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Unusual Nazarov Cyclization in Near-Critical Water

Tuomo Leikoski,† Juha Kaunisto,‡ Martti Alkio,‡ Olli Aaltonen,*,‡ and Jari Yli-Kauhaluoma*,†

Drug Discovery and Development Technology Center, Faculty of Pharmacy, P.O. Box 56 (Viikinkaari 5 E), FI-00014, University of Helsinki, Finland, and VTT Processes, Technical Research Centre of Finland, P.O. Box 1602 (Biologinkuja 7, Otaniemi), FI-02044 VTT, Finland

Abstract:

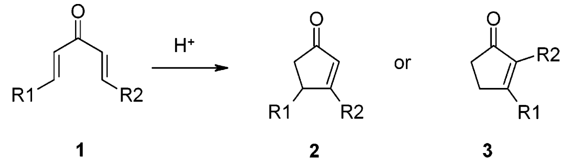
The Nazarov reaction of *trans,trans*-dibenzylidene acetone in near-critical water with or without additional carbon dioxide produces 2,3-diphenyl-2-cyclopentenone instead of the conventional Nazarov product, 3,4-disubstituted 2-cyclopentenone. The use of organic solvents and strong mineral acids, generally required for this reaction, is avoided by using water and carbonic acid as a proton source. After an optimization procedure, 38% yield of 2,3-diphenyl-2-cyclopentenone was obtained. The presence of carbon dioxide had a clear positive effect on yield.

Introduction

The Nazarov reaction is an acid-catalyzed cyclization of divinyl ketones to 2-cyclopentenones.[1] The reaction has been used in construction of many complex, natural, and biologically important target molecules and their synthetic intermediates possessing the cyclopentenone moiety, such as jasmonoids[2] and prostanoids.[3] The Nazarov reaction involves a conrotatory 4π electrocyclization of the pentadienyl cation, and it is therefore considered as a pericyclic reaction. The pericyclic reactions are highly useful in the construction of carbon−carbon bonds.

The Nazarov reaction produces normally 3,4-disubstituted 2-cyclopentenones **2** from β,β′-disubstituted cross conjugated divinyl ketones **1** (Scheme 1). However, Hirano et al. have reported about the abnormal Nazarov reaction, in which the main product is a 2,3-disubstituted 2-cyclopentenone **3**.[2,4] They postulated that this unexpected product is formed by the addition of a hydroxylic solvent, such as water or carboxylic acid, to the oxyallyl cation **5** after the electrocyclic ring closure of the protonated divinyl ketone **4** (Scheme 2). This would give rise to the hydroxy- or acyloxycyclopentenone intermediate **6**, which isomerises to **7**. After removal of water, the second oxyallyl cation **8** isomerises to the most stable cation **9**, deprotonation or deacylation of which furnishes the final 2,3-substituted **3** with formal 1,2-shift of the carbonyl group. The normal 3,4-substituted Nazarov product **2** would be obtained after direct deprotonation of the oxyallyl cation **5**. In fact, Hirano et al. observed also formation of the conventional 3,4-disubstituted 2-cyclopentenones in the presence of less nucleophilic solvent, where deprotonation can compete with the nucleophilic substitution by the solvent.[2]

Scheme 1



Despite its usefulness as a simple one-step procedure, the Nazarov reaction suffers from some limiting drawbacks, including harsh reaction conditions with high temperature and the use of strong acid (typically used as a solvent or as a catalyst; e.g., 47% HBr/HOAc (1:3), $BF_3{\cdot}Et_2O/CH_2Cl_2$, 85% H_3PO_4/90%HCO_2H (1:1), and $SnCl_4/CH_2Cl_2$), chlorinated solvents, variable yields, and poor regioisomeric control. The objective of our study was to perform the Nazarov reaction in hot, near-critical water, which would serve as a source of proton donating oxonium ions instead of strong acids, due to the increased ion product of water at elevated temperatures. The ionization constant of water is maximized at 250 °C where it is 3 orders of magnitude higher than that at room temperature.[5] The term near-critical water refers to liquid water at 250−300 °C which approaches but remains below the critical temperature of plain water (374 °C). Further, water's dielectric constant drops rapidly with increasing temperature rendering it a good solvent for polar organic compounds. At 300 °C water exhibits a polarity and density similar to those of acetone at room temperature.[6] Water above the critical temperature (374 °C) has been studied recently as a new medium for the pericyclic Diels−Alder reactions[7] and subcritical water as a medium for the pericyclic ene reactions[8] due to the high solubility of the reagents.

