan durch Oxidation eines alizyklischen Hydrazins. Einfluß des *pH*-Wertes auf die Umlagerung von Diazenen

Zusammenfassung. 3,4-Diazabicyclo[4,3,0]-non-2-en und N,N′-Azo-3-azabicyclo[3,3,0]oktan sind die Hauptreaktionsprodukte der Oxidation von N-Amino-3-azabicyclo[3,3,0]oktan durch Chloramin. Die Interaktion führt übergangsweise zur Bildung eines gesättigten bizyklischen Aminonitrens (Diazens). Oberhalb des *pH*-Wertes 13 lagert sich das Diazen intramolekular um und bildet ein Hydrazon. Unterhalb des *pH*-Wertes 9 fällt ein weißer Niederschlag aus (Tetrazen), der von einer Dimerisierung zwischen for molekularen und protonierten Form von Aminonitren herrühren dürfte. Für die dazwischenliegenden Werte ($9 < pH < 13$) erhält man eine Mischung aus beiden Verbindungen. Sie wurden isoliert und mit Hilfe von UV, GC/MS, IR, und $^1H/^{13}C$-NMR untersucht. Ein Reaktionsmechanismus wird vorgeschlagen.

Introduction

N-amino-3-azabicyclo[3,3,0]octane (**1**) is a heterocyclic precursor in the manufacturing of hypoglycemic sulfamides [1, 2]. One of the difficulties in the synthesis is the amination of 3-azabicyclo[3,3,0]octane (**2**) to give the corresponding hydrazine. Presently, the only method described in the literature consists of nitrosating the amine [3], followed by the hydrogenation of the nitrosated derivative with $LiAlH_4$.

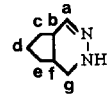
This second step involves toxic (carcinogenic) reagents and inflammable solvents, which imply several problems for industrial application. In order to avoid these inconveniences, we have restored to the *Raschig* procedure [4], which consists of reacting the chloramine with an excess of **2** in a basic aqueous medium. This more environmentally sound route involves numerous secondary products due principally to the oxidizing power of the haloamine upon the hydrazine. The realization of this process requires the identification of the reaction mechanisms and the characterization of the products formed by the oxidation of N-amino-3-azabicyclo[3,3,0]octane with chloramine. The optimal conditions are between *pH* 12 and 13.5. The concurrent formation of two compounds prompted us to expand the range to $pH = 8$ in order to ensure continuity in the mechanistic study. At first, we have studied the interactions at the limits of this interval to favor one of the other mechanism.

Results and Discussion

I) Strongly basic medium

The reaction at 25 °C under stoichiometric conditions (15 to 50 $\times 10^{-3}$ mol/l) shows the formation of product **3**, which presents a high absorption at $\lambda = 229$ nm. GC analysis indicates the formation of a single product, of which the growing is delayed in time with respect to the disappearance of reactants. The mechanism must therefore include an undetected intermediate, the concentration of which passes through a maximum. Over the course of the reaction and at different contents, the integrated areas of **3** are proportional to those of the reagents. GC/MS analysis attributes this to a M^+ peak at $m/z = 124$. An isotopic study of the ion fragments gives an empirical formula of $C_7H_{12}N_2$.

In an attempt to isolate and characterize **3**, a complementary experiment was performed in a concentrated medium ($[NH_2Cl] = [C_7H_{12}NNH_2] = 0.5$ mol/l). Its purity is close to 99.2% by GC and the microanalysis confirms the above formula. IR analysis reveals two intense bands at $\nu = 1620$ and 3320 cm^{-1}, which correspond to C=N and N–H vibrations. Figure 1 shows the two-dimensional $^1H/^{13}C$ NMR spectrum of **3**. Interpretation of the cross-peaks is consistent with the following formula:



The deshielding of the carbons located in α-position of the nitrogen atoms is due to the paramagnetic effect of the π-electrons of the imine group ($\delta_{C=N} = 144.4$ ppm) as well as to the mesomeric effect ($\delta_{C-N} = 45.3$ ppm) of the $-\overset{+}{N}H=N-C^-$ form. Discrimination between CH_2 and CH carbons was accomplished by the standard DEPT sequence [5]. The chemical shifts of the C and H nuclei are given in the experimental section.

