Synthesis of ^{11}C-Labeled Guanidines in Supercritical Ammonia

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Abstract: The synthesis of ten ^{11}C-labeled aromatic and aliphatic guanidines in supercritical ammonia is described. The corresponding amines were first converted into cyanamides by reaction with [^{11}C]cyanogen bromide. The aliphatic amines gave high yields of ^{11}C-labeled cyanamides (70−98%), whereas the yields for the aromatic amines was dependent on the functional groups on the ring, ranging from 0% yield for the electron-withdrawing nitro group to 90% for the electron-donating methoxy group. The conversion of the ^{11}C-labeled cyanamides to ^{11}C-labeled guanidines was achieved in both supercritical ammonia and aqueous ammonia solutions. The latter method gave low and irreproducible yields as compared to performing the reactions in an automated supercritical fluid synthesis (SFS) system (designed for use with supercritical ammonia). Using the SFS system, total radiochemical yields of ^{11}C-labeled guanidines of 30−85% were obtained from the aromatic amines (depending on the substituents) and 2−36% for the aliphatic amines. A simultaneous synthesis of $^{11/13}$C-labeled phenylguanidine was performed to verify the labeling position by comparing the ^{13}C-NMR of the labelled product to authentic reference compound.

Introduction

Supercritical fluids (SF) are attractive as media for chemical reactions since their physical properties can be manipulated by small changes in pressure and temperature, and several of these properties (*e.g.*, density, viscosity, diffusivity) are intermediate between those of a gas and a liquid.[1,2] Instead of changing between solvents with different physical properties, and therefore different chemical structure, the properties of one single SF can be varied continuously to study for example solvent effects on reaction mechanisms or to control rates and selectivities of reactions. The greater diffusivity in a SF compared to a liquid can increase the rate of diffusion-controlled reactions, one example being enzyme catalyzed reactions in supercritical CO_2.[3] Enhanced solubility in the supercritical phase can sometimes be achieved, something that has been utilized in, *e.g.*, oxidation of organic wastes in supercritical water[4] and in homogeneous and heterogeneous catalysis.[5−7]

Monosubstituted guanidines are frequently occurring structural units in many biologically and pharmaceutically interesting compounds and should be relevant targets for labeling with short-lived positron emitters such as ^{11}C, allowing their use in both *in vivo* positron emission tomography (PET) studies and *in vitro* assays.[8] In the synthesis of ^{11}C-labeled compounds, the choice of suitable labeling precursors and reaction conditions are of crucial importance on account of the short half-life of the radionuclide (for ^{11}C $t_{1/2}$ = 20.3 min), requiring efficient procedures for synthesis, purification, and analysis of the products.[9] Therefore, the development of new labeling precursors and methods for rapid labeling synthesis are of great importance. A supercritical fluid synthesis (SFS) system, designed for use with supercritical ammonia, has been developed for this purpose, allowing automated microscale (nanomolar range) synthesis to be performed.[10] The possibility to accurately control the temperature and pressure from 25−200 (±0.2) °C and 9−450 (±1%) bar in the SFS system has given highly reproducible yields.

Synthesis of guanidines can be achieved by reacting a cyanamide with an amine salt to give the guanidine directly.[11,12] Using this method, Iwata *et al*. prepared benzyl [^{11}C]guanidine in low yields by reacting benzylamine with [^{11}C]cyanamide, the latter obtained by proton irradiation of calcium nitride.[13] An alternative route is offered by first converting the amine to a cyanamide, using [^{11}C]cyanogen bromide,[14] followed by reaction with ammonia or a primary amine. Symmetrically substituted 1,3-di(2-tolyl)-[^{11}C]guanidine has been synthesized by this method by reacting the ^{11}C-cyanamide with another equivalent of amine.[15]

In this paper, synthesis of monosubstituted ^{11}C-labeled

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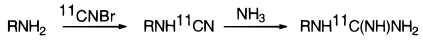

Figure 1. The aromatic or aliphatic amines were first converted to the corresponding ^{11}C-labeled cyanamides by reaction with [^{11}C]-cyanogen bromide. Further reaction with ammonia produced the ^{11}C-labeled guanidines.

guanidines is described. The reactivity of ten aliphatic and aromatic amines (4-methoxyaniline, 4-methylaniline, aniline, 4-aminobenzamide, 4-aminoacetophenone, 4-nitroaniline, benzylamine, *n*-hexylamine, cyclohexylamine, and piperidine) toward [^{11}C]cyanogen bromide followed by treatment with ammonia was investigated (Figure 1). Both aqueous ammonia solutions and supercritical ammonia was used in the guanidine reactions. The solvent in the cyanamide reaction and pressure and temperature in the SFS system were varied to study the effect on the radiochemical yields of the ^{11}C-labeled guanidines.

