

Supporting Information

Ureido-functionalization through amine-urea transamidation under mild reaction conditions

Natalia Guerrero-Alburquerque ^{1,2}, Shanyu Zhao ¹, Daniel Rentsch ³, Matthias M. Koebel ¹, Marco Lattuada ², Wim J. Malfait ^{1*}

¹ Laboratory for Building Energy Materials and Components, Swiss Federal Laboratories for Materials Science and Technology, Empa, Überlandstrasse 129, 8600 Dübendorf, Switzerland

² Department of Chemistry, University of Fribourg, Chemin du Musée 9, CH-1700 Fribourg, Switzerland

³ Laboratory for Functional Polymers, Swiss Federal Laboratories for Materials Science and Technology, Empa, Überlandstrasse 129, 8600 Dübendorf, Switzerland

* corresponding author: wim.malfait@empa.ch, +41 58 765 4983

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Section S1.

Synthesis conditions of experiments without catalysts

Table S1. Experimental conditions and pH before, during and after reaction. The pH measured directly in the reactant solution, either by pH strips reported with a precision of ± 0.5 or ± 1 ; pH values measured with a pH meter reported with a precision of 0.1. For the experiments with HCl/NaOH, acid/base solution was added until the targeted pH value was reached.

Reactant [v/v]	Reactant:Urea [molar ratio]	Solvent	T [°C]	pH initial	time [h]	pH after
Ethanolamine 10%	1:0.5	D ₂ O	80		48	11
Ethanolamine 10%	1:1	D ₂ O	80		48	11
Ethanolamine 10%	1:2	D ₂ O	80		48	11
Ethanolamine 10%	1:3	D ₂ O	80		48	11
Ethanolamine 10%	1:4	D ₂ O	80		48	11
Ethanolamine 10%	1:6	D ₂ O	80		48	11
Ethanolamine 2%	1:0.5	D ₂ O	80		48	
Ethanolamine 2%	1:1	D ₂ O	80		48	
Ethanolamine 2%	1:2	D ₂ O	80		48	
Ethanolamine 2%	1:3	D ₂ O	80		48	
Ethanolamine 2%	1:4	D ₂ O	80		48	
Ethanolamine 2%	1:6	D ₂ O	80		48	
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	1	48	1
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	2	48	2
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	3	48	3
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	4	48	4
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	5	48	6
Ethanolamine 2%	1:0.5	10% D ₂ O/ HCl sol	80	6	48	7
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	14	48	14
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	13	48	13
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	12	48	11
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	11	48	11
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	10	48	11
Ethanolamine 2%	1:0.5	10% D ₂ O/ NaOH sol	80	9	48	11
Ethanolamine 4.4%	1:0.5	H ₂ O/10% D ₂ O	80	10-11	1/2/3/4/5 weeks	

Ethanolamine 4.4%	1:0.5	H ₂ O/10% D ₂ O	80	11.0	0/1/2/4/8/12/24 /48/72/96 h - 7/8/10/14/16/18 /22/29/36/43/50 /57/64/80/92/11 4 days	
					-	-
Ethanolamine 3.7%	1:6	H ₂ O/10% D ₂ O	90	11.5	1	10.5
					2	10.5
					4	11.5
					6	11.5
					8	11.5
					12	11.5
					24	10.0
					46	9.5
Ethanolamine 3.7%	1:6	H ₂ O/10% D ₂ O	80	11.5	1	10.5
					2	10.5
					4	11.5
					6	11.5
					8	11.5
					12	11.5
					24	10.5
					46	9.5
Ethanolamine 3.7%	1:6	H ₂ O/10% D ₂ O	70	11.5	1	10.5
					2	10.5
					4	11.5
					6	11.5
					8	11.5
					12	11.5
					24	11.5
					46	10.5
Ethanolamine 3.7%	1:6	H ₂ O/10% D ₂ O	60	11.5	1	10.5
					2	10.5
					4	11.5
					6	11.5
					8	11.5
					12	11.5
					24	11.5
					46	11.0

Ethanolamine 3.7%	1:6	H ₂ O/10% D ₂ O	50	11.5	1	10.5
					2	10.5
					4	11.5
					6	11.5
					8	11.5
					12	11.5
					24	11.5
					46	11.0
Ethanolamine 3.7%	1:6	0% EtOH pure / 100% (H ₂ O/10% D ₂ O)	80	10.5	1	10.5
					2	10.5
					4	10.5
					6	10.5
					8	10.5
					12	10.5
					24	7.5
					48	9.0
Ethanolamine 3.7%	1:6	25% EtOH pure / 75% (H ₂ O/10% D ₂ O)	80	10.5	1	10.5
					2	10.5
					4	10.5
					6	10.5
					8	10.5
					12	10.5
					24	9.0
					48	9.0
Ethanolamine 3.7%	1:6	50% EtOH pure / 50% (H ₂ O/10% D ₂ O)	80	10.5	1	10.5
					2	10.5
					4	10.5
					6	10.5
					8	10.0
					12	10.0
					24	9.5
					48	9.0

Ethanolamine 3.7%	1:6	75% EtOH pure / 25% (H ₂ O/10% D ₂ O)	80	10.5	1	9.5
					2	9.5
					4	9.5
					6	9.5
					8	9.5
					12	10.0
					24	9.0
Ethanolamine 3.7%	1:6	90% EtOH pure / 10% D ₂ O	80	10.5	48	9.0
					1	9.5
					2	9.5
					4	9.5
					6	9.5
					8	9.5
					12	10.0
Ethanolamine 3.7%	1:6	100% EtOH pure / 0% D ₂ O (Addition of D ₂ O after the reaction)	80	7	24	9.0
					48	9.0
					1	7.5
					2	7.5
					4	7.7
					6	7.8
					8	7.9
Ethanolamine 3.7%	1:6	98% EtOH pure / 2% D ₂ O (Addition of D ₂ O after the reaction)	80	-	12	8.1
					24	8.4
					48	8.7
					1	11.0
					2	-
					4	-
					6	-
Ethanolamine 3.7%	1:6				8	-
					12	-
					24	-
					48	-

Ethanolamine 3.7%	1:6	95% EtOH pure / 5% D ₂ O (Addition of D ₂ O after the reaction)	80	-	1	11.0
					2	11.7
					4	11.7
					6	11.7
					8	11.6
					12	11.6
					24	11.3
Ethanolamine 3.7%	1:6	90% EtOH pure / 10% D ₂ O (Addition of D ₂ O after the reaction)	80	10.5	48	11.2
					1	11.0
					2	11.8
					4	11.7
					6	11.7
					8	11.6
					12	11.6
Hexamethylenediamine 3.6%	1:12	H ₂ O/10% D ₂ O	80	13	24	11.3
					48	11.2
					1	12.5
					2	12.5
					4	12.0
					8	12.0
					12	12.0
Bis-(Hexamethylene)triamine 3.9%	1:18	H ₂ O/10% D ₂ O	80	13	24	10.0
					48	10.0
					1	12.5
					2	12.5
					4	12.0
					8	12.0
					12	11.5
5-amino-1-pentanol 4.1%	1:6	H ₂ O/10% D ₂ O	80	11.5	24	10.0
					48	10.0
					1	12.0
					2	12.0
					4	11.9
					8	11.7
					12	11.4
					24	10.6
					48	10.3

N,N'-Dimethyl-1,3-propanediamine 3.6%	1:6	H ₂ O/10% D ₂ O	80	12.5	1	12.5
					2	12.2
					4	12.0
					8	11.7
					12	11.3
					24	10.8
					48	10.5
Glycine 2.6%	1:6	H ₂ O/10% D ₂ O	80	7	1	7.5
					2	7.5
					4	7.7
					8	7.9
					12	8.0
					24	8.3
					48	8.6
Pyrrole 3.8%	1:6	H ₂ O/10% D ₂ O	80	-	-	-

Section S2. Synthesis conditions of experiments with catalysts

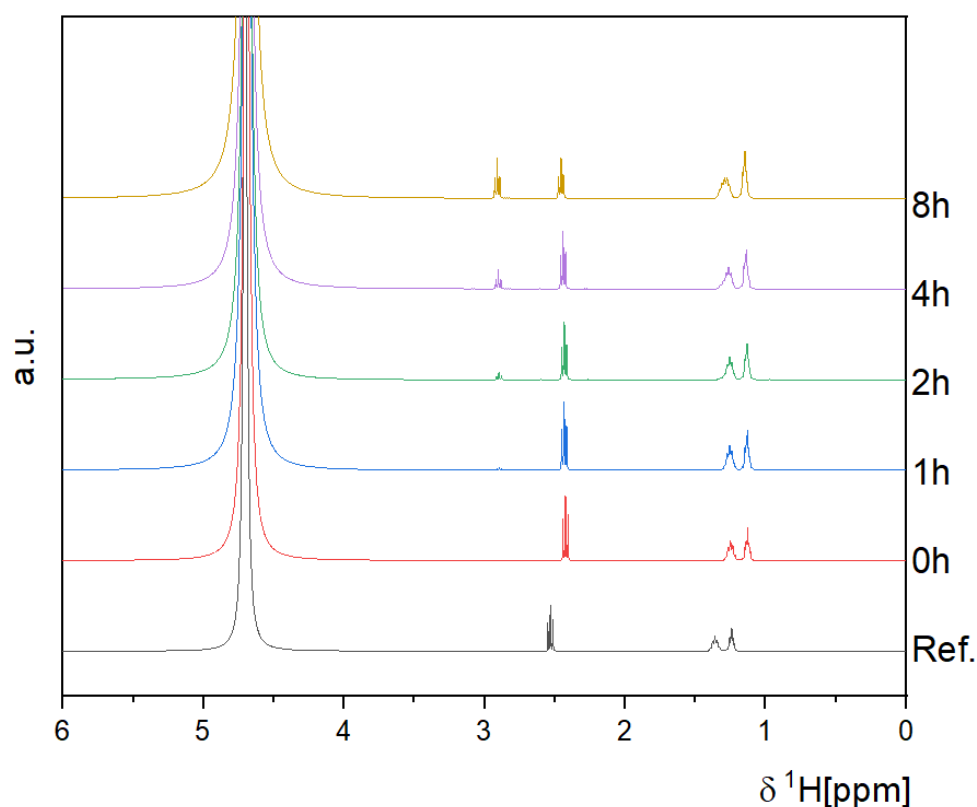
Table S2. Synthesis conditions for the experiments with catalysts: reactant, buffer and catalyst concentrations, solvent composition, pH, temperature and time. The reference pH corresponds to the pH value of the solutions before adding the catalyst. The pH measured directly in the reactant solution, either by pH strips reported with a precision of ± 0.5 or ± 1 ; pH values measured with a pH meter reported with a precision of 0.1.

Reactant [v/v]	Reactant:Urea [molar ratio]	Catalyst [mg]	Solvent	Solution [mL]	HEPES [M]	Ref. pH _i - pH _f	pH _i	pH _f	T [°C]	time [h]
Ethanolamine 5%	1:0.5	Urease 0.45	H ₂ O/10% D ₂ O	2	-		10	10	37	24
Ethanolamine 0.5%	1:0.5	Urease 0.19	HEPES H ₂ O / 10% D ₂ O	5	0.5	6.5-7	6.5	7	37	24
Ethanolamine 0.5%	1:0.5	Urease 0.38	HEPES H ₂ O / 10% D ₂ O	5	0.5	6.5-7	6.5	7/8*	37/50 *	24/24 *
Ethanolamine 0.5%	1:0.5	Urease 0.56	HEPES H ₂ O / 10% D ₂ O	5	0.5	6.5-7	6.5	7/8*	37/50 *	24/24 *
Ethanolamine 0.5%	1:0.5	Urease 0.75	HEPES H ₂ O / 10% D ₂ O	5	0.5	6.5-7	6.5	7/8*	37/50 *	24/24 *
Ethanolamine 1.5%	1:0.5	Urease 2.26	HEPES H ₂ O / 10% D ₂ O	5	0.5	8-8	8	8.5	37	24
Ethanolamine 1.5%	1:0.5	Urease 5.65	HEPES H ₂ O / 10% D ₂ O	5	0.5	8-8	8.5	9	37	24
Ethanolamine 1.5%	1:0.5	Urease 5.65	H ₂ O/ 10% D ₂ O	5	-	11-11	11	10	37	24
Ethanolamine 1.5%	1:0.5	Urease 5.65	HEPES H ₂ O / 10% D ₂ O	5	0.5	8-8	8	8.5	80	24
Ethanolamine 5%	1:0.5	DBTL 11.31	MeOH/10% CD ₃ OD	5					60	24/48
Ethanolamine 5%	1:0.5	DBTL 3.76	MeOH/10% CD ₃ OD	5					60	24/48
Ethanolamine 5%	1:0.5	DBTL 1.13	MeOH/10% CD ₃ OD	5					60	24/48
Ethanolamine 5%	1:0.5	DBTL 0.0	MeOH/10% CD ₃ OD	5					60	24/48
Ethanolamine 5%	1:0.5	DABCO 11.31	H ₂ O/10% D ₂ O	5					80	24/48