In order to determine the UV spectral properties of **3**, a series of calibrated solutions (0.5–5 $\times 10^{-3}$ mol/l) at $pH = 12$ were prepared and analyzed. Application of *Lambert–Beer*'s law leads to a molar extinction coefficient $\varepsilon = 2685 \pm 15$ l/mol·cm.

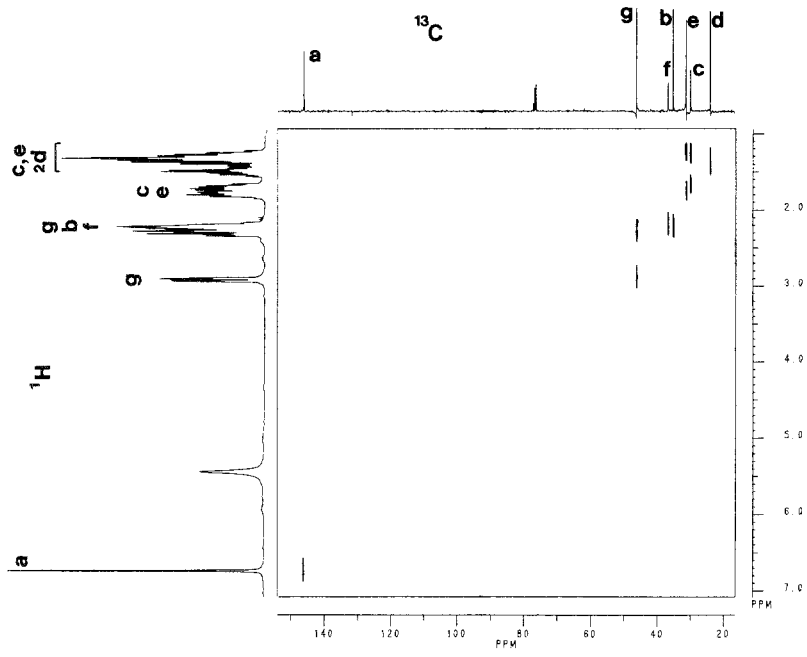
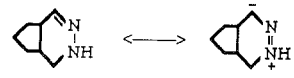


Fig. 1. 2D $^1H/^{13}C$ NMR spectrum of 3,4-diazabicyclo[4,3,0]non-2-ene in $CDCl_3$

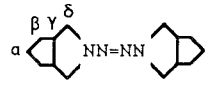
This strong absorption is linked to the resonance effect of the hydrazone chromophore and is similar to that of monosubstituted hydrazones, in particular that of formaldehyde monomethylhydrazone ($\lambda = 229$ nm, $\varepsilon = 6059$ l/mol·cm) [6].



II) Weakly basic medium

The relative acidification of the solution induces a decrease in the formation of **3** in favor of a new compound **4**, which precipitates and becomes preponderant in the neighbourhood of $pH \approx 9$. At the end of the reaction, the white solid is filtered, washed, dried under vacuum and analysed by MS, IR, NMR, and UV.

The mass spectrum exhibits a molecular ion $M^+ = 248$, which *a priori* corresponds to a dimer of **3**. Figures 2 and 3 show the 2D $^1H/^{13}C$ and DEPT NMR spectra. Four carbon signals are slightly more deshielded than in **2**, implying the existence of symmetry in the molecule. The DEPT sequence and the absence of $\nu_{C=N}$ and ν_{NH} bands exclude a simple dimerization of **3**. On the other hand, this compound shows two absorption bands in hexane at $\lambda_1 = 282$ and $\lambda_2 = 255$ nm, which are characteristic of tetrazenes. Combination of these results as well as the microanalysis leads us to postulate that **4** is N,N′-azo-3-azabicyclo[3,3,0]octane. The molar extinction coefficients corresponding to the above wavelengths are $\varepsilon_1 = 11900$ l/mol·cm and $\varepsilon_2 = 6120$ l/mol·cm.