Experimental Section

General Methods. [^{11}C]Carbon dioxide was produced at the Uppsala University PET Centre using an MC 17 cyclotron (Scanditronix AB, Uppsala, Sweden) by irradiation of a target containing 99.95% nitrogen gas (AGA 6.0) and 0.05% oxygen gas (AGA 6.0) with a 17 MeV proton beam, producing ^{11}C by the ^{14}N(p,α)^{11}C nuclear reaction. The [^{11}C]carbon dioxide formed was converted to hydrogen [^{11}C]-cyanide using the Scanditronix RNP-17 radionuclide production system according to published procedures.[16,17] [^{11}C]Cyanogen bromide was produced according to either of two different procedures. In the first procedure, hydrogen [^{11}C]cyanide was trapped in triethyleneglycol dimethyl ether (triglyme) and reacted with bromine at room temperature. The [^{11}C]cyanogen bromide was then distilled into the reaction vessel containing the amine solution. A second synthetic procedure was devised during the course of the experimental investigation, involving a solid-phase synthesis which allowed a simplified automated synthesis of [^{11}C]cyanogen bromide. Briefly, hydrogen [^{11}C]cyanide was passed through a bed of pyridinium bromide perbromide at room temperature, and the [^{11}C]cyanogen bromide obtained was then trapped directly in the reaction vessel.[18] Both procedures gave comparable yields of ^{11}C-labeled cyanamides.

LC analyses were performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV detector in series with a β^+-flow detector. A Beckman Ultrasphere Octyl column (4.6 × 250 mm, 5 μm) was used with a mobile phase of A: 5 mM trifluoroacetic acid (TFA, E. Merck, p.a. grade) in Nano-pure water (Barnsted) and B: 5 mM TFA in acetonitrile (E. Merck gradient grade), flow 1.5 mL/min and wavelength 230 nm. A linear gradient of 5−15% B at 2−4 min and 15−85% B at 4−10 min was used for all amines except 4-aminobenzamide, where the gradient was 0−85% B in 5−11 min. In the LC analyses of the ^{11}C-labeled guanidines, unlabelled reference compounds were added, and the UV and radiochromatograms were compared. The reference compounds were synthesized according to literature procedures.[19,20]

The LC-MS equipment consisted of a Beckman 126 gradient pump (Beckman, USA), a CMA 240 autosampler (CMA Microdialysis, Stockholm, Sweden), and a VG Platform single quadrupole mass spectrometer equipped with pneumatically assisted electrospray and an RF ion bridge (Fisons Instruments, Cheshire, UK). A KromaSil C18 column (100 × 4.6 mm) and a post column 1:50 split was used, with 2% of the total flow delivered to the electrospray probe and 98% delivered to a Beckman 166 variable wavelength UV detector followed by a β^+-flow detector. Mobile phases A and B, as described above, were used with a linear gradient from 5−100% B in 6 min. LC-MS analysis was run on each ^{11}C-labeled guanidine together with the authentic reference compound. The mass associated with the ^{11}C-labeled guanidines was too low to be observed using the LC-MS system, so co-elution of the radio signal with the added reference was used to verify the mass of the products.