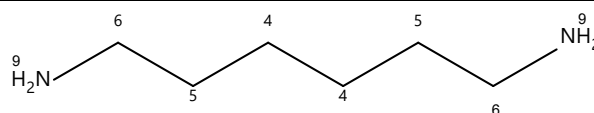
Ethanolamine 5%	1:0.5	DABCO 3.76	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	DABCO 1.13	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	DABCO 0	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	p-TSA 11.31	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	p-TSA 3.76	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	p-TSA 1.13	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	p-TSA 0	H ₂ O/10% D ₂ O	5	80	24/48
Ethanolamine 5%	1:0.5	TEA 11.31	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	TEA 3.76	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	TEA 1.13	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	TEA 0	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	Al(acac) ₃ 11.31	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	Al(acac) ₃ 3.76	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	Al(acac) ₃ 1.13	MeOH/10% CD ₃ OD	5	60	24/48
Ethanolamine 5%	1:0.5	Al(acac) ₃ 0	MeOH/10% CD ₃ OD	5	60	24/48

**After the first 24h, the temperature of the reaction was increased to 50 °C and it was kept additionally at this temperature another 24h.*

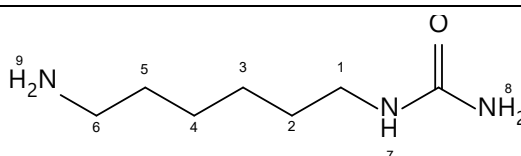
Section S3. NMR spectra and assignment



hexamethylenediamine



(6-aminohexyl)urea



1,1'-(hexamethylene)diurea

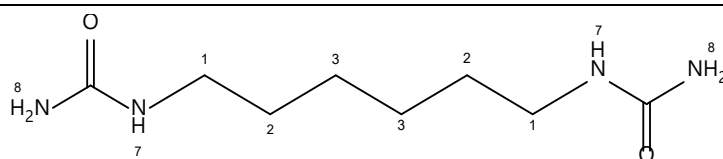
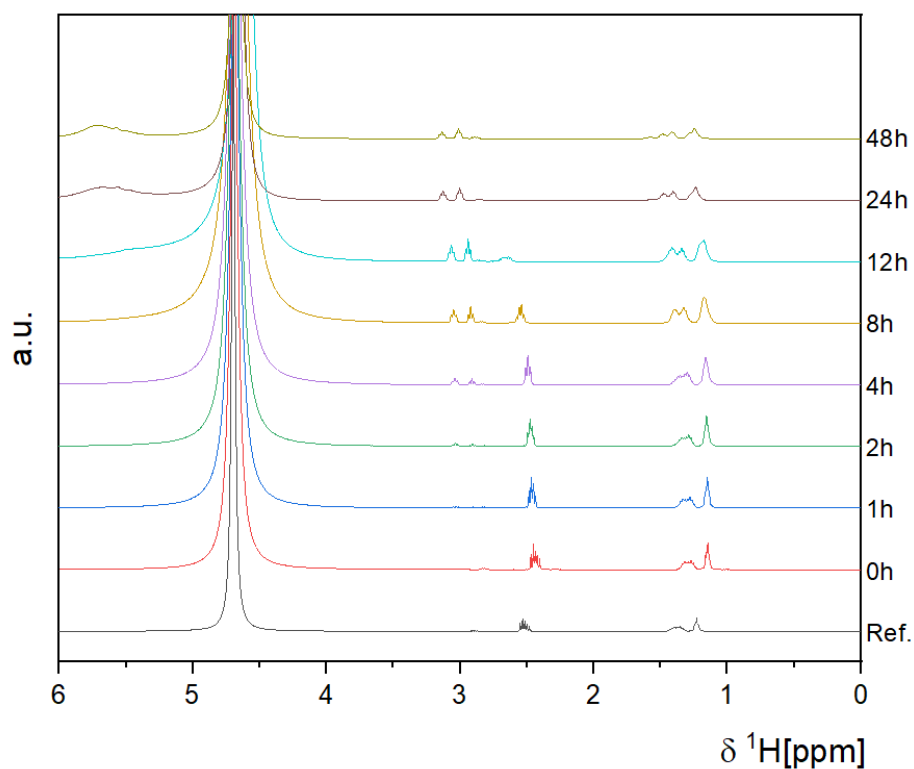
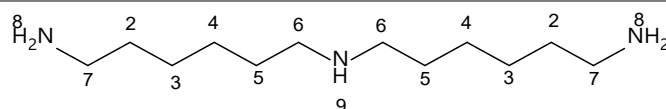


Figure S1. ^1H NMR spectra and numbering of positions of the products of hexamethylenediamine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of hexamethylenediamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 12-fold urea excess (hexamethylenediamine:urea 1:12).

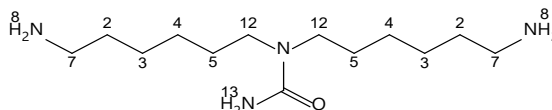
^1H NMR parameters derived from the spectrum collected after 8 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ^1H -NMR (400.2 MHz, 10% $\text{D}_2\text{O}/\text{H}_2\text{O}$, 298K): δ = 2.91 (t, J =7.0, 2H, H1), 2.45 (t, J =7.7, 2H, H6), 1.28 (m, 8H, H2,H5), 1.15 (m, 4H, H3&H4).



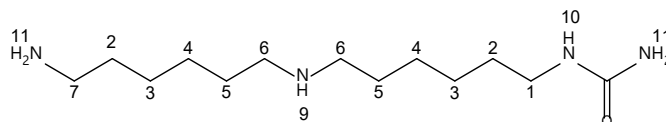
bis-(hexamethylene)
triamine



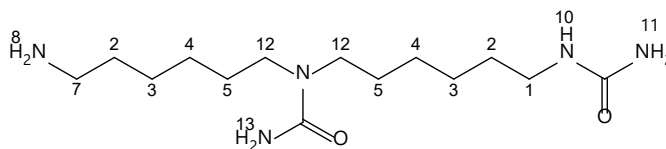
1,1-bis(6-aminohexyl)urea



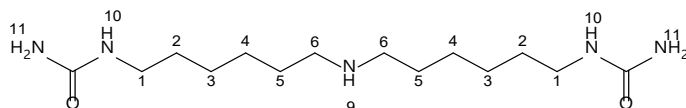
1-(6-(6-amino)hexyl)amino)hexylurea



1-(6-amino)hexyl)-1-(6-ureido)hexyl)urea



1,1'-(azanediylbis(hexane-6,1-diyl))diurea



1,1-bis
(6-ureido)hexyl)urea

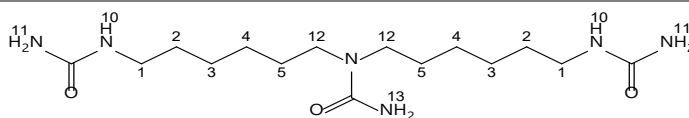
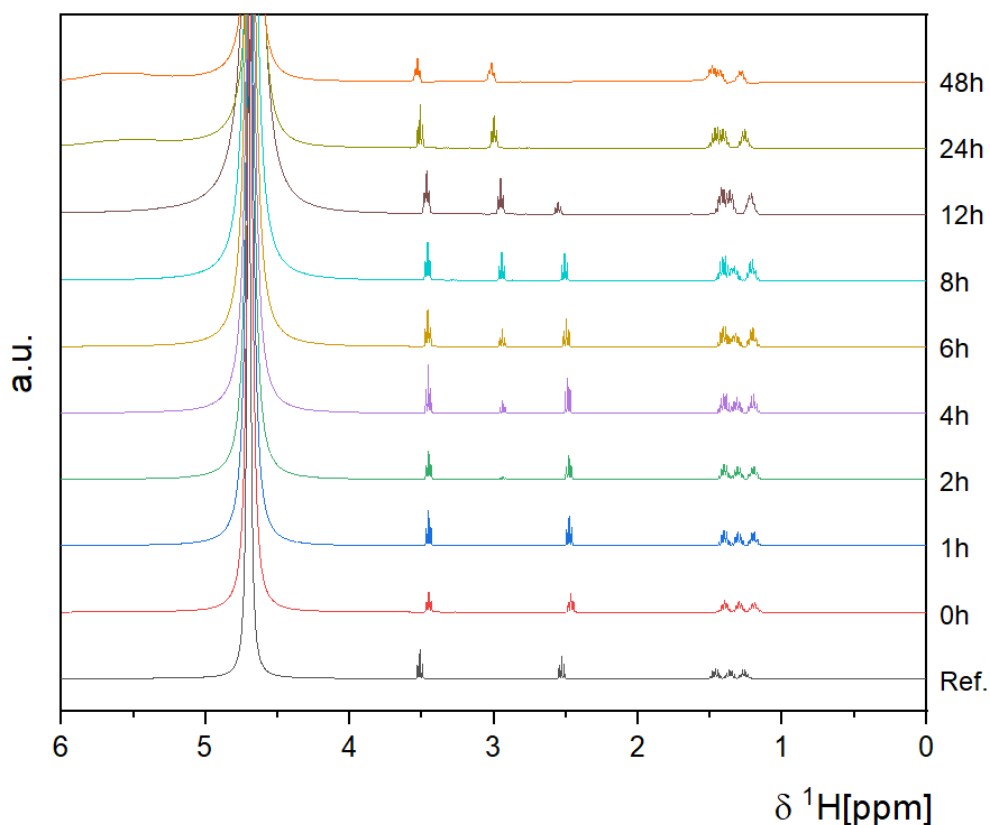
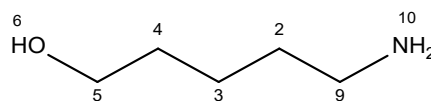


Figure S2. ^1H NMR spectra and numbering of positions of the possible reaction products of bis-(hexamethylene)triamine with urea. The reaction was conducted at 80 °C with 5%v/v of bis-(hexamethylene)triamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 18-fold urea excess with respect to the urea:amine ratio, corresponding to (bis-(hexamethylene)triamine:urea 1:18). Note that the H2, H3, H4 and H5 protons of the possible reaction products all overlap into single multiplets.

^1H NMR parameters derived from the spectrum collected after 24 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ^1H -NMR (400.2 MHz, 10% $\text{D}_2\text{O}/\text{H}_2\text{O}$, 298K): δ = 3.12 (t, J =7.2, 4H, H12), 3.00 (t, J =6.4, 4H, H1), 2.85 (t, J = 7.7, impurity), 1.56 (t, J =6.9, 4H, H5), 1.47 (t, J =6.1, 4H, H2), 1.40 (t, J =6.5, 4H, H3), 1.24 (s broad, 4H, H4).



5-amino-1-pentanol



1-(5-hydroxypentyl)urea

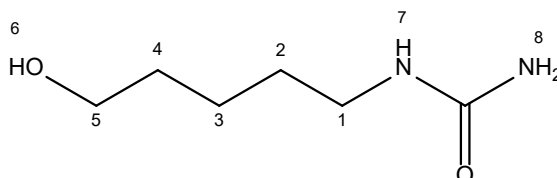
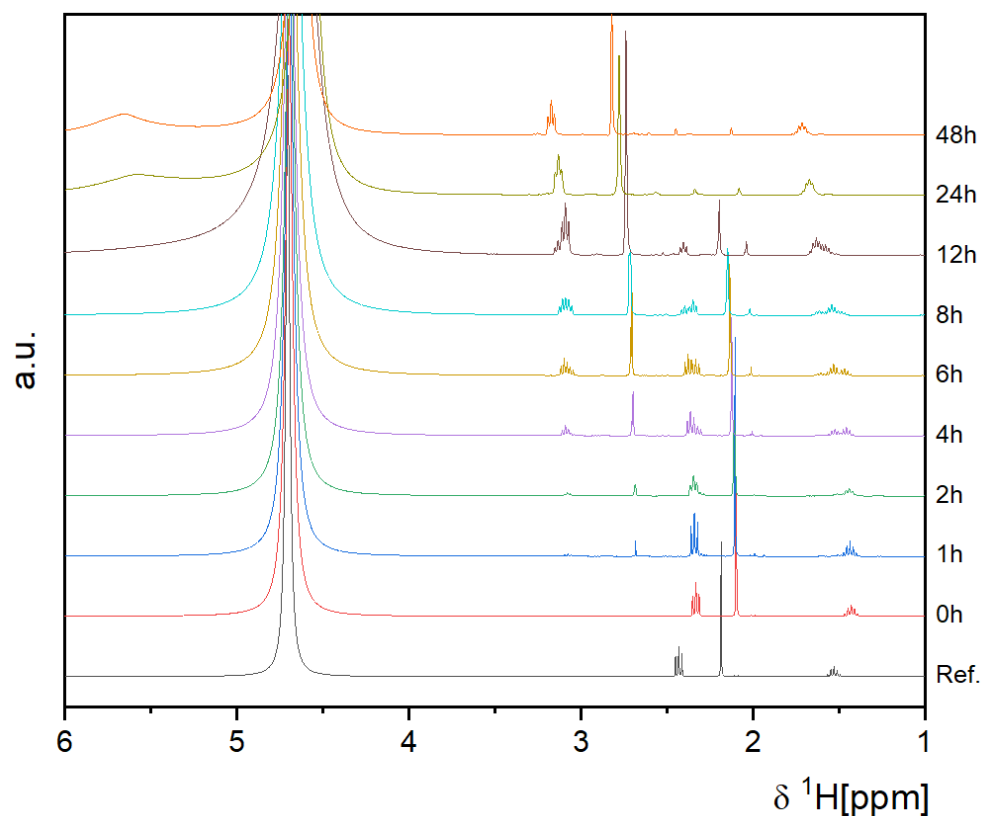
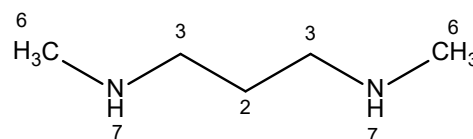


Figure S3. ^1H NMR spectra and numbering of positions of the possible reaction products of 5-amino-1-pentanol after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of 5-amino-1-pentanol in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 6-fold urea excess (5-amino-1-pentanol:urea 1:6).