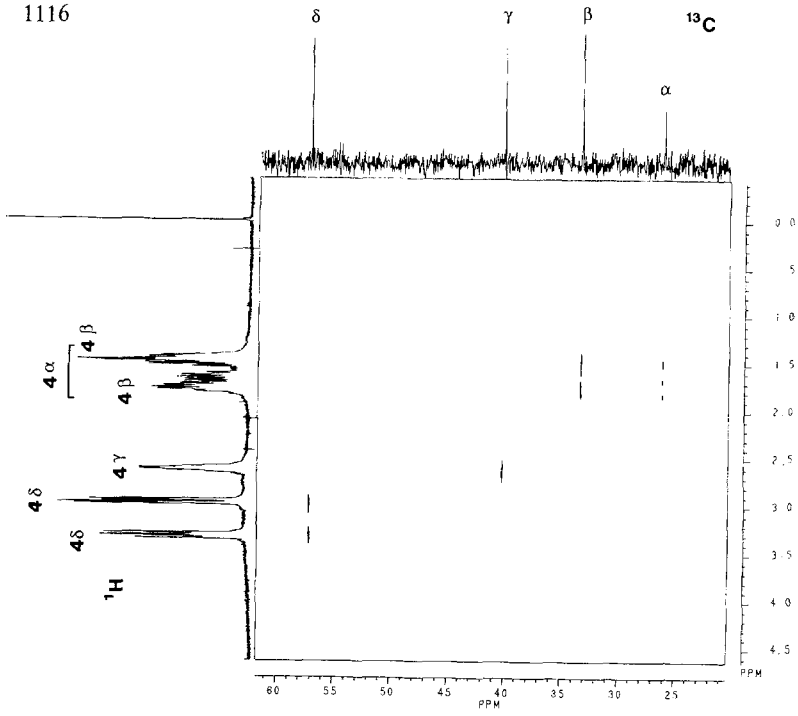


Fig. 2. 2D $^{1}H/^{13}C$ NMR spectrum of N,N′-azo-3-azabicyclo[3,3,0] octane in $CDCl_3$