The calculations of the phase properties of the reaction mixtures were performed using the PPDS2 v 1.0 software (NEL, Scotland, UK) based on the Peng-Robinson equation of state. No experimental data for the mixture of ammonia with the solvents used (butanol, acetonitrile, toluene, and dimethylformamide) were available which allowed the interaction parameters to be calculated, so they were set to 0.[21]

Supercritical Fluid Synthesis System, Figure 2. The supercritical fluid synthesis (SFS) system consisted of a Model 308 pump equipped with a 10SC pump head, a Model 821 pressure regulator, and a Model 421 column oven (Gilson Medical Electronics S.A.). The SFS system was used as described previously with the following modifications (Figure 2). Two injection loops (5 μL) were used to inject the reaction mixture into the reaction cell (473 ± 5 μL) located inside the oven. The reactants were loaded into the injection loops on valve V_1 (AC10WHC, Valco Instruments Co. Inc., Houston), while the flow was kept at 0.5 mL/min through the system. To inject the reactants and simultaneously build the ammonia pressure in the cell, valve V_2 (A3C3WEHCY, Valco) was kept in position 2, valve V_3 (A3CST4UWHCY, Valco) was closed to position 4, and V_1 was switched to inject position. The liquid ammonia then pushed the reactants into the closed reaction cell, assuring a positive forward flow of ammonia with dissolved reactants. When the desired reaction pressure was reached in the reaction cell, valve V_2 was switched to position 1, and the pump flow was reduced to 0.05 mL/min to retain pressure between the pump and reaction cell. The reaction was carried out for 5 min after which valve V_2 was switched back to position 2, and V_3 was opened to position 1, forcing the products out of the cell and through the restrictor positioned in the collection solvent.

Synthesis of ^{11}C-Labeled Cyanamides. [^{11}C]Cyanogen bromide was trapped at room temperature in a solution containing 70−110 μmol (0.17−0.27 M) amine (4-methoxyaniline, 4-methylaniline, aniline, 4-aminobenzamide, 4-aminoacetophenone, 4-nitroaniline, benzylamine, *n*-hexylamine, cyclohexylamine, or piperidine) in 400 μL solvent (butanol (BuOH), acetonitrile (MeCN), dimethylformamide (DMF), or toluene) in a 5 mL reaction vessel equipped with a septum. The reaction mixture was heated (MeCN: 80 °C, toluene: 100 °C, BuOH: 120 °C, DMF: 130 °C) for 5 min, and a sample (25 μl) was analyzed by LC.

Synthesis of ^{11}C-Labeled Guanidines in Supercritical Ammonia Media. The cyanamide reaction mixture was loaded into both injection loops (2 × 5 μL, ca 1−3 μmol amine) on the SFS system and injected into the reaction cell. After 5 min reaction with ammonia at the selected pressure and temperature, the product mixture was trapped directly into ca. 1 mL of water and analyzed by LC.

Synthesis of ^{11}C-Labeled Guanidines in Aqueous Ammonia Solutions. An aqueous solution of either A, 25% ammonium hydroxide (NH_4OH), or B, 30% ammonium formate in 25% NH_4OH, was added to 200 μL of the ^{11}C-cyanamide reaction mixture in a 1.5 mL reaction vessel equipped with a septum. After 5 min reaction at 80−130 °C (depending on the solvent used in the cyanamide reaction) the product mixture was analyzed by LC.

Synthesis of Phenyl [$^{11/13}$C]Guanidine. Hydrogen (^{13}C)cyanide (30 mg, 454 μmol, 99 atom % ^{13}C, Sigma-Aldrich) was dissolved in 500 μL of triglyme and 100 μL of water. A solution of bromine (23 μl, 449 μmol) in 500 μL of triglyme was added, and the (^{13}C)cyanogen bromide formed was distilled through a drying tower containing antimony and phosphorous pentoxide (Sicapent) and collected in a flask kept at −72 °C. The (^{13}C)cyanogen bromide (ca. 14 mg) was dissolved in 500 μL of butanol. [^{11}C]Cyanogen bromide was trapped in a solution of 10 μl (109.6 μmol) of aniline and 400 μL of butanol. The (^{13}C)-cyanogen bromide solution was added, and the reaction mixture was heated at 130 °C for 8 min. A 500 μL solution of 30% ammonium formate in 25% NH_4OH was added, and the mixture was heated an additional 8 min. The reaction mixture was injected on a preparative LC column (Beckman Ultrasphere C-18, 10 × 250 mm, mobile phases A and B, 5−85% B in 0−7 min), and the fraction containing phenyl [$^{11/13}$C]guanidine was collected and evaporated to dryness. The residue was dissolved in CD_3OD and ^{13}C-NMR spectra recorded on a Varian