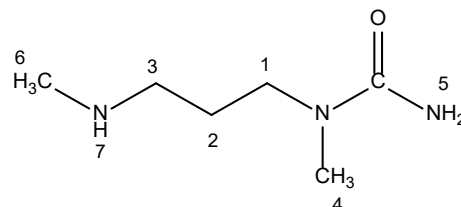
^1H NMR parameters derived from the spectrum collected after 24 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ^1H -NMR (400.2 MHz, 10% $\text{D}_2\text{O}/\text{H}_2\text{O}$, 298K): δ = 3.51(*t*, J =6.57, CH_2 , 2H, H5), 2.99(*t*, J =6.89, CH_2 , 2H, H1), 2.75 (*t*, J = 7.45, CH_2 , 2H, H9), 1.46 (*quint*, J =7.12, CH_2 , 2H, H4), 1.41(*quint*, J =7.43, CH_2 , NH_2 , 2H, H2,H7), 1.25 (*quint*, J = 8.02, CH_2 , 2H, H3)



n,n'-dimethyl-1,3-propanediamine



1-methyl-1-(3-(methylamino)propyl)urea



1,1'-(propane-1,3-diyl)bis(1-methylurea)

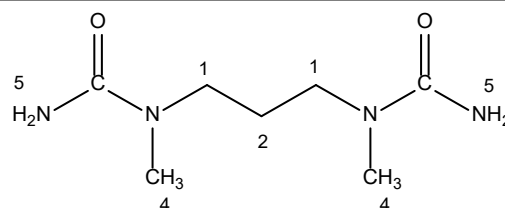
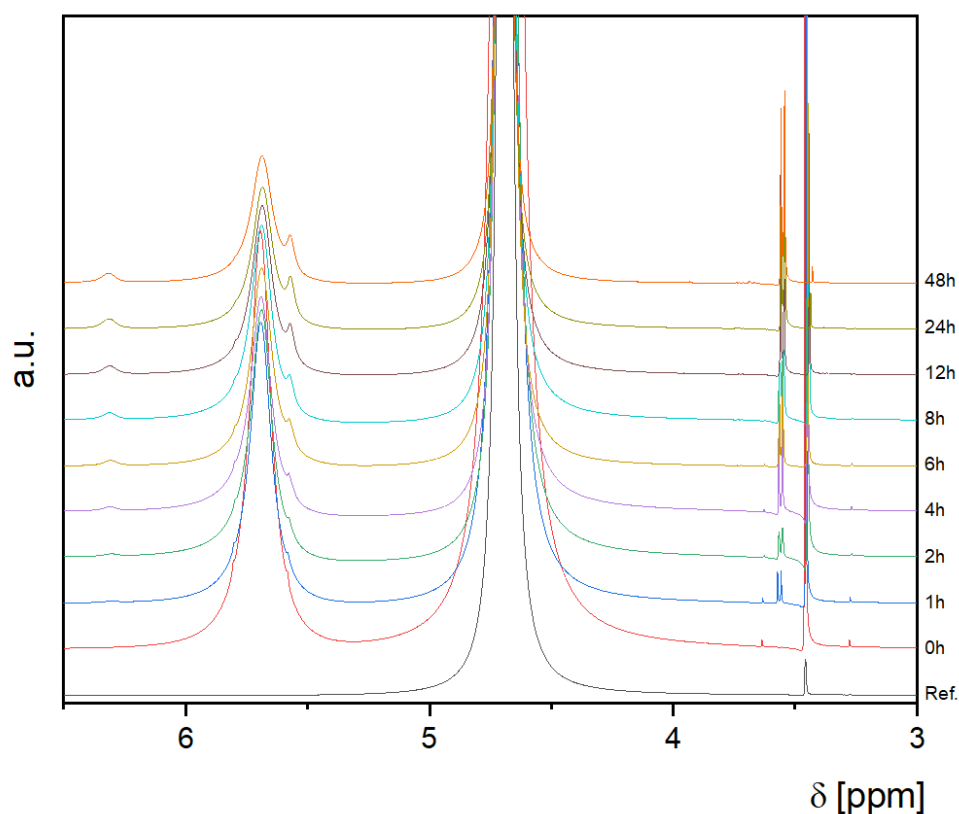
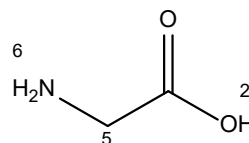


Figure S4. ^1H NMR spectra and numbering of positions of the possible reaction products of *N,N'*-dimethyl-1,3-propanediamine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of *N,N'*-dimethyl-1,3-propanediamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 12-fold urea excess (*N,N'*-dimethyl-1,3-propanediamine:urea 1:12).

^1H NMR parameters derived from the spectrum collected after 24 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ^1H -NMR (400.2 MHz, 10% $\text{D}_2\text{O}/\text{H}_2\text{O}$, 298K): δ = 3.16(t, J = 7.47, CH_2 , 2H, H1), 2.80 (s, CH_3 , 3H, H4&H6), 2.34 (s, CH_2 , 2H, H3), 1.70 (quint, J =7.31, CH_2 , 2H, H2)



glycine



hydantoic acid

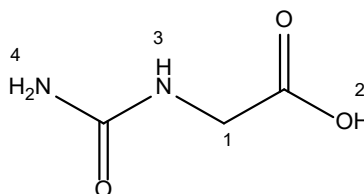
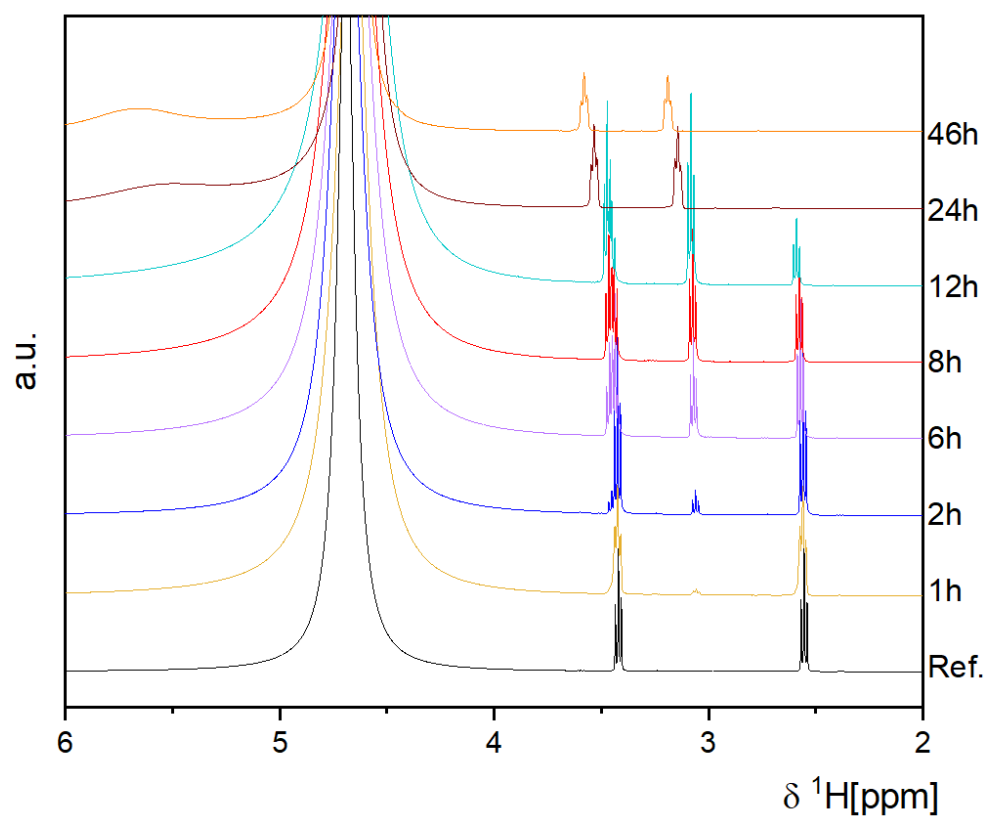
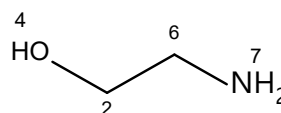


Figure S5. ¹H NMR spectra and numbering of positions of the possible reaction products of glycine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of glycine in H₂O/D₂O and with a 6-fold urea excess (glycine:urea 1:6).

¹H NMR parameters derived from the spectrum collected after 24 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ¹H-NMR (400.2 MHz, 10% D₂O/H₂O, 298K): δ= 6.33 (s, NH, 1H, H3), 3.54 (d, J= 5.91, 2H, H1), 3.43 (s, 2H, H5). The resonance of H-1 at δ= 3.54 is split into a doublet due to the coupling with H-3 of the ureido group, which under the measuring conditions shows slow chemical exchange with water (broadening of NH resonance at 6.33 ppm). In a ¹H-¹H DQF-COSY NMR spectrum the expected cross peak of H-1 to the NH proton was clearly observed.



ethanolamine



2-hydroxyethyl urea

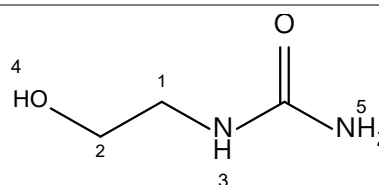


Figure S6. ¹H NMR spectra and numbering of positions of the possible reaction products of ethanolamine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of ethanolamine in H₂O/D₂O and with a 6-fold urea excess (ethanolamine:urea 1:6)

¹H NMR parameters derived from the spectrum collected after 24 h of reaction. The peak positions shift at different reaction times because of changes in pH, hence, only the peak positions relative to each other are considered relevant: ¹H-NMR (400.2 MHz, 10% D₂O/H₂O, 298K): δ=, 3.52 (t, J= 5.56, 2H, H₂), 3.15 (t, J= 5.50, 2H, H₁), 2.65(t, J= 5.61, 2H, H₆)

Section S4. Information Monte Carlo simulation

Matlab code for Monte Carlo simulation of expected concentrations of hexamethylenediamine, (6-aminoethyl)urea and 1,6-(hexamethylene)diurea as a function of reaction progress.

```
a0start=100000;           % number of hexamethylenediamine molecules
a0=a0start; a1=0; a2=0;    % starting concentrations
for i=1:2*a0start
    if rand<1.0*a1/(a1+a0) % set probability to calculate
        a1=a1-1; a2=a2+1; % conversion of a1 into a2
    else
        a0=a0-1; a1=a1+1; % conversion of a0 into a1
    end
    a0s(i)=a0; a1s(i)=a1; a2s(i)=a2; % log concentrations
end
pma=(a1s+2*a2s)/a0start; % calculate average reaction progressio
```

Section S5. Effect of pH in the reaction of ethanolamine:urea

The effect of pH on the ethanolamine:urea (ratio 1:0.5) reaction to form (2-hydroxyethyl)urea was studied after 48h hours at 80 °C in solution. Experiments were carried out after adjustment of the initial pH with either HCl or NaOH solutions, depending on the target pH.