Another objective of our work was to find out how the addition of carbon dioxide would affect the conversion and yield. The use of carbonic acid as a catalyst, instead of strong

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* Corresponding authors. (Jari Yli-Kauhaluoma) Fax: +358 9 191 59556. Telephone: +358 9 191 59170. E-mail: Jari.Yli-Kauhaluoma@helsinki.fi. (Olli Aaltonen) Fax: +358 20 722 7026. Telephone: +358 20 722 5301. E-mail: Olli.Aaltonen@vtt.fi.

† University of Helsinki.

‡ Technical Research Centre of Finland.

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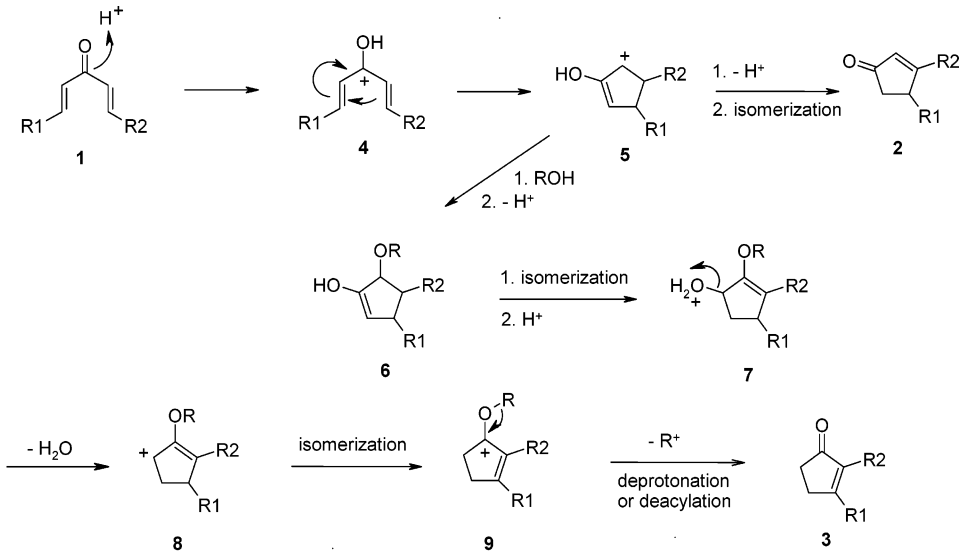
Scheme 2



mineral acid, would provide an environmentally friendlier procedure with fewer process steps. Carbonic acid has been shown, e.g., to accelerate the hydrolysis of carbohydrates, including xylan.[9]

We embarked on studying the reaction of *trans*,*trans*-dibenzylidene acetone (**1**, R1 = R2 = Ph) because of the relatively limited amount of reports about Nazarov cyclications of β,β'-diaryl substituted divinyl ketones.[10,11] We wanted to study the course of the Nazarov cyclization in water and water/carbon dioxide instead of strongly acidic solvent/catalyst mixtures that are used generally in this process. This method would enable also the Nazarov cyclizations of acid sensitive substrates. Moreover, the effect of the nucleophilic water molecules on the reaction pathway can be studied. Both the classical Nazarov-type cyclopentenone **2** and the unusual **3** have been synthesized previously by means of the Pauson−Khand reaction and its modifications,[12,13] 2-cyclopentenol producing cyclizations followed by oxidation[14] and dehydroxylation of 3,4-diphenyl-3-hydroxycyclopent-4-enones.[15]

Results and Discussion

We used the modified Simplex optimization method to find the maximum yield and to locate optimum temperature and time with the least number of experiments. The temperatures and reaction times in the first three experiments were chosen using an educated guess (Table 1). The conditions in the subsequent experiments were then chosen according to the modified Simplex procedure. The yield of the product **3** in the previous experiment was used in choosing the reaction conditions of the next experiments. The procedure was continued until no further improvement in yield was obtained. A drawback of the Simplex routine is that a local optimum may be found instead of a global one.