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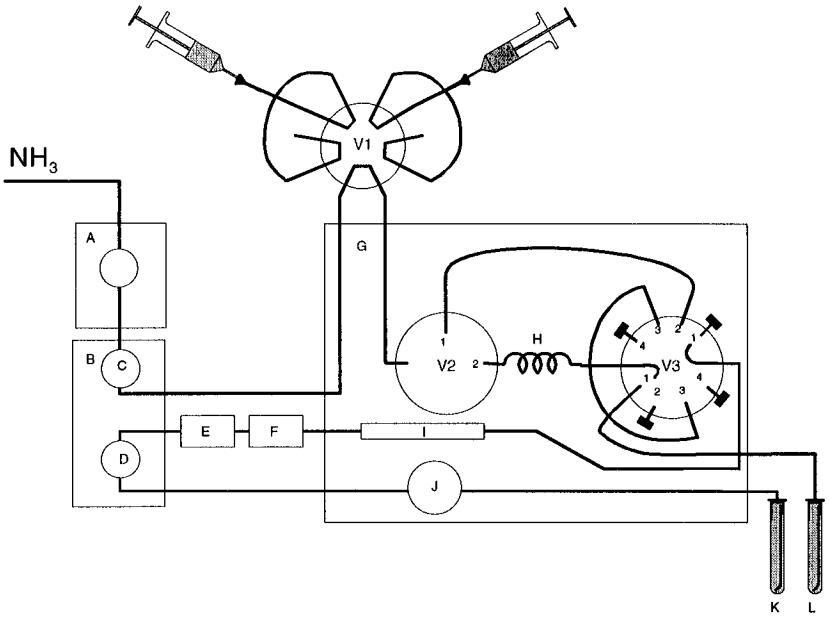

Figure 2. Schematic of the SFS (supercritical fluid synthesis) system. V_n are switching valves. A: Gilson 308 pump, B: Gilson 821 pressure regulator, C: pulse dampener, D: pressure regulator valve, E: radio detector, F: UV detector, G: Gilson 421 oven, H: reaction cell, 473 μl, I: SFC column, J: Rheodyne 7037 pressure relief valve, K: trapping position after SFC purification, L: trapping position directly from reaction cell.

Table 1. Radiochemical Yields[a] of ^{11}C-Cyanamides

amine	1-butanol	acetonitrile	toluene
4-methoxyaniline	90 (4)	54 (13)	39 (8)
4-methylaniline	68 (3)	33 (4)	18 (4)
aniline	66 (8)	26 (10)	55 (30)
4-aminobenzamide	49 (4)	0	0
4-aminoacetophenone	29 (8)	3 (1)	8 (4)
4-nitroaniline	0	0	0
benzylamine	70 (16)	89 (12)	73 (10)
n-hexylamine	93 (7)	66 (8)	99 (2)
cyclohexylamine	95 (3)	88 (4)	89 (3)
piperidine	98 (2)	61 (7)	98 (4)

[a] The radiochemical yields were calculated from the decay-corrected LC chromatograms. The mean value from four experiments are given with the standard deviation in parentheses.

XL 300 spectrometer. A peak at δ 159 ppm was obtained corresponding to the guanidine carbon in phenylguanidine as compared to an authentic reference compound.

Results

The reactivity of ten aliphatic and aromatic amines (4-methoxyaniline, 4-methylaniline, aniline, 4-aminobenzamide, 4-aminoacetophenone, 4-nitroaniline, benzylamine, *n*-hexylamine, cyclohexylamine, and piperidine) toward [^{11}C]cyanogen bromide was studied in four different solvents, *i.e.*, 1-butanol, acetonitrile, toluene and dimethylformamide. [^{11}C]Cyanogen bromide was trapped directly into the amine solutions and after heating for 5 min, and a sample was analyzed by LC to determine the radiochemical yield of the respective [^{11}C]-cyanamides (Table 1). For the aromatic amines, the yield of cyanamide was lower in acetonitrile and toluene, whereas the aliphatic amines gave comparable results in toluene and lower yields in acetonitrile, as compared to 1-butanol. When running the reactions in dimethylformamide, the yields were lower for all amines and several side-products were obtained that were not found in any of the other solvents. For the aromatic amines, changing the substituent on aniline, from electron-withdrawing to electron-donating, increased the yield of cyanamide correlating to the basicity of the amine. For example, in 1-butanol the yield of cyanamide ranged from 0% for *p*-nitrophenylamine to 90% conversion for *p*-anisidine. The conversion to cyanamide was increased by longer reaction times for some amines, but due to the decay of ^{11}C it was not useful to prolong the reaction times.