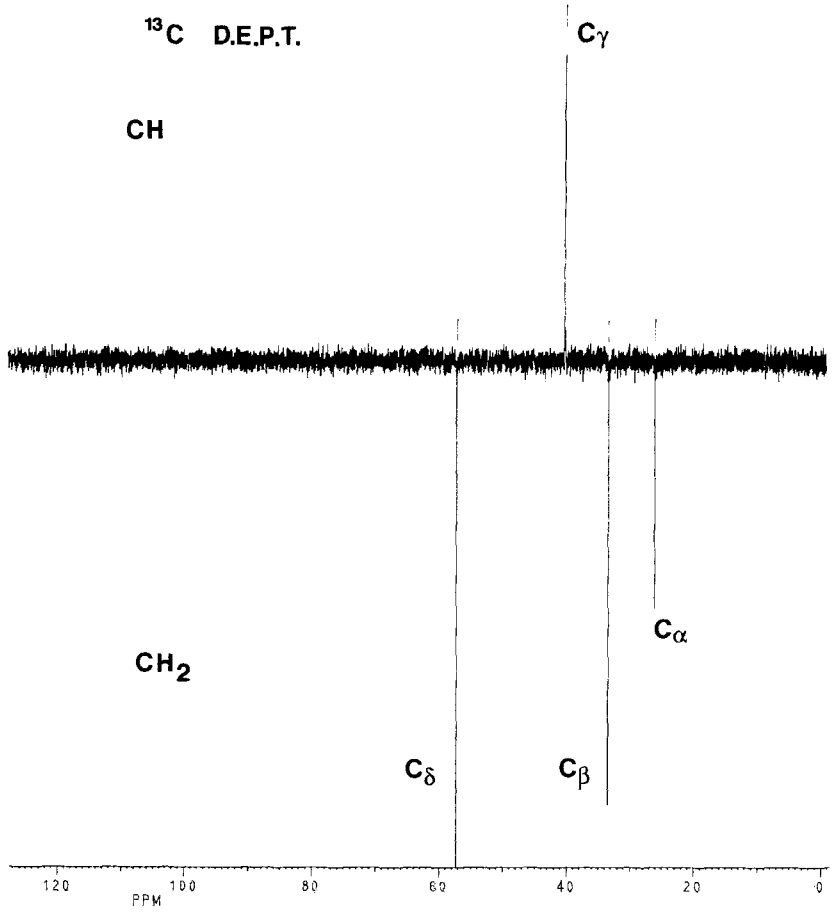


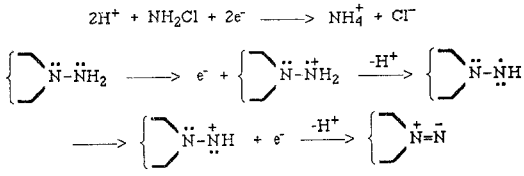
Fig. 3. DEPT spectrum of N,N′-azo-3-azabicyclo[3,3,0] octane in $CDCl_3$

III) Reaction mechanisms

The preceding results show that the formation of 3,4-diaza-bicyclo[4,3,0]non-2-ene proceeds in two consecutive steps. By analogy with the phenomena observed in the oxidation of unsymmetrical dialkylhydrazines [7, 8], the first elementary step corresponds to the formation of a diazene (aminonitrene):

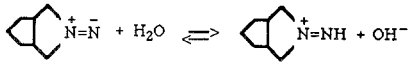
Scheme 1

The two redox half-reactions can be written as:



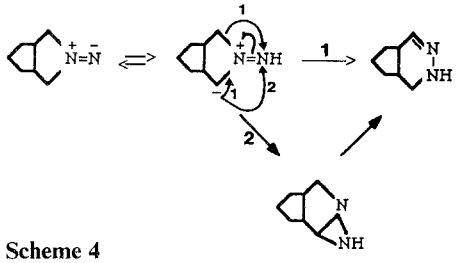
Scheme 2

This very reactive intermediate has only been isolated in a few specific cases [9]. Its existence is suggested in other reactions, notably the thermal decomposition of 1,1-disubstituted 2-sulfonylhydrazine salts, the reduction of nitrosamines, and the oxidation of secondary amines by difluoramine [11]. The influence of *pH* on the diazene rearrangement has been discussed in the Ref. [12]. The conversion of the 1,1-disubstituted diazene intermediate to a hydrazone occurs in basic or protic medium. On the other hand, in all attempts performed in acid or aprotic medium, the tetrazenes have been most frequently postulated as the reaction products [12, 13]. According to experimental conditions, several mechanisms for mono and disubstituted hydrazines have been proposed but very few cases concern the transposition of heterocyclic diazenes to hydrazones [14–16]. The only one consistent with our results would be the following: in aqueous medium, the diazene can be considered as a base liable to dissociate according to the following acid-base equilibrium:



Scheme 3

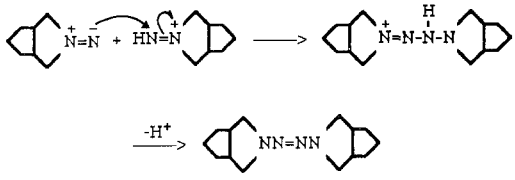
In alkaline medium, this equilibrium is shifted toward the neutral state. In such a case, the hydrogen atom in vicinal position to the nitrogen has acidic character due to the withdrawing effect of the electrophilic site. This results in a tautomerization and the intermediate formation of azomethinimine:



Scheme 4

Two mechanisms are possible which yield hydrazone: an expansion of the cycle (mechanism 1) or a nucleophilic attack of the carbanion (mechanism 2) on the terminal nitrogen and the transient formation of a diaziridine. This second hypothesis seems less likely as no diaziridine was detected by GC/MS in the reaction mixture, which is in agreement with the conclusion of *Lemal* [17]. Taking into account the stoichiometry of the reaction (yield = 97% with respect to NH_2Cl), it is evident that the hydrazone must be formed by the intramolecular rearrangement of the azomethinimine.