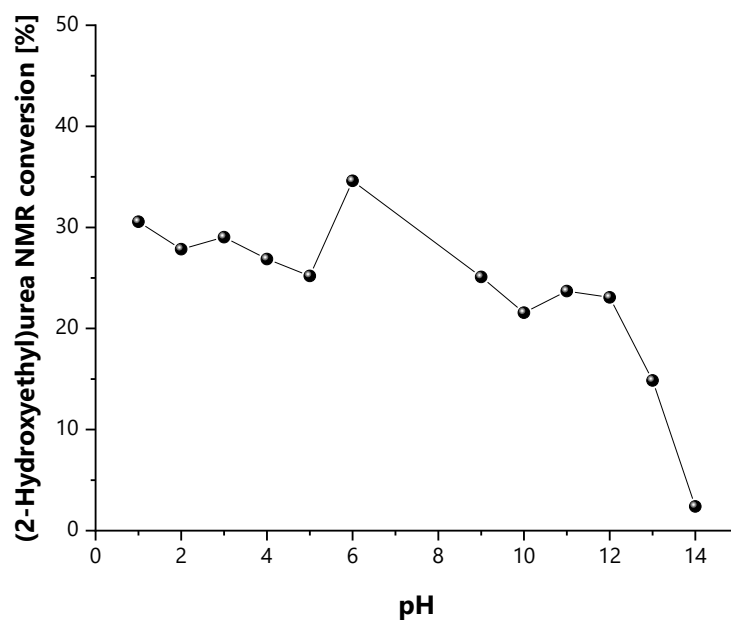


Figure S7. pH study of (2-hydroxyethyl)urea NMR conversion as a function of pH. The reaction with 2% v/v of ethanolamine in H_2O/D_2O , and ethanolamine:urea ratio of 1:0.5 were conducted at 80 °C for 48h.

Section S6. Catalyst screening for the ethanolamine:urea reaction

Group 1: Water compatible catalysts.

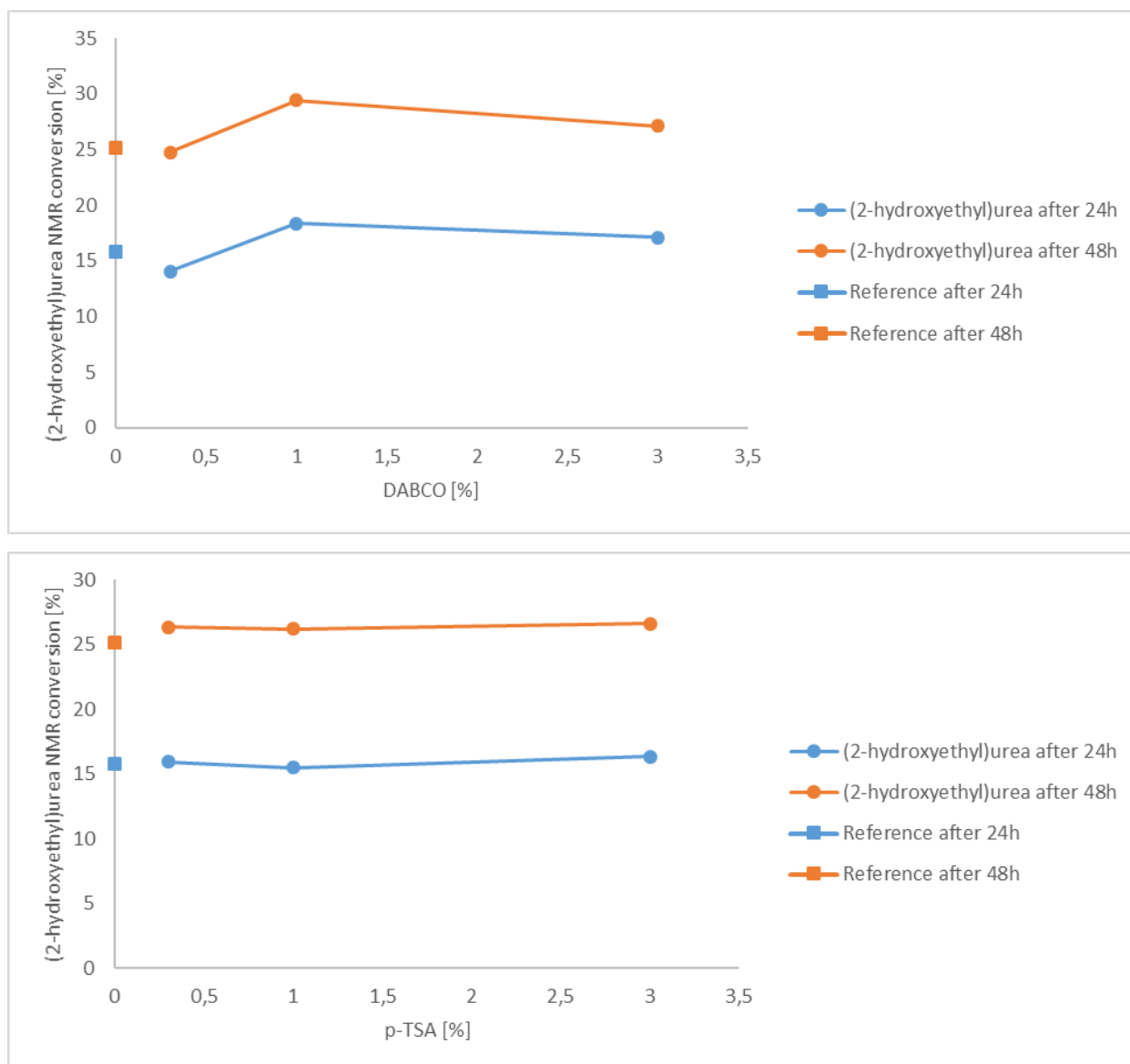


Figure S8. NMR conversion as a function of catalyst concentration. Group 1: The reactions were conducted with 5% v/v ethanolamine in H_2O/D_2O at 80 °C (ethanolamine:urea 1:0.5)

Group 2: Water incompatible catalysts: reaction in methanol.

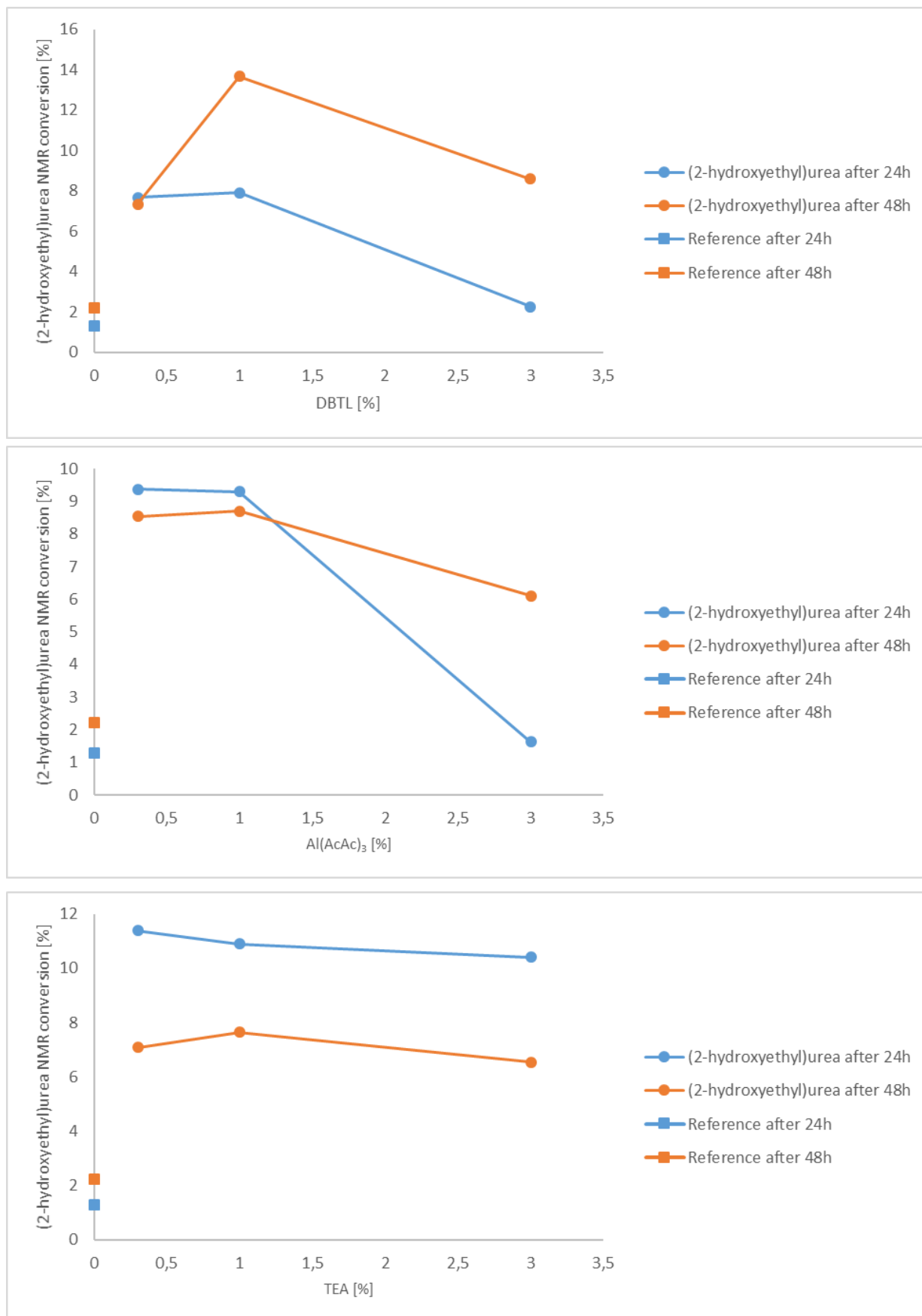


Figure S9. NMR conversion as a function of catalyst concentration. Group 2: The reactions were conducted with 5% v/v ethanolamine in methanol at 60 °C (ethanolamine:urea 1:0.5)

Section S7. Effect of the temperature on ethanolamine:urea reaction

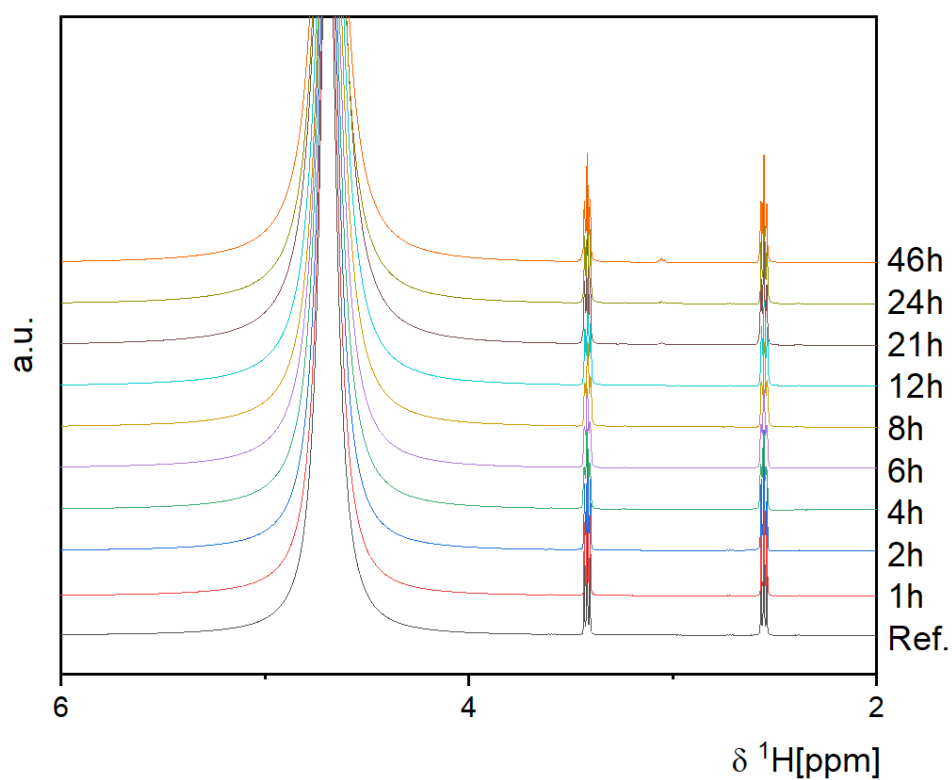


Figure S10. ^1H NMR spectra of experiment with 5% v/v ethanolamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ with a ratio of ethanolamine:urea 1:6 at 50 °C.