The material balance was well closed in the series of experiments. The sum amount of recovered liquid and solid materials after the reaction varied between 92 and 100% of the sum amount of water and **1** charged in the reactor. Therefore, material losses during the reaction and during the depressurization and opening stages of the reactor may be considered small.

Because temperature and reaction time were simultaneously changed between experiments, we used combination functions to describe the severity of the reaction conditions in each experiment. The following two severity functions were used:

$$\mathrm{SF1} = t \times (\mathrm{T} - \mathrm{T}_0)$$

and

$$\mathrm{SF2} = t \times lg[(T - T_0)/14.75]$$

where t is reaction time interval and T is the average temperature of the reaction mixture over the time interval t. T_0 is the reference temperature which is used in determining the reaction time (see Experimental Section). T is expressed in Centigrades, and t, in minutes.

Severity function SF1 is a simple area below the reaction temperature history curve in the temperature/time graph. SF2 attempts to take into account the nonlinear effect of temperature on reaction rates. SF2 has been used previously to describe the severity of hydrolysis reaction conditions.[9] The yields of cyclopentenone **3** are plotted against the two severity functions in Figures 1 and 2.

In addition to the modified Simplex procedure, further experiments were run to find the effect of temperature on the yield of **3**. The optimal residence time which was located

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Table 1. **Reaction conditions and results**

	CO_2 in aq. phase (wt % of water)	max temp (°C)	max pressure (bar)	reaction time at $T > 150$ °C (min)	severity function values: SF1 at $T > 150$ °C ($\times 1000$)	SF2 at $T > 150$ °C ($\times 10^{6}$)	conversion of **1** (wt %)	yield of product **3** (%)
2A	0	302	96	230	29.1	4.23	100	15.0
2B	5.9	301	247	250	31.6	4.52	100	12.4
3A	0	264	53	110	8.2	0.12	$\ll 100$	22.3
3B	5.2	262	203	115	9.5	0.13	100	36.3
4A	0	284	74	160	15.0	0.69	100	25.0
4B	5.7	285	224	140	15.1	0.75	100	36.1
5A	0	295	85	185	21.1	2.00	100	19.6
5B	6.7	293	215	200	22.0	1.80	100	28.9
6A	0	262	49	75	4.6	0.08	<50	7.5
6B	6.6	264	204	80	4.9	0.07	100	2.1
7A	0	283	72	125	11.3	0.56	100	20.0
7B	5.2	289	223	118	11.7	0.76	100	33.8
8A	0	306	101	125	10.9	1.33	100	23.0
8B	6.8	303	222	127	11.3	1.15	100	38.3
9A	0	184	12	135	3.4	0.001	0	0.0
9B	2.1	185	229	130	3.3	0.001	0	0.0