An aliquot (10 μL) of the cyanamide reaction mixture was injected into the SFS system for the subsequent reaction with ammonia to form the guanidine compound. The ^{11}C-cyanamide solutions in 1-butanol, acetonitrile, and toluene were compared in the reaction with ammonia at 145 °C and 250 bar (Table 2). The use of 1-butanol gave the highest yields of ^{11}C-guanidine and was therefore used for all subsequent reactions. The substituents on aniline had less effect on the conversion from ^{11}C-cyanamide to ^{11}C-guanidine as compared to conversion from amine to ^{11}C-cyanamide. In 1-butanol, a 66−77% conversion from the corresponding cyanamide to guanidine was obtained, except for *p*-anisidine, which gave >90% yield. The aliphatic amines all gave considerably lower yields of ^{11}C-guanidine, and in some cases, no reaction took place.

The guanidine reactions were studied at a range of temperatures and pressures from 100−200 °C and 100−450 bars in the SFS system. At constant temperature, increasing the pressure also increased the yield of guanidine, but an even greater increase in yield was obtained by raising the temperature at any given pressure. The yields decreased markedly when the temperature and pressure was decreased below 125 °C and 150 bar, and highest yields overall were obtained at the temperature and pressure limits of the SFS system, *i.e.*, 200 °C and 450 bar (Table 2).

The conversion of ^{11}C-cyanamides to ^{11}C-guanidines was also performed in aqueous ammonia solutions, which is an option if no high pressure reaction vessel for ammonia is available. From the same solution of ^{11}C-cyanamide, 10 μL was injected into the SFS system (145 °C, 250 bar), and 200 μL was added to an equal volume of either of the two liquid ammonia solutions, *i.e.* 25% NH_4OH or 30% ammonium formate in 25% NH_4OH (Table 3). The reactions were performed for 5 min with each method. Generally, the SFS system afforded higher yields and provided a more practical procedure. In order for the reaction to proceed in the aqueous ammonia solutions, the septum-sealed reaction vessel must be heated to 80−120 °C (depending on the solvent used) upon which the ammonia evaporates from the solution under considerable pressure

Table 2. Radiochemical Yields of ^{11}C-Guanidines[a]

^{11}C-cyanamide	145 °C/250 bar			200 °C/450 bar 1-butanol
	1-butanol	acetonitrile	toluene	
4-methoxyphenyl[^{11}C]cyanamide	83 (6)	45 (25)	47 (20)	85 (1)
4-methylphenyl[^{11}C]cyanamide	45 (3)	20 (4)	23 (13)	67 (4)
phenyl [^{11}C]cyanamide	51 (12)	26 (4)	51 (23)	71 (2)
4-[^{11}C]cyanamidobenzamide	35 (7)	0	0	33(1)
4-acetyl phenyl[^{11}C]cyanamide	22 (6)	0	0	30 (4)
benzyl [^{11}C]cyanamide	35 (14)	17 (7)	12 (5)	36 (5)
n-hexyl [^{11}C]cyanamide	7 (1)	4 (3)	10 (4)	19 (14)
cyclohexyl [^{11}C]cyanamide	2 (2)	0	4 (1)	13 (9)
1-azacyclohexyl[^{11}C]cyanamide	0	0	0	2 (1)

[a] The radiochemical yields for conversion of [^{11}C]cyanogen bromide to ^{11}C-guanidines were calculated from the decay-corrected LC chromatograms. The mean value from four experiments are given with the standard deviation in parentheses.

Table 3. Reactivity of ^{11}C-Cyanamides in SC- and Aq-NH_3 Solutions[a]

^{11}C-cyanamide	SC-NH_3	25% NH_4OH	30% AMF/25% NH_4OH	solvent
4-methoxyphenyl[^{11}C]cyanamide	63		20	toluene
4-methoxyphenyl[^{11}C]cyanamide	87		25	BuOH
phenyl [^{11}C]cyanamide	41	4		BuOH
4-[^{11}C]cyanamidobenzamide	34	0		BuOH
n-hexyl [^{11}C]cyanamide	8	1	3	BuOH
n-hexyl [^{11}C]cyanamide	3	6	19	toluene
n-hexyl [^{11}C]cyanamide	6		0	MeCN

[a] Five min reactions were performed in either aqueous or supercritical ammonia. The radiochemical yields for conversion of [^{11}C]cyanogen bromide to ^{11}C-guanidines were calculated from the decay corrected LC chromatograms.

buildup, resulting in irreproducible results. In the automated SFS system on the other hand, the possibility to accurately control the reaction conditions and perform the reaction in a closed reaction cell gave reproducible results (Table 2).