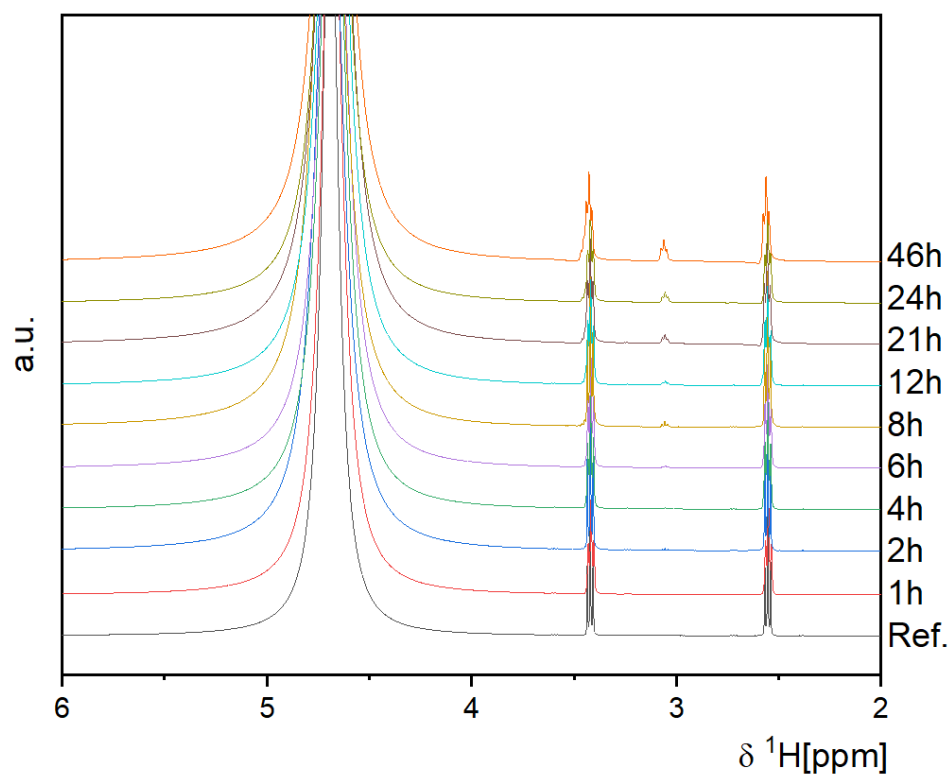


Figure S11. ^1H NMR spectra of experiment with 5% v/v ethanolamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ with a ratio of ethanolamine:urea 1:6 at 60 °C.

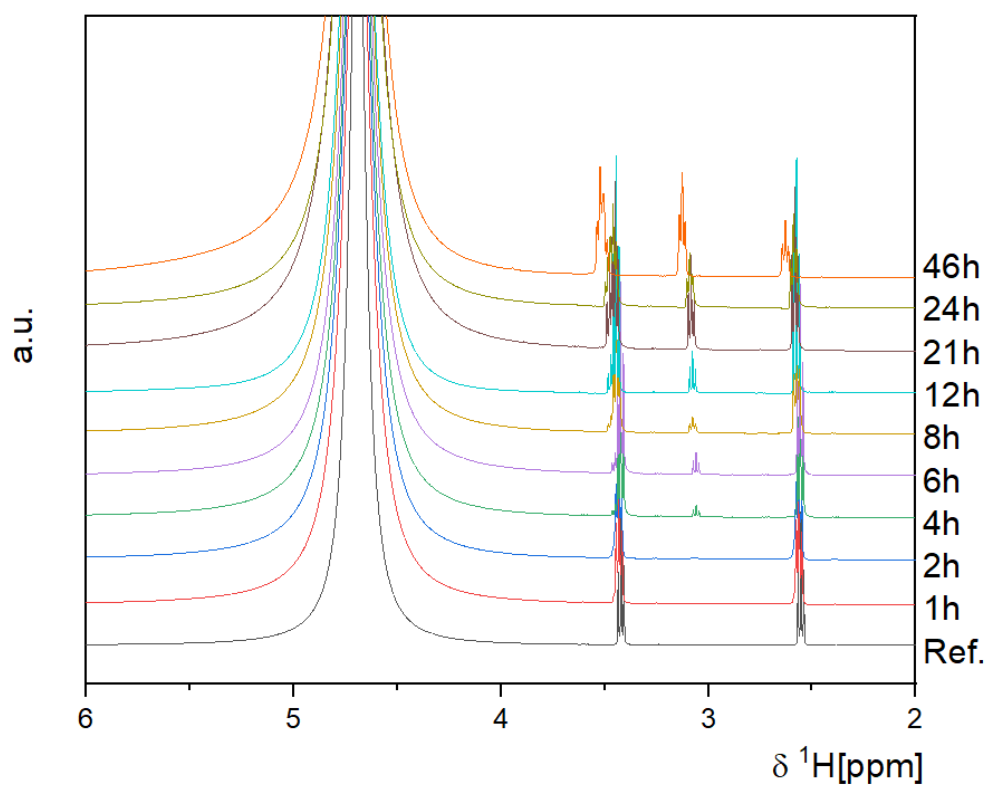


Figure S12. ^1H NMR spectra of experiment with 5% v/v ethanolamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ with a ratio of ethanolamine:urea 1:6 at 70 °C.

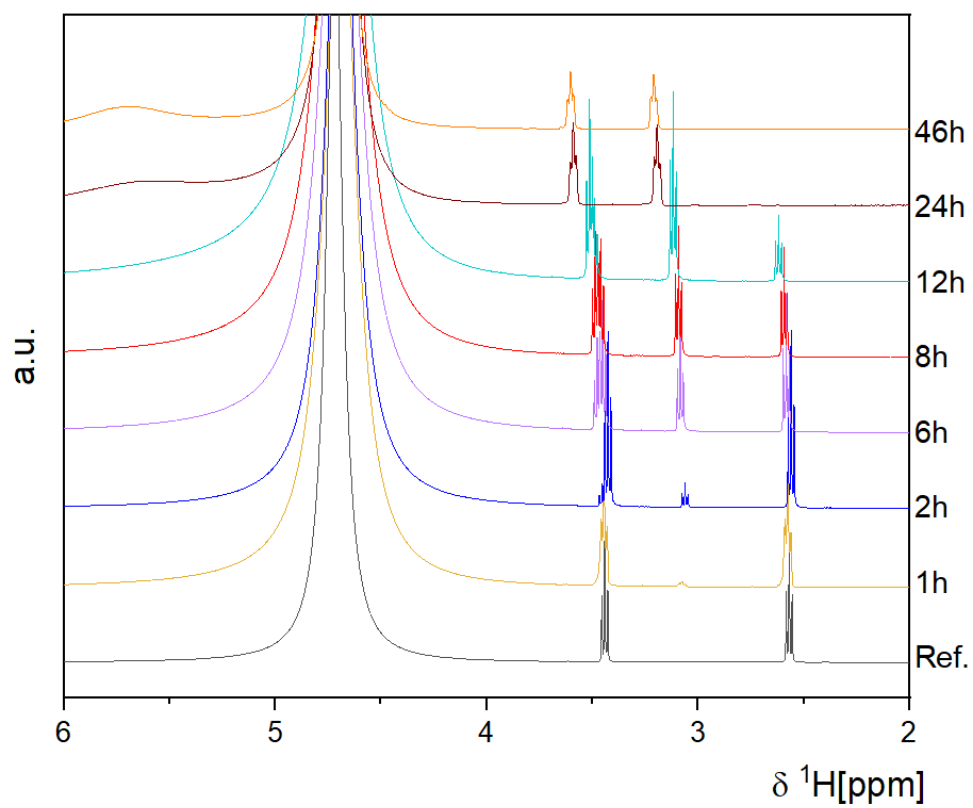


Figure S13. ^1H NMR spectra of experiment with 5% v/v ethanolamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ with a ratio of ethanolamine:urea 1:6 at 80 °C.

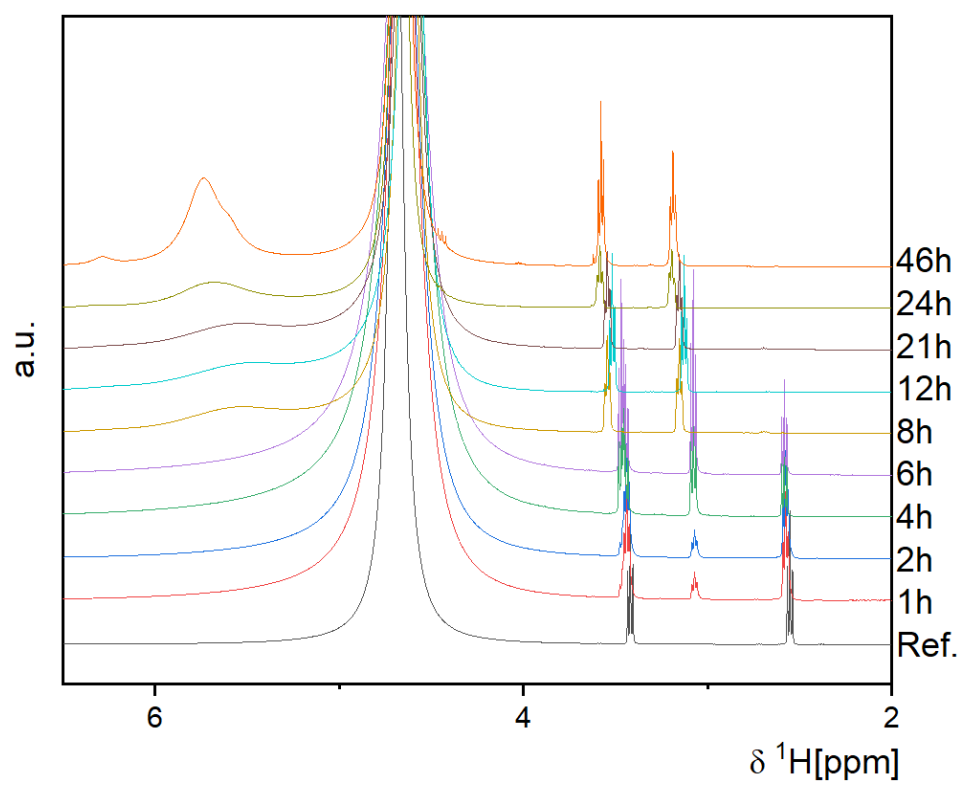


Figure S14. ^1H NMR spectra of experiment with 5% v/v ethanolamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ with a ratio of ethanolamine:urea 1:6 at 90 °C.

Section S8. Effect of the solvent on ethanolamine:urea reaction

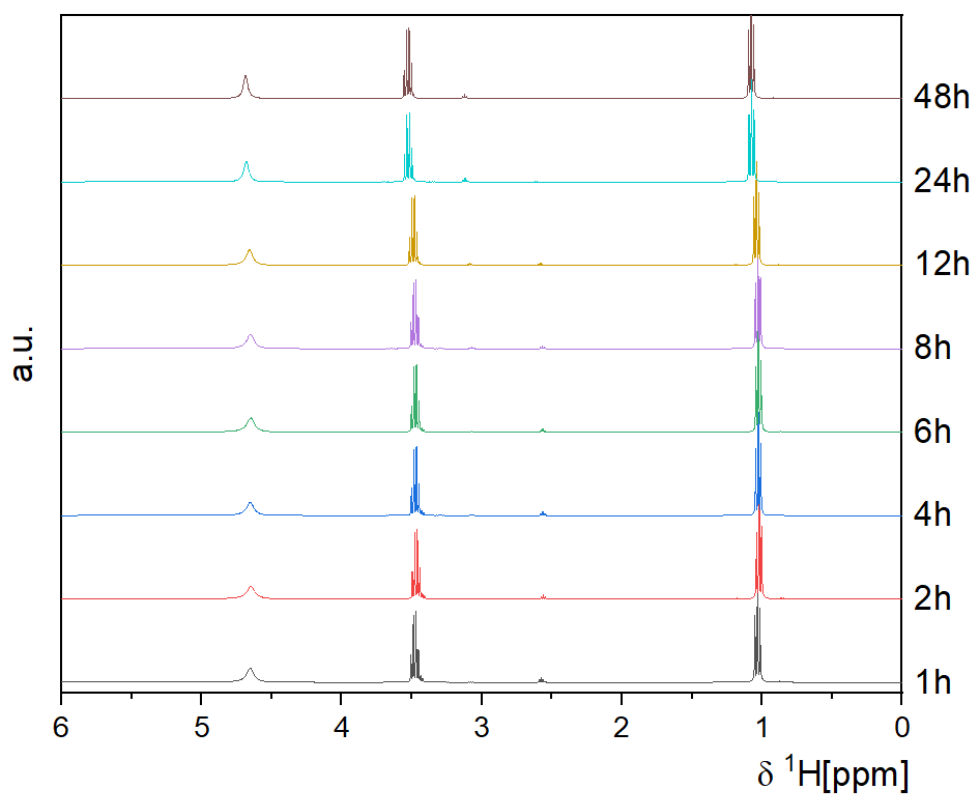


Figure S15. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 100% EtOH / 0% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 °C.