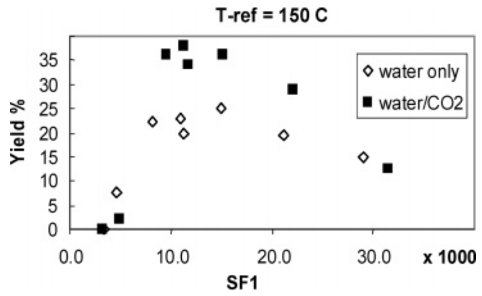

Figure 1. **Yield of cyclopentenone 3 against linear severity function SF1.**

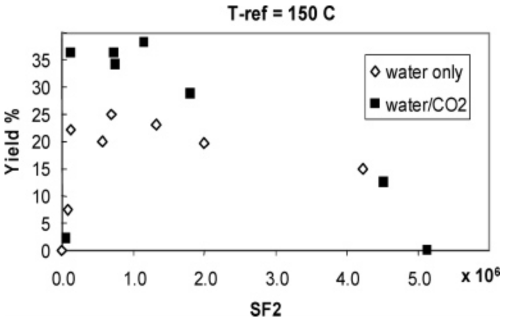

Figure 2. **Yield of 3 versus logarithmic severity function SF2.**

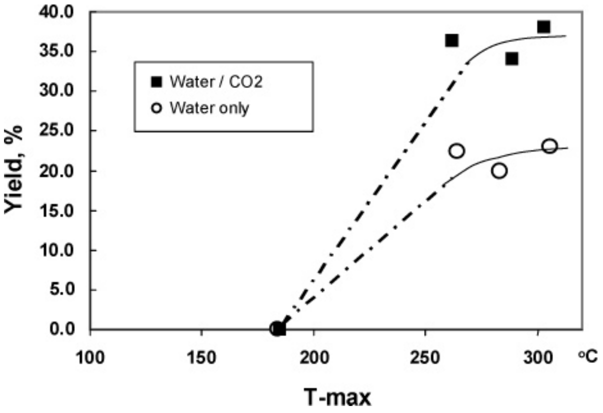

Figure 3. **Respective yields of 3 with and without CO_2 in solution versus maximum reaction temperature at approximately constant reaction times of 110 to 135 min ($T_0 > 150$ °C).**

in the Simplex series of experiments was kept approximately constant while extending the temperature range. The results are shown in Figure 3.

The effect of the severity of the reaction conditions on the yield of **3** remained unchanged regardless of which reference temperature was used for determining reaction time (150 °C, 200 °C, or 250 °C where applicable; see Experimental Section for definition). The SF vs yield patterns derived at different reference temperatures were very similar to the ones shown in Figures 1 and 2. Therefore, they are not repeated here. It is also evident from comparing Figures 1 and 2 that the form of the severity function (either linear SF1 or logarithmic SF2 in respect to temperature) does not change the order of the experimental points in the yield/severity plot. This implies that once a "threshold" temperature is exceeded, the yield of **3** is no longer affected by the reaction temperature. The yield of cyclopentenone **3** is then only dependent on the reaction time. This behaviour is even more apparent from Figure 3. The maximum isolated yield of **3** was found to be 25% when the reaction was carried out in near-critical water without the presence of carbon dioxide.

The formation of the classical Nazarov cyclopentenone **2** could not be detected by means of GC−MS or ^{1}H NMR analyses of the reaction mixtures. Carbon dioxide had an increasing effect on the yield of **3**, but only at close to optimum reaction severities where the yields were at maximum level (Figure 3). At its best there was a 60% increase in the yield of the abnormal Nazarov product **3** when carbon dioxide was added. The maximum yield of cyclopentenone **3** after SiO_2 column chromatography was found to be 38%. The formation of the classical product **2** was not detected.

In conclusion, we have obtained first results of a potentially sustainable method to carry out Nazarov reaction in a near-critical water or near-critical water/carbon dioxide