To confirm the position of the ^{11}C-label in the guanidines a simultaneous synthesis of phenyl ($^{11/13}$C)guanidine was performed and the labeling position determined by ^{13}C-NMR. By performing the ^{13}C-synthesis in parallel with the ^{11}C-synthesis, the radionuclide was used for tracing the label in the purification and analysis of the product. The ^{13}C-NMR spectrum was compared to that of the authentic reference compound and showed one single peak at δ 159 ppm which corresponds to the guanidine carbon.

Discussion

The addition of reactants and solvents to ammonia in the SFS system affects the supercritical point of the mixture, as compared to pure ammonia. In an attempt to calculate the phase properties of the reaction mixtures the Peng−Robinson (PR) equation of state was chosen, a two-constant equation of state which has been shown to give improved predictions in the critical region.[21] The PR equation has been used mostly for nonpolar molecules, but since the polarity of ammonia decreases with increased temperature and the dielectric constant was between 2−6 at the reaction conditions used, compared to ca. 15 at room temperature, this equation seemed appropriate.[22] Also, when using the PR equation to calculate phase diagrams for ammonia/water mixtures, the results were comparable to published values.[23] Unfortunately, no experimental data for mixtures of ammonia with butanol, toluene, acetonitrile or dimethylformamide exist, that allow the interaction parameters for these mixtures to be calculated. Therefore, the interaction parameters were set to zero and the results obtained were only treated as approximate.

For every reaction, the same volume of ^{11}C-cyanamide solution was injected into the reaction cell and only the concentration of ammonia varied with temperature and pressure. Using radioactivity as a probe, the solvent solution was followed from the injection loops, to the cell and into the trapping solution, confirming that the entire reaction mixture had reached the reaction cell.

Phase envelopes were calculated for ammonia/solvent mixtures at various temperatures and pressures. The dew and bubble points for ammonia/butanol at 100, 145, and 200 °C are shown in Figure 3. In some regions the calculations did not converge, and the dew and bubble points were joined schematically (dotted lines). Below 200 °C no immiscibility was apparent and the mixture seems to follow class I phase behavior, i.e., the critical points of the pure components are continuously connected by a critical line.[24] This prediction was made on the data available from our calculations, and further experimental data are needed. Calculations were also performed on three-component systems, e.g., ammonia (9.325 mmol), butanol (0.107 mmol), and aniline (26.7 nmol), but the further changes in the phase calculations were negligible. The small amounts of reactants added into the cell were therefore neglected in the phase calculations.

For the mixture of ammonia/butanol, the molar ratio was calculated to be 9.390/0.109 at 125 °C/150 bar, 9.325/0.109 at 145 °C/250 bar and 8.633/0.109 at 200 °C/450 bar. In all cases the reaction cell contained more than 98 mol % ammonia. The phase envelope for 2 mol % butanol in ammonia is shown in Figure 4. At 145 °C/250 bar and 200 °C/450 bar, the conditions were well above and out of range of the uncertainties in the estimated critical point in the phase envelope, and these reactions were therefore predicted to be run in a homogeneous supercritical phase.