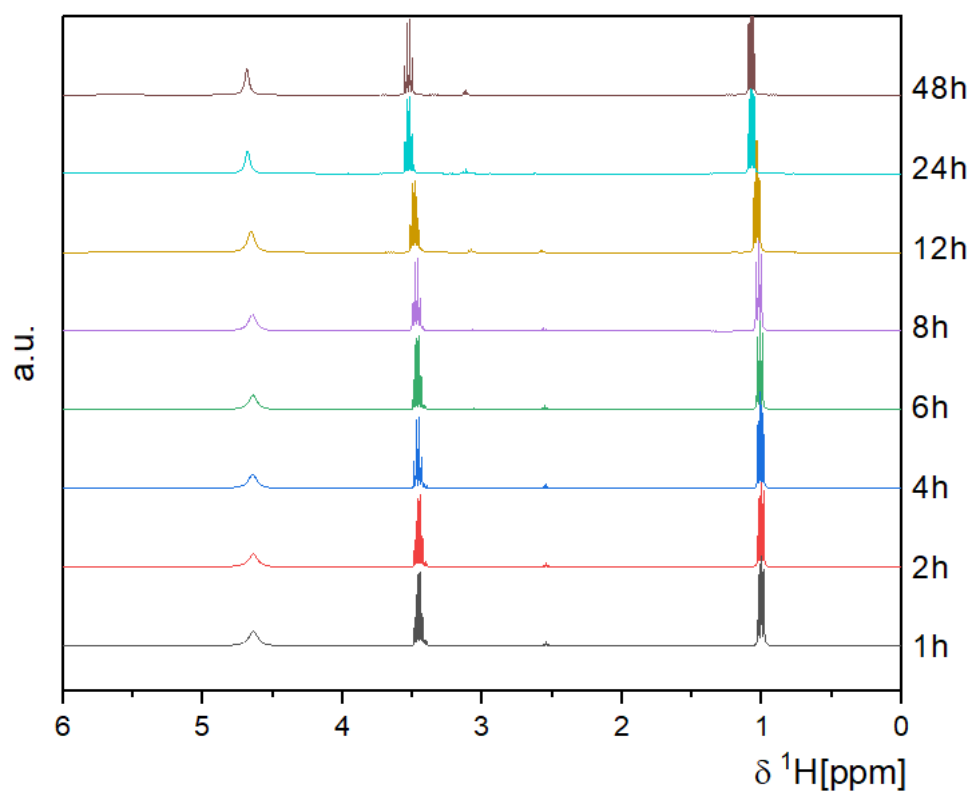


Figure S16. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 98% EtOH / 2% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 $^\circ\text{C}$.

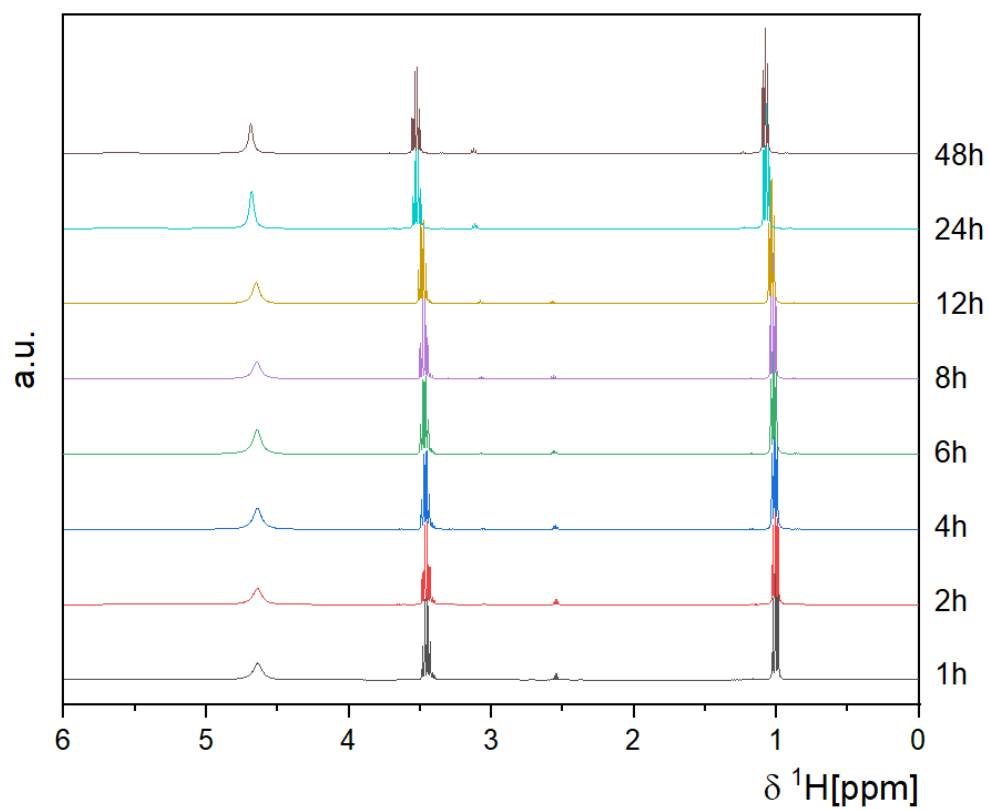


Figure S17. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 95% EtOH / 5% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 $^\circ\text{C}$.

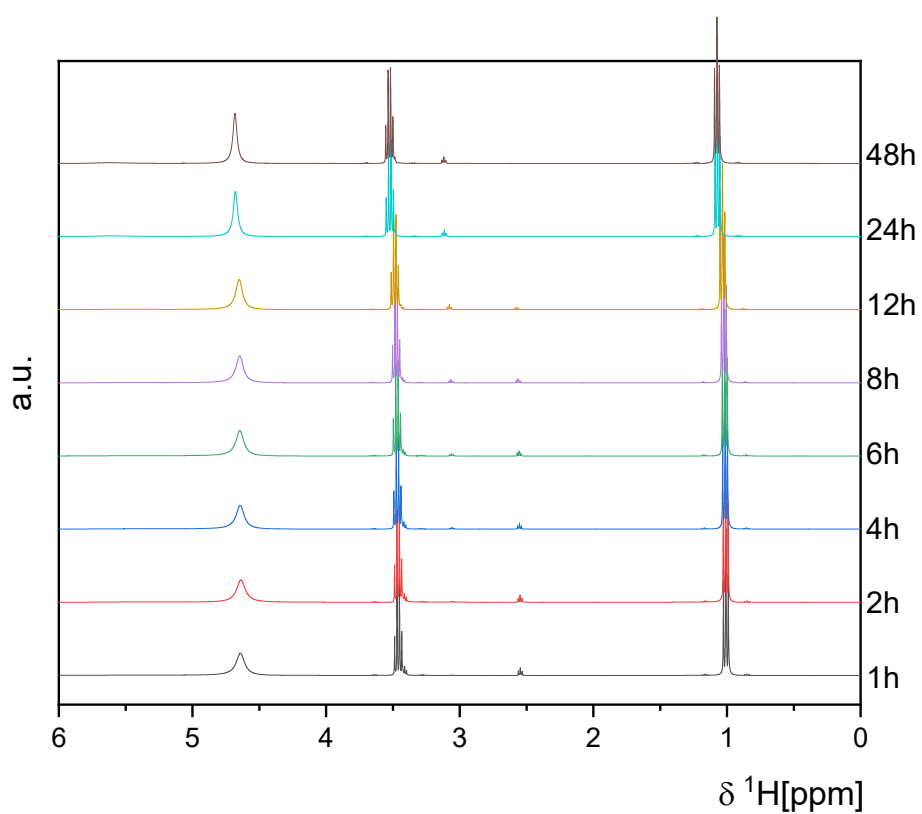


Figure S18. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 90% EtOH / 10% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 °C.

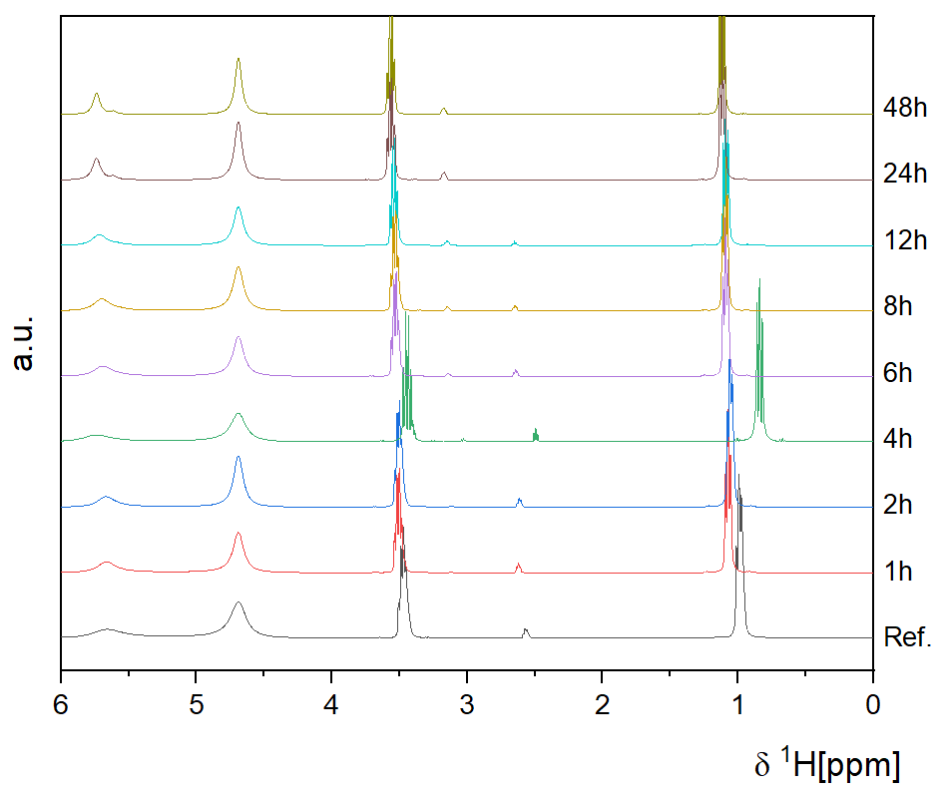


Figure S19. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 75% EtOH / 25% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 °C.

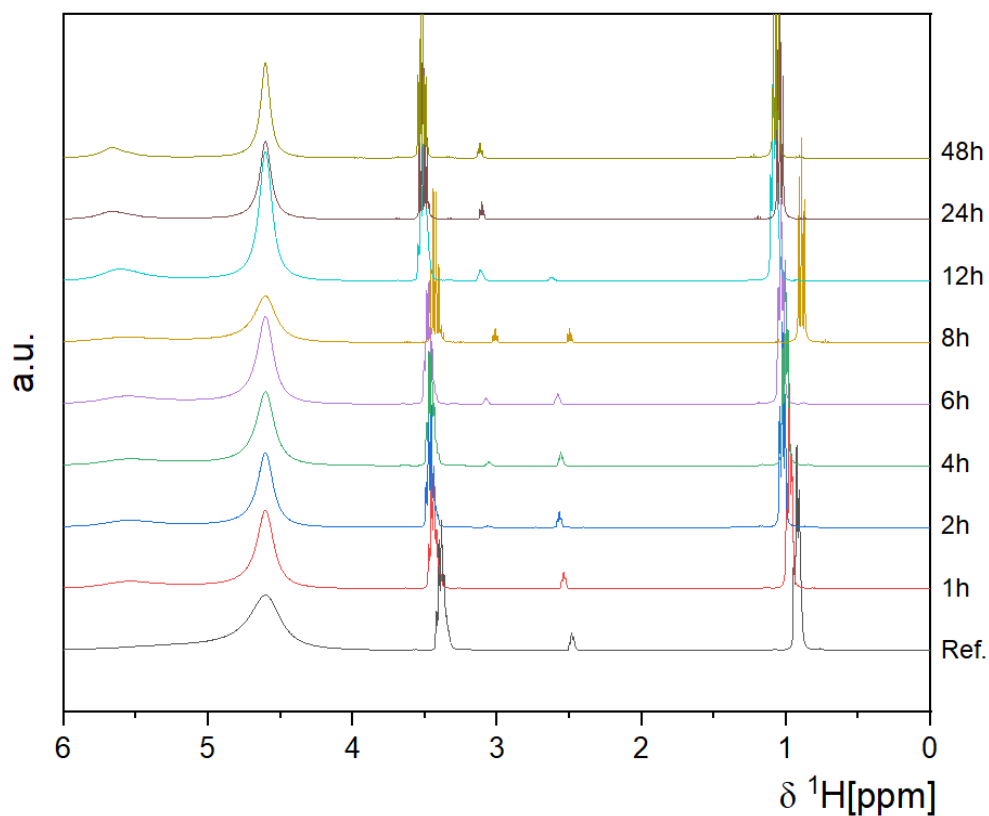


Figure S20. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 50% EtOH / 50% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 $^\circ\text{C}$.