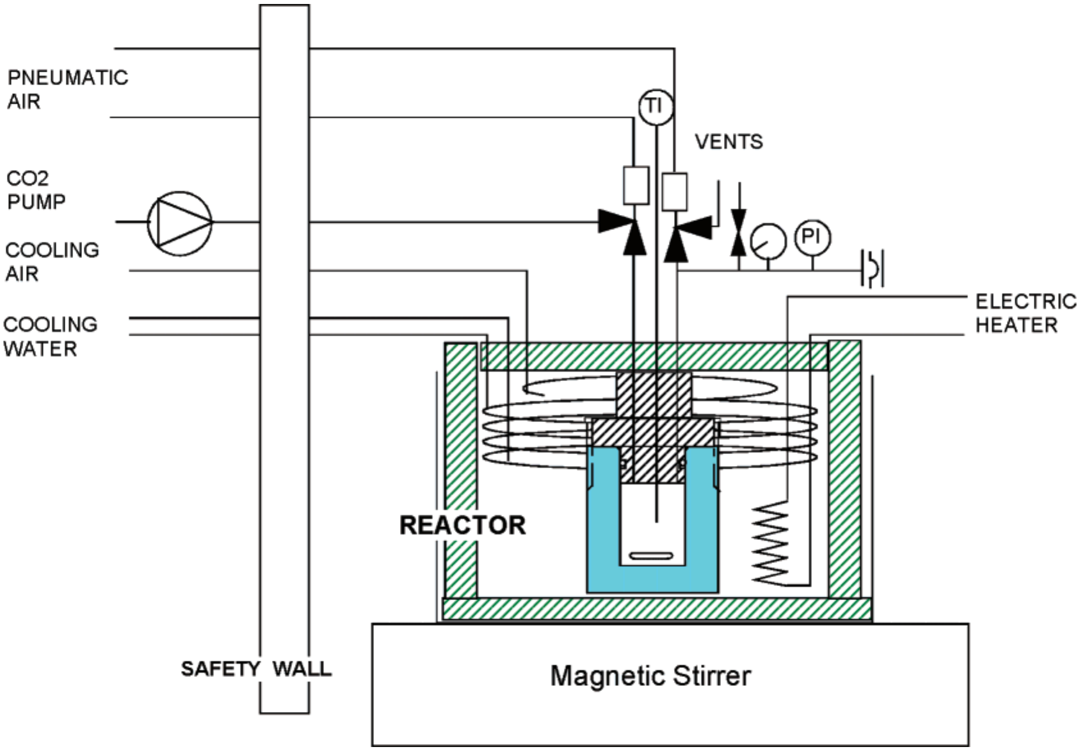

Figure 4. **Reactor setup.**

system. The regiochemistry of the Nazarov reaction in near-critical water favours the abnormal product isomer **3**, thus complementing the classical Nazarov procedure. We also realised that the use of carbonic acid as a mild acid catalyst in near-critical water increased the yield of the abnormal 2-cyclopentenone **3** by 60% when compared to the same reaction in plain near-critical water. Hence, there is no need to use a strongly acidic solvent/catalyst system in the reaction. This methodology may be applicable also to the other pericyclic reactions of general and industrial interest.

Scaling up of this and similar methods may be done following the designs adopted in the continuous supercritical water oxidation processes. Water, starting materials, and liquid carbon dioxide may be continuously pumped into a tube reactor at close to ambient temperature. The aqueous reaction mixture is then preheated using the heat of the product stream leaving the reactor. Heating to reaction temperature is done in a fired, electrical, or hot oil heater. An open tubular reactor of sufficient length may be used to allow adequate residence time for the reaction. The reaction mixture leaving the reactor tube is then continuously led to atmospheric pressure using either a pressure reduction valve or a long pressure let-down tubing. Carbon dioxide is released at pressure let-down, and the products are collected with liquid water.

Experimental Section

Materials. Food grade carbon dioxide, 99.7%, was obtained from Oy Aga Ab, Finland. All the chemicals and reagents were obtained from Aldrich Chemical Co., Germany. Melting points were obtained with a Bibby Stuart Scientific SMP3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 Plus spectrometer. Chemical shifts (δ) are reported in ppm relative to the tetramethylsilane signal (0.00 ppm) in proton spectra and to the NMR solvent signal ($CDCl_3$, 77.2 ppm) in carbon spectra. FT-IR spectra of the products were recorded on a Bruker Vertex 70 FT-IR spectrometer equipped with the Harrick MVP2 unit. GC−MS analyses were performed with a Hewlett-Packard gas chromatograph 5890A connected to the 5970 series mass-selective detector. Thin-layer chromatography (TLC) was performed with Merck TLC aluminium supported plates, silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (0.040−0.063 mm).

Reactions. All reactions were run in a 40 mL high-pressure vessel. The reactor was run with a remote-control system. The setup is depicted in Figure 4. Deionized water (20 mL) saturated with nitrogen and *trans*,*trans*-dibenzylidene acetone **1** (1.00 g, 4.27 mmol) were loaded in the reactor along with a magnetic stirring bar. After closing the vessel, it was first test pressurized at room temperature with nitrogen at 150 bar. The vessel was then slowly exhausted to atmospheric pressure. This treatment also removed oxygen from the gas phase.

The reactor was placed in an electrically heated (2 kW) and thermostated oven, equipped with water and air cooling. All valves were pneumatically controlled from behind a safety wall. Temperatures were digitally monitored using K- and J-type thermocouples. Reactor pressure was monitored using a Wika pressure transducer with digital display.