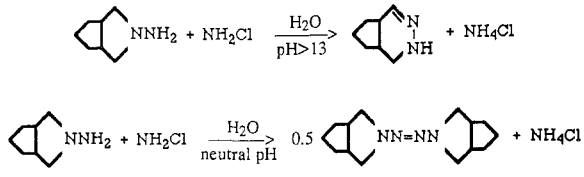
In weakly basic medium, the conjugated form of the diazene comes into play. In this case, N,N'-azo-3-azabicyclo[3,3,0]octane would result from a fast dimerization between the molecular and protonated forms of bicycloaminonitrene, whence, the observation of a quantitative yield at neutral *pH* (yield = 98% with respect to NH_2Cl).



Scheme 5

This study is consistent with the hypothesis suggested by *McBride* for the rearrangement of aliphatic diazenes [9]. Furthermore, the calculated yield excludes the possibility of direct interaction between the aminonitrene and hydrazine. A mixture of two species is obtained at intermediate *pH* values ($[NH_2Cl]_0 = [\mathbf{3}]_\infty + 2[\mathbf{4}]_\infty$). Their respective concentrations are controlled by the acidity constant of diazene and the reaction rate. This study is presently in progress.

The present work has allowed us to characterize the products and to demonstrate the fundamental role of *pH* in favoring the formation of **3** or **4**. The overall reaction scheme is the following:



Scheme 6

A previous experiment [18] has shown that the synthesis of **1** should be performed in basic medium. Under these conditions, **3** will be the only by-product to consider in later treatments.

Experimental

NMR spectra were obtained with a high resolution Bruker AM 300 spectrometer at 300 MHz for ^1H and 75 MHz for $^{13}3$. Samples were recorded in $CDCl_3$ solution with $SiMe_4$ as the internal standard. IR and UV spectra were measured with a Beckman 842 instrument (CsI cells) and a Cary IE double beam spectrophotometer, respectively. GC analyses were carried out on a HP 5830A chromatograph

using a column (inox, 150 cm × 0.2 cm i.d.) packed with 28% Pennwalt 223 + 4% KOH on gas chrom R. GC/MS spectra were performed with a Delsi Nermag mass spectrometer with a BP 20 capillar column (50 m) and an ion source of 70 eV. Thermodynamic data have been determined using a differential scanning calorimeter DSC 111 Setaram.

Monochloramine: unstable in water, therefore prepared at −10 °C extemporaneously by reacting 25 ml of 2 mol/l sodium hypochlorite (44° chlorometric) and 20 ml of an aqueous ammonia-ammonium chloride solution (3.6 mol/l NH_3–2.3 mol/l NH_4Cl) in the presence of diethyl ether (40 ml) [19]. The organic layer (0.8–1 mol/l) was shaken and washed several times with aliquots of distilled water. NH_2Cl in aqueous solution was obtained by re-extraction from the ethereal phase. Its content was determined by UV spectroscopy at $\lambda = 243$ nm ($\varepsilon = 458$ l/mol·cm).

N-amino-3-azabicyclo[3,3,0]octane (**1**) was produced continuously in biphasic solution in a cylindrical reaction vessel vigorously agitated by a coaxial overhead stirrer equipped with perpendicular blades in order to maintain the mixture emulsionized. A 1 mol/l solution of NH_2Cl(2 l), 3-aza-bicyclo[3,3,0]-octane (3.8 l of an aqueous solution of 30%) and 6 mol/l sodium hydroxide (0.5 l) were simultaneously introduced using a 5 fold excess of amine over haloamine and *pH* fixed at 13.4 [20]. The reaction temperature was maintained around 60 °C. A mixture with about 0.26 mol/l hydrazine was obtained (yield = 82%). After elimination of the ammonia, the reaction solution was distilled at atmospheric pressure to separate the 3-aza-bicyclo[3,3,0]octane in the form of a heteroazeotrope (30%). The hydrazine is then isolated by addition of sodium hydroxide and rectified under vacuum (mechanical pump). The global yield reaches 72% (182 g) and the final purity is around 99.8% by GC. Compound **1** was analysed directly by GC or UV after reaction with an excess of formaldehyde in a buffered solution at *pH* = 6.9. The absorbance of the resulting hydrazone was measured at 237 nm ($\varepsilon = 5352 \pm 20$ l/mol·cm) [21].