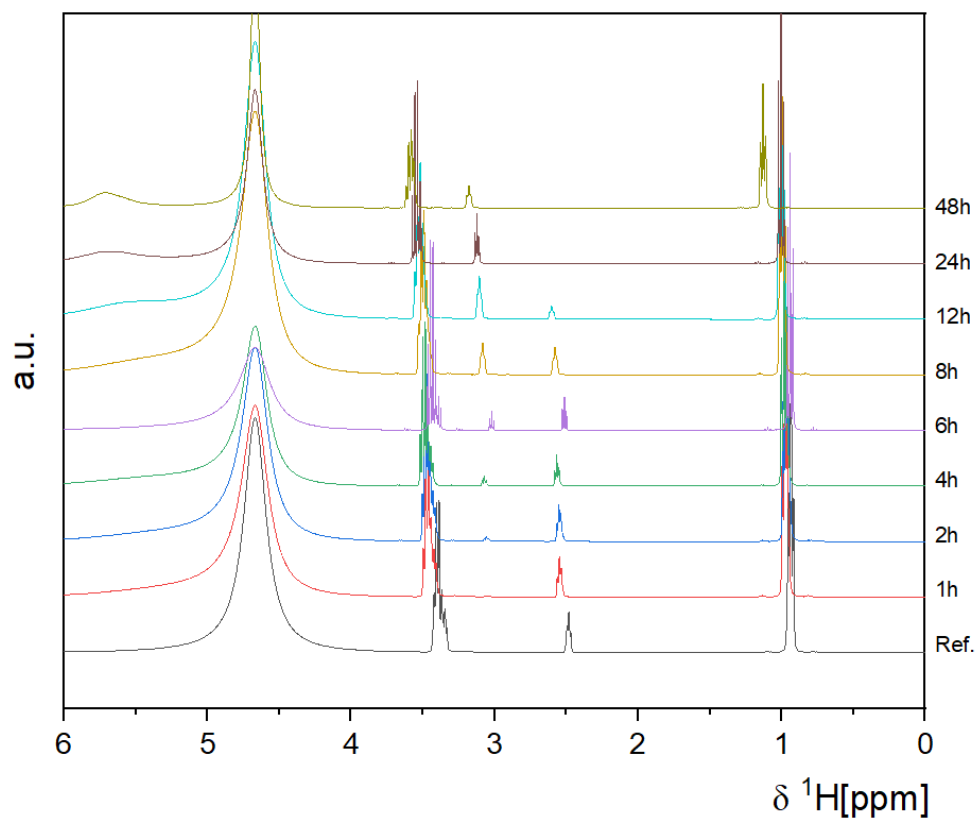


Figure S21. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 25% EtOH / 75% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 $^\circ\text{C}$.

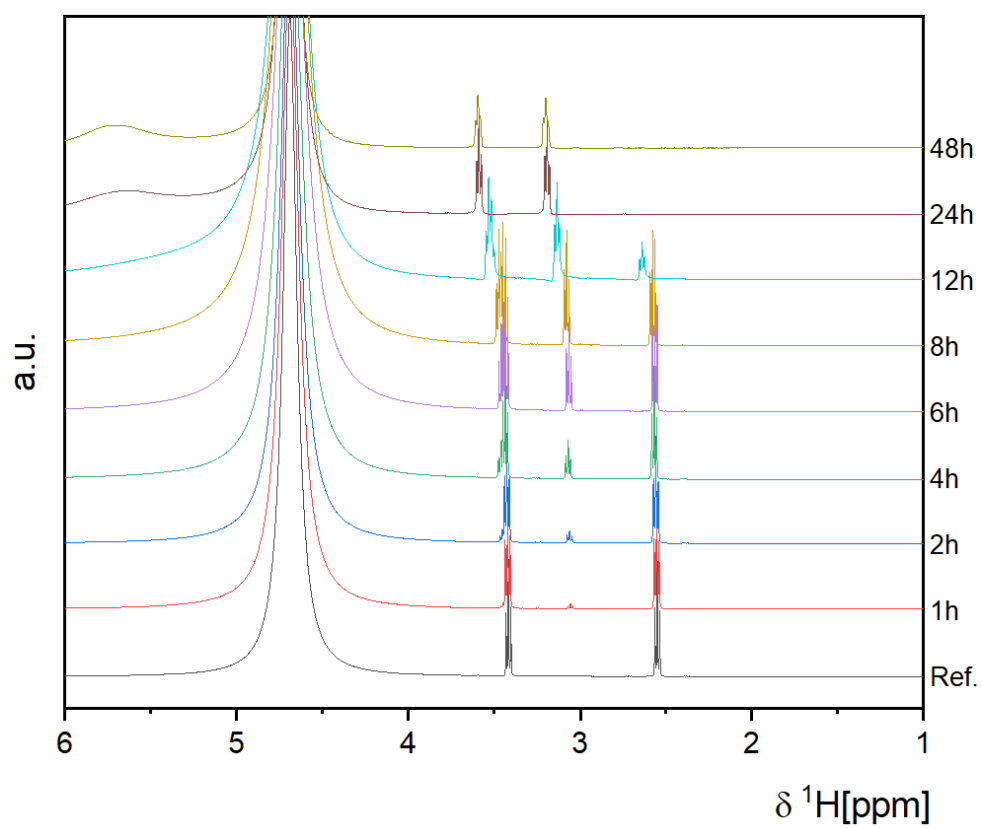
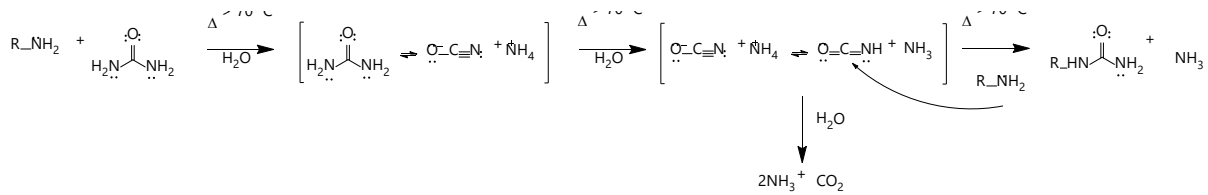


Figure S22. ^1H NMR spectra of experiment with 5% v/v ethanolamine in 0% EtOH/ 100% H_2O and a 6-fold urea excess (ethanolamine:urea = 1:6) at 80 $^\circ\text{C}$.

Section S9. Kinetic model

The kinetic model is based on the following mechanism, discussed in the introduction of the manuscript:



It is assumed that each reaction in the model is an elementary reaction. In the case of a primary amine, the equations are the following:

$$\begin{aligned}
 \frac{d[\text{OC}(\text{NH}_2)_2]}{dt} &= -k_1[\text{OC}(\text{NH}_2)_2] + k_{-1}[\text{OCNH}][\text{NH}_3] \\
 \frac{d[\text{OCNH}]}{dt} &= k_1[\text{OC}(\text{NH}_2)_2] - k_{-1}[\text{OCNH}][\text{NH}_3] - k_2[\text{OCNH}][\text{RNH}_2] - k_4[\text{OCN}^-] \\
 \frac{d[\text{RNH}_2]}{dt} &= -k_2[\text{OCNH}][\text{RNH}_2] \\
 \frac{d[\text{NH}_3]}{dt} &= k_1[\text{OC}(\text{NH}_2)_2] - k_{-1}[\text{OCNH}][\text{NH}_3] + k_2[\text{OCNH}][\text{RNH}_2] + k_4[\text{OCN}^-] \\
 \frac{d[\text{RNHCONH}_2]}{dt} &= k_2[\text{OCNH}][\text{RNH}_2] - k_3[\text{RNHCONH}_2] \\
 \frac{d[\text{HCO}_3^-]}{dt} &= +k_4[\text{OCN}^-]
 \end{aligned} \tag{0.1}$$

In addition to the kinetic equations, all acid-base equilibria must be used to relate the concentration of ions to those of undissociated species, in addition to the electroneutrality condition:

$$\begin{aligned}
 K_a &= \frac{[\text{OCN}^-][\text{H}^+]}{[\text{OCNH}]}; K_{b2} = \frac{[\text{RNH}_3^+][\text{OH}^-]}{[\text{RNH}_2]}; K_b = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3]}; K_w = [\text{H}^+][\text{OH}^-] \\
 K_{ac2} &= \frac{[\text{CO}_3^{2-}][\text{H}^+]}{[\text{HCO}_3^-]}; K_{ac1} = \frac{[\text{HCO}_3^-][\text{H}^+]}{[\text{H}_2\text{CO}_3]}; K_h = \frac{[\text{H}_2\text{CO}_3]}{[\text{CO}_2]_{aq}} \\
 [\text{OCN}^-] + [\text{OH}^-] + 2[\text{CO}_3^{2-}] + [\text{HCO}_3^-] &= [\text{NH}_4^+] + [\text{RNH}_3^+] + [\text{H}^+]
 \end{aligned} \tag{0.2}$$

After some algebraic manipulations, the equilibrium relations can be combined to the kinetic equations as follows:

$$\left\{ \begin{aligned}
\frac{d[OC(NH_2)_2]}{dt} &= -k_1[OC(NH_2)_2] + k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]} \right) [OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]} \right) \\
\frac{d[OCNH]_0}{dt} &= k_1[OC(NH_2)_2] - [OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]} \right) \\
&\left(k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]} \right) + k_2[RNH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}} \right) \right) - k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\
\frac{d[RNH_2]_0}{dt} &= -k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]} \right) [RNH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}} \right) \\
\frac{d[NH_3]}{dt} &= k_1[OC(NH_2)_2] + [OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]} \right) \\
&\left(-k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]} \right) + k_2[RNH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}} \right) \right) + k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\
\frac{d[RNHCONH_2]}{dt} &= k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]} \right) [RNH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}} \right) - k_3[RNHCONH_2] \\
\frac{d[HCO_3^-]_0}{dt} &= +k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]}
\end{aligned} \right. \quad (0.3)$$

Where the concentration of hydroxyl ions can be found from the electroneutrality equation, which is written as follows:

$$\begin{aligned}
&\frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} + [OH^-] + [HCO_3^-]_0 \left(1 - \frac{K_w + [OH^-]^2 \frac{K_{ac2}K_{ac1}K_h}{(1+K_h)K_w}}{\left(K_{ac1} - \frac{K_{ac1}}{1+K_h} \right) [OH^-] + K_w + [OH^-]^2 \frac{K_{ac2}K_{ac1}K_h}{(1+K_h)K_w}} \right) \\
&+ 2 \frac{[HCO_3^-]_0 [OH^-]^2 \frac{K_{ac2}K_{ac1}K_h}{(1+K_h)K_w}}{\left(K_{ac1} - \frac{K_{ac1}}{1+K_h} \right) [OH^-] + K_w + [OH^-]^2 \frac{K_{ac2}K_{ac1}K_h}{(1+K_h)K_w}} = \frac{[NH_3]_0 K_b}{K_b + [OH^-]} + \frac{[RNH_2]_0 K_{b2}}{[OH^-] + K_{b2}} + \frac{K_w}{[OH^-]}
\end{aligned} \quad (0.4)$$

The above algebraic equation must be numerically solved at every integration step. In the manner, the pH of the solution can be also calculated immediately as a function of time. The reaction of consumption of ureido has been introduced in order to explain the disappearance of ureido in the very long-term kinetic experiment of consumption of ethanolamine.