When carbon dioxide was used it was loaded in two stages to control the final pressure at the target temperature. The reactor was first loaded at room temperature with CO_2 gas to ca. 45 bar. Heating was then switched on, and when the inside temperature of the reactor had reached a predetermined

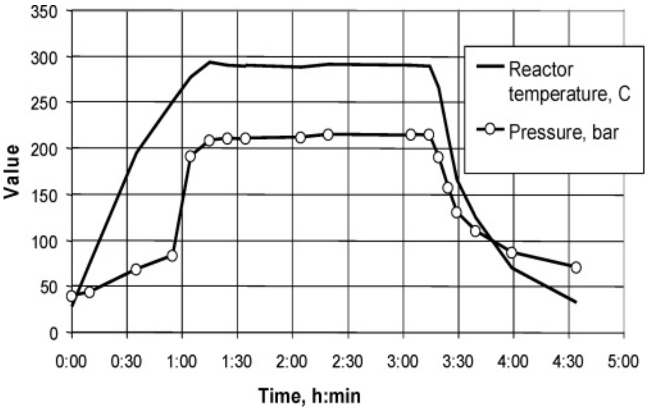

Figure 5. **Temperature and pressure profiles of typical experiments when CO_2 was used.**

reference value (e.g., 250 °C) more CO_2 was pumped with a Jasco 987 SF-pump until the pressure reached 200 bar. Heating was continued until the target maximum reaction temperature was reached and then maintained until cooling stage started.

Reaction time is here defined as the time interval between the moment when the temperature exceeded the reference temperature T_0 during heating and the moment when it decreased below T_0 during cooling (cf. Figure 5). Three reference temperatures were considered in this work: 150 °C, 200 °C, and 250 °C. A typical temperature profile of the experiment is given in Figure 5.

The amount of total CO_2 in the reaction vessel was calculated from measured total pressures at various temperatures using the equation of state data for pure CO_2 and saturated steam. The partial pressure of CO_2 was approximated by subtracting the vapour pressure of water from total pressure.

Experiments without CO_2 were run otherwise identically, except that no carbon dioxide was added and the resulting pressure in the reactor was caused by the vapour pressure of water alone.

When the set reaction time at maximum temperature had elapsed the heater was switched off. Tap water and cooling air were switched on, and air was circulated past the tap water coils to enhance the cooling of the oven. The reactor was cooled in this way until the inside temperature was less than 50 °C. For safety reasons, the reactor was allowed to stay overnight in the bunker until it was depressurized and opened in the laboratory. The aqueous phase of reactor contents was decanted, and the semisolid product was washed from the reactor vessel with several portions of acetone. The aqueous and acetone phases were combined for analysis.

Water was evaporated from the reaction mixtures azeotropically with 2-propanol. Product **3** (2,3-diphenyl-2-cyclopentenone) was obtained after the column chromatography on silica gel (ethyl acetate−hexane gradient 1:3 to 1:2) as a yellow oil. $R_f = 0.27-0.28$ (EtOAc−hexane 1:2). GC−MS (intensities relative to the main peak): *m*/*z* 234 (100%), 233 (99%), 191 (65%), 205 (33%), 202 (20%). IR (neat): 1702, 1353, 1161, 761, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 2.68−2.72 (2 H, m); 3.03−3.07 (2 H, m); 7.18−7.24 (2 H, m); 7.28−7.36 (8 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 29.7, 35.0, 128.0, 128.3, 128.6, 128.7, 129.6, 130.0, 132.5, 135.9, 140.1, 168.2, 207.7. This compound has been described previously, and these spectral data are in agreement with the published ones.[16] Mp of 2,4-dinitrophenylhydrazone 226−227 °C (lit.[17] mp 227−228 °C).

In the NMR spectra, the DEPT signals and COSY correlations of the adjacent ring CH_2 groups were also in agreement with the structure.

The authors would like to stress the following safety considerations in running this and similar experiments. It is strongly recommended that unknown batch reactions at such high temperatures and pressures are controlled from behind a safety wall. All parts of the reactor system (including the connectors, valves, pressure transducer, etc.) which come in contact with high pressure and temperature must be rated accordingly. Pressure testing of the reactor system with cold water should always be carried out prior to running reactions. The electrical heating system of the reactor must be designed so that it is automatically turned off if the temperature or pressure rises exceedingly. A manual turn off possibility from behind the safety wall must also be installed. The reactor vessel must be equipped with a mechanical safety valve or a burst disk assembly which cannot be shut off from reactor contents with a valve.

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