The increased yields obtained at 200 °C/450 bar were not an effect of higher ammonia concentration since this was actually lower under these conditions. Instead, the increase may be caused by increased rate constants at higher temperatures. At

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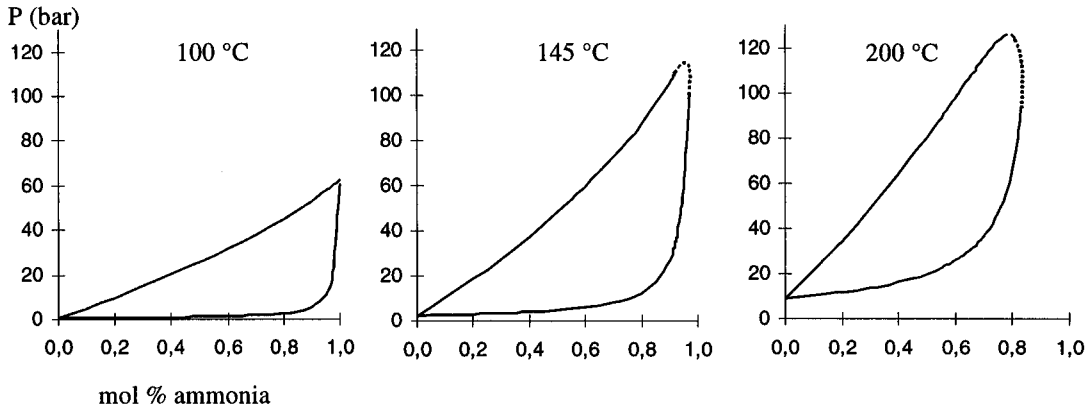

Figure 3. Phase diagrams of ammonia/1-butanol mixtures at 100, 145, and 200 °C. Calculations were based on the PR equation with the interaction parameters set to zero. In some regions the calculations did not converge, and the dew and bubble points were joined schematically (dotted lines).

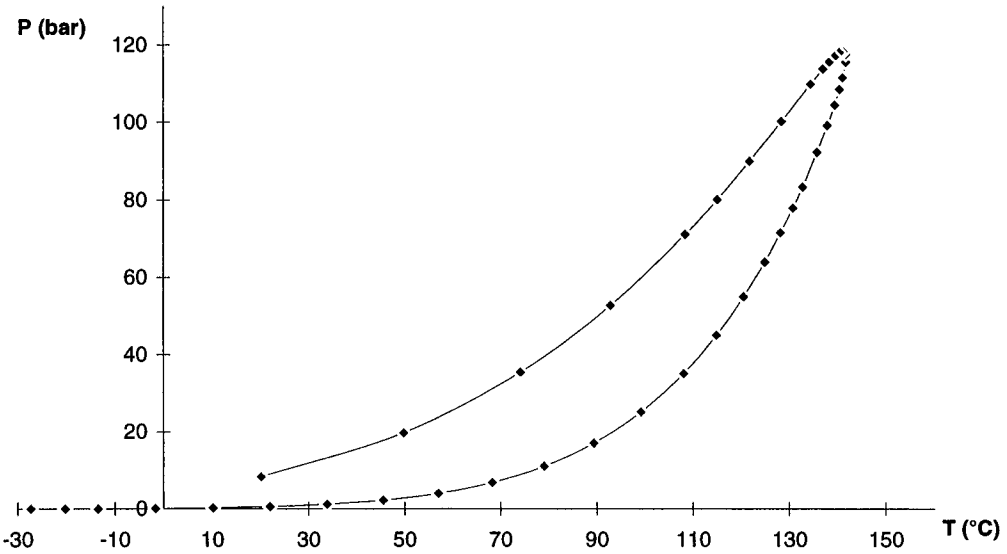

Figure 4. Phase envelope for 2% 1-butanol in ammonia. Calculations were based on the PR equation with the interaction parameters set to zero.

125 °C/150 bar, the reactions were run below the supercritical temperature of the mixture and the lower yields obtained at or below these conditions could either be an effect of lower temperature or from obtaining a two phase system.

Conclusions

In this work, we have demonstrated that by using supercritical ammonia as a reaction medium, we can produce ^{11}C-labeled monosubstituted guanidines in an efficient and reliable manner, and that the SFS system which has been developed can be used in practical applications. In the development of new methods and techniques for labeling of short-lived radionuclides, we are interested in utilizing the unique properties of supercritical fluids in synthesis combined with its use in chromatography. Work is now in progress to perform on-line preparative supercritical fluid chromatography (SFC) of the reaction mixture. After completion of the labeling reaction, the reaction cell can be used as an injection loop for injecting the entire reaction mixture directly onto an SFC column, using ammonia as the mobile phase. The on-line purification of the ^{11}C-labeled product will reduce the total reaction time of the synthesis, and, in addition, no product is lost when transferring the reaction mixture onto the SFC column.

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