3,4-diazabicyclo[4,3,0]non-2-ene was prepared at 25 °C by acting NH_2Cl (1 l, 0.5 mol/l) on an alkaline solution of N-amino-3-azabicyclo[3,3,0]octane (1 l, 0.5 mol/l $C_7H_{12}NNH_2$, 0.75 mol/l NaOH). The reaction is instantaneous (yield = 97%) and upon addition of sodium hydroxide, the reaction mixture separates. The organic phase is distilled at a pressure below 1 mm Hg. In the head of the column, one obtains the residual hydrazine **1** followed by **3** which condenses at 37–38 °C (39 g). Its purity is close to 99.2% by GC (TC detector).

N,N'-azo-3-azabicyclo(3,3,0)octane was synthesized at 25 °C and *pH* ≈ 8 by reacting **1** and NH_2Cl in equimolecular conditions (0.1 mol/l). The precipitated solid was then filtered, washed and dried under vacuum (0.6 g, yield = 98%).

Compound **3**: IR: ν_{max} 3320 (NH), 2800–3000 (broad), 1620 (C=N), 1440–1480, 1310, 1090, and 720 cm^{-1}; UV: $\lambda_{max} = 229$ nm, $\varepsilon = 2685$ l/mol·cm; ^{1}H NMR: $\delta(CDCl_3)$ 6.88 (1H, d, a), 3.07–3.03 (1H, m, g), 2.48–2.31 (1H, m, g), 2.48–2.31 (2H, m, b-f), 1.99–1.70 (2H, m, e-c), 1.56–1.36 (2H, m, e-c), 1.67–1.36 (2H, m, d); ^{13}C NMR: $\delta(CDCl_3)$ 23.2 (C-d), 29.2 (C-e), 30.5 (C-c), 34.4 (C-f), 35.9 (C-b), 45.3 (C-g), 144.4 (C-a); MS: *m/z* (70 eV) 124 (M^+, 100%), 123 (40), 95 (23.3), 94 (10.6), 83 (28), 82 (11), 81 (54), 68 (25), 67 (37), 55 (14), 41 (25), 39 (21), 30 (53.5), 28 (31); Microanalysis: found: C 67.69, H 9.64, N 22.71; $C_7H_{12}N_2$ requires: C 67.74, H 9.67, N 22.58.

Compound **4**: IR: ν_{max} 2800–3000 (broad), 1440–1480, 1380, 1090, 720 and 560 cm^{-1}; UV (hexane): $\lambda_1 = 282$ nm ($\varepsilon_1 = 11900$ l/mol·cm), $\lambda_2 = 255$ nm ($\varepsilon_2 = 6120$ l/mol·cm); ^{1}H NMR: $\delta(CDCl_3)$ 3.35–3.29 (4H, q, δ), 2.99–2.94 (4H, q, δ), 2.65–2.59 (4H, m, γ), 1.80–1.61 (4H, m, β), 1.80–1.43 (4H, m, α), 1.55–1.43 (4H, m, β); ^{13}C NMR: $\delta(CDCl_3)$ 26.1 (C-α), 33.3 (C-β), 40.2 (C-γ), 57.1 (C-δ); MS: *m/z* (70 eV) 248 (M^+, 60), 110 (27), 93 (14), 81 (100%), 68 (30), 67 (61), 55 (51), 54 (47), 53 (34), 44 (41), 43 (34), 42 (91.5), 41 (90), 40 (13), 39 (56), 30 (84), 29 (40), 28 (27), 27 (34); Microanalysis: found: C 67.58, H 9.74, N 22.77; $C_{14}H_{24}N_4$ requires: C 67.74, H 9.67, N 22.58; m.p. = 74.4 °C, $\Delta H_f = -2 \times 10^4$ KJ/mol.

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