In the case of a glycine, which is an amino acid, the ionic equilibria are more complex, because of the additional dissociation reactions:

$$K_{am1} = \frac{[CO_2^-CH_2NH_3^+]K_w}{[CO_2HCH_2NH_3^+][OH^-]}; K_{am2} = \frac{[CO_2^-CH_2NH_2]K_w}{[CO_2^-CH_2NH_3^+][OH^-]}; K_{am3} = \frac{[CO_2^-CH_2NH_2]K_w}{[CO_2HCH_2NH_2][OH^-]} \quad (0.5)$$

Even the corresponding ureido, which is hydantoic acid, has a dissociation equilibrium:

$$K_{a3} = \frac{[CO_2^-CH_2NHCONH_2]K_w}{[CO_2HCH_2NHCONH_2][OH^-]} \quad (0.6)$$

Therefore, the electroneutrality condition is still In the case of a diamine, there are two dissociation equilibria:

$$K_{b2} = \frac{[NH_2RNH_3^+][OH^-]}{[NH_2RNH_2]}; K_{b3} = \frac{[NH_3RNH_3^{2+}][OH^-]}{[NH_2RNH_3^+]} \quad (0.7)$$

The kinetic equations become:

$$\begin{aligned} \frac{d[OC(NH_2)_2]}{dt} &= -k_1[OC(NH_2)_2] + k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]}\right) [OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) \\ \frac{d[OCNH]_0}{dt} &= k_1[OC(NH_2)_2] - k_{-1}[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) \\ \left(k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]}\right) + k_2[RNH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}}\right) - \alpha k_2[NH_2RNHCONH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}}\right) \right) &- k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\ \frac{d[NH_2RNH_2]_0}{dt} &= -k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) [NH_2RNH_2]_0 \left(1 - \frac{([OH^-]K_{b2} + K_{b3}K_{b2})}{[OH^-]^2 + [OH^-]K_{b2} + K_{b3}K_{b2}}\right) \\ \frac{d[NH_3]}{dt} &= k_1[OC(NH_2)_2] + [OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) \\ \left(-k_{-1}[NH_3]_0 \left(1 - \frac{K_b}{K_b + [OH^-]}\right) + k_2[NH_2RNH_2]_0 \left(1 - \frac{([OH^-]K_{b2} + K_{b3}K_{b2})}{[OH^-]^2 + [OH^-]K_{b2} + K_{b3}K_{b2}}\right) \right) &+ k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\ &+ \alpha k_2[NH_2RNHCONH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}}\right) \\ \frac{d[NH_2RNHCONH_2]_0}{dt} &= k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) [NH_2RNH_2]_0 \left(1 - \frac{([OH^-]K_{b2} + K_{b3}K_{b2})}{[OH^-]^2 + [OH^-]K_{b2} + K_{b3}K_{b2}}\right) - \\ &\alpha k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) [NH_2RNHCONH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}}\right) \\ \frac{d[NH_2CONHRNHCONH_2]}{dt} &= \alpha k_2[OCNH]_0 \left(1 - \frac{K_a[OH^-]}{K_w + K_a[OH^-]}\right) [NH_2RNHCONH_2]_0 \left(1 - \frac{K_{b2}}{[OH^-] + K_{b2}}\right) \\ \frac{d[HCO_3^-]_0}{dt} &= +k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \end{aligned} \quad (0.8)$$

The factor α was introduced to account for the different reactivity of the second amidation reaction. It was found by fitting the experimental data, that α is equal to about 0.5, in fairly close agreement with the simple Monte-Carlo calculation reported in the paper.

The last case is the triamine. The complexity in this case is related to the many intermediate species that can be formed. The triamine has three dissociation equilibria:

$$K_{b2} = \frac{[H_2NRNHRNH_3^+][OH^-]}{[H_2NRNHRNH_2]}; K_{b3} = \frac{[H_3NRNHRNH_3^{2+}][OH^-]}{[H_2NRNHRNH_3^+]}; K_{b4} = \frac{[H_3NRNH_2RNH_3^{3+}][OH^-]}{[H_3NRNHRNH_3^{2+}]}$$

Accounting for all of them, we have the following:

$$\begin{aligned}
& \frac{d[OC(NH_2)_2]}{dt} = -k_1[OC(NH_2)_2] + k_{-1}[NH_3][OCNH] \\
& \frac{d[OCNH]_0}{dt} = k_1[OC(NH_2)_2] - [OCNH] \left(\begin{aligned} & k_{-1}[NH_3] + 3k_2[H_2NRNHRNH_2] + 2k_2[OCNH_2RNHRNH_2] \\ & + 2k_2[H_2NRCONH_2RNH_2] + k_2[CONH_2RCONH_2RNH_2] + \\ & k_2[OCNH_2RNHROCNH_2] \end{aligned} \right) \\
& -k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\
& \frac{d[H_2NRNHRNH_2]_0}{dt} = -3k_2[OCNH][H_2NRNHRNH_2] \\
& \frac{d[OCNH_2RNHRNH_2]}{dt} = 2k_2[OCNH][H_2NRNHRNH_2] - 2k_2[OCNH][OCNH_2RNHRNH_2] \\
& \frac{d[H_2NRCONH_2RNH_2]}{dt} = k_2[OCNH][H_2NRNHRNH_2] - 2k_2[OCNH][H_2NRCONH_2RNH_2] \\
& \frac{d[CONH_2RCONH_2RNH_2]}{dt} = 2k_2[OCNH][H_2NRCONH_2RNH_2] + k_2[OCNH][OCNH_2RNHRNH_2] \\
& -k_2[OCNH][CONH_2RCONH_2RNH_2] \\
& \frac{d[OCNH_2RNHROCNH_2]}{dt} = k_2[OCNH][OCNH_2RNHRNH_2] - k_2[OCNH][OCNH_2RNHROCNH_2] \\
& \frac{d[OCNH_2RCONH_2ROCNH_2]}{dt} = k_2[OCNH][OCNH_2RNHROCNH_2] + k_2[OCNH][CONH_2RCONH_2RNH_2] \\
& \frac{d[NH_3]}{dt} = k_1[OC(NH_2)_2] + [OCNH] \left(\begin{aligned} & -k_{-1}[NH_3] + 3k_2[H_2NRNHRNH_2] + 2k_2[H_2NRCONH_2RNH_2] \\ & + 2k_2[OCNH][OCNH_2RNHRNH_2] + k_2[OCNH][CONH_2RCONH_2RNH_2] \\ & + k_2[OCNH][OCNH_2RNHROCNH_2] \end{aligned} \right) \\
& +k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]} \\
& \frac{d[HCO_3^-]_0}{dt} = +k_4 \frac{K_a[OH^-][OCNH]_0}{K_w + K_a[OH^-]}
\end{aligned} \tag{0.9}$$

The assumption made in Table S3 contains the values of the various kinetic and equilibrium constants used in the simulations, with the corresponding references where they were found. In some cases, instead of values, an expression providing a function of the temperature has been reported. Table S4 instead shows the values of the kinetic constant k_2 obtained from the various amines, and in the case of ethanolamine at different temperatures.

Table S3. Equilibrium constants and kinetic constants used in the simulations

Constant	Expression or value	Reference
K_a	$2.1 \cdot 10^{-4} \cdot \exp(5400/R \cdot (1/T - 1/298.15))$ [Mol/L]	1
K_w	$\exp(148.9802 - 13847.26/T - 23.6521 \cdot \log(T))$ [Mol ² /L ²]	2
K_{ac1}	$10^{-(3404.71/T + 0.032786 - 14.8435)}$ [Mol/L]	2
K_{ac2}	$10^{-(2902.39/T + 0.02379 - 6.4980)}$ [Mol/L]	2
K_h	$10^{(2622.38/T + 0.01784717 - 15.5873)}$	2
K_{b2} (ethanolamine)	$K_w \cdot \exp(53900/R/T)$ [Mol/L]	3
K_b (ammonia)	$K_w \cdot 10^{10.0423 - (0.0315536 \cdot (T - 273.15))}$ [Mol/L]	4
K_{b2} (5-amino 1-pentanol)	$3.625 \cdot 10^{-5}$ [Mol/L]	5
K_{am1}	0.0049 [Mol/L]	6
K_{am2}	$2.3988 \cdot 10^{-10}$ [Mol/L]	6
K_{am3}	$4.8978 \cdot 10^{-5}$ [Mol/L]	6
K_a (hydantoic acid)	$1.3305 \cdot 10^{-4}$ [Mol/L]	7
K_{b2} (N,N'-dimethyl-1,3-propanediamine)	$4.1687 \cdot 10^{-4}$ [Mol/L]	7
K_{b3} (N,N'-dimethyl-1,3-propanediamine)	$1.9953 \cdot 10^{-11}$ [Mol/L]	7
K_{b2} (hexamethyldiamine)	$5.0119 \cdot 10^{-4}$ [Mol/L]	8
K_{b3} (hexamethyldiamine)	$1.9953 \cdot 10^{-11}$ [Mol/L]	8
K_{b2} (bis-(Hexamethylene)triamine)	$5.0119 \cdot 10^{-4}$ [Mol/L]	7
K_{b3} (bis-(Hexamethylene)triamine)	$1.9953 \cdot 10^{-11}$ [Mol/L]	7
K_{b4} (bis-(Hexamethylene)triamine)	10^{-13} [Mol/L]	7
k_1	$4 \cdot 10^{14} \cdot \exp(-135560/8.314/T)$ [s ⁻¹]	9
k_3	$1.017 \cdot 10^{-7}$ [s ⁻¹]	Fitted
k_4	$7.2 \cdot 10^8 \cdot \exp(-10900/T)$ [L/Mol·s]	1
k_{-1}	$10^{11} \cdot \exp(-95718/R/T) \cdot K_a K_b / K_w$ [L/Mol·s]	10

Table S4. Fitted values of k_2 rate constants for the reaction of isocyanic acid with various amines

k_2 ethanolamine, 90°C	278 [L/Mol/s]
k_2 ethanolamine, 80°C	278 [L/Mol/s]
k_2 ethanolamine, 70°C	278 [L/Mol/s]
k_2 ethanolamine, 60°C	278 [L/Mol/s]
k_2 ethanolamine, 50°C	278 [L/Mol/s]
k_2 5-amino 1-pentanol, 80°C	2566 [L/Mol/s]
k_2 glycine, 80°C	2762710 [L/Mol/s]
k_2 N,N'-dimethyl-1,3-propanediamine, 80°C	2279 [L/Mol/s]
k_2 hexamethylenediamine, 80°C	5093 [L/Mol/s]
k_2 bis-(hexamethylene)triamine, 80°C	1216 [L/Mol/s]

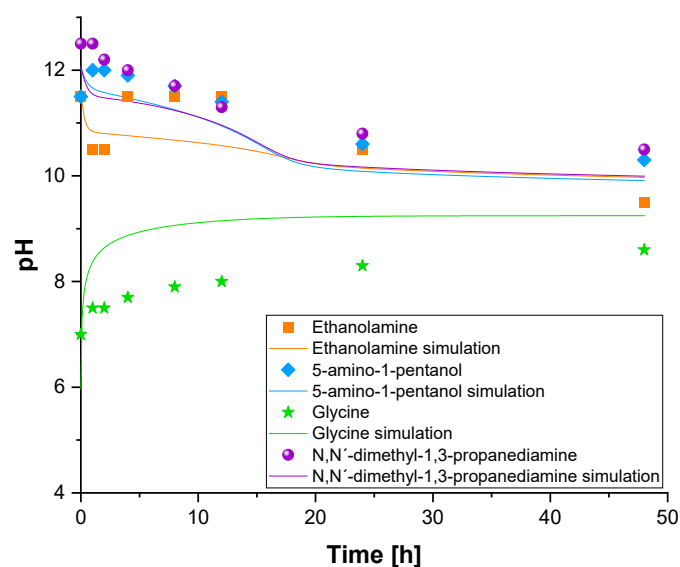


Figure S23. pH variation as a function of reaction time for different substrates. The fitted lines correspond to the results of the kinetic modelling (See section 3.5). The reactions were conducted at 80 °C with 5% v/v of amine molecule in H_2O/D_2O and with a 6-fold urea excess: ethanolamine : urea = 1:6, 5-amino-1-pentanol : urea = 1:6, glycine : urea = 1:6, N,N'-dimethyl-1,3-propanediamine:urea = 1:12.

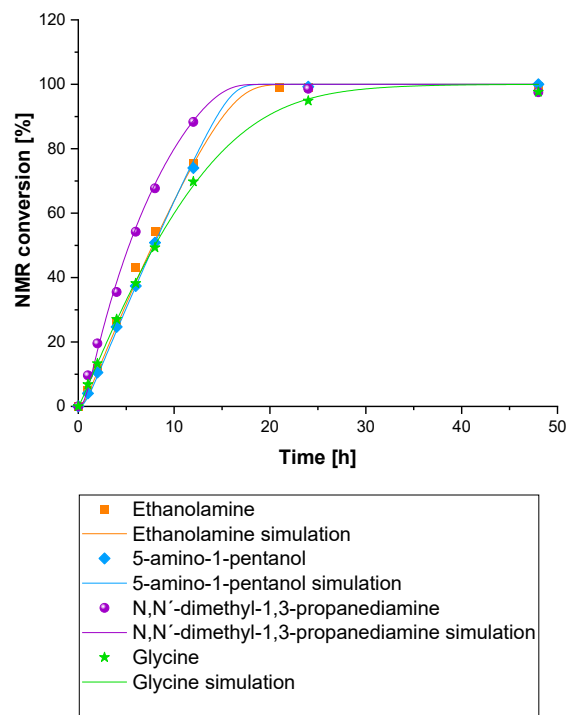


Figure S24. Ureido NMR conversion as a function of reaction time for different substrates. The reactions were conducted at 80 °C with 5% v/v of amine molecule in H_2O/D_2O and with a 6-fold urea excess: ethanolamine : urea = 1:6, 5-amino-1-pentanol : urea = 1:6, N,N'-dimethyl-1,3-propanediamine:urea = 1:12, glycine : urea = 1:6. The fitted lines correspond to the results of the kinetic modelling (See section 3.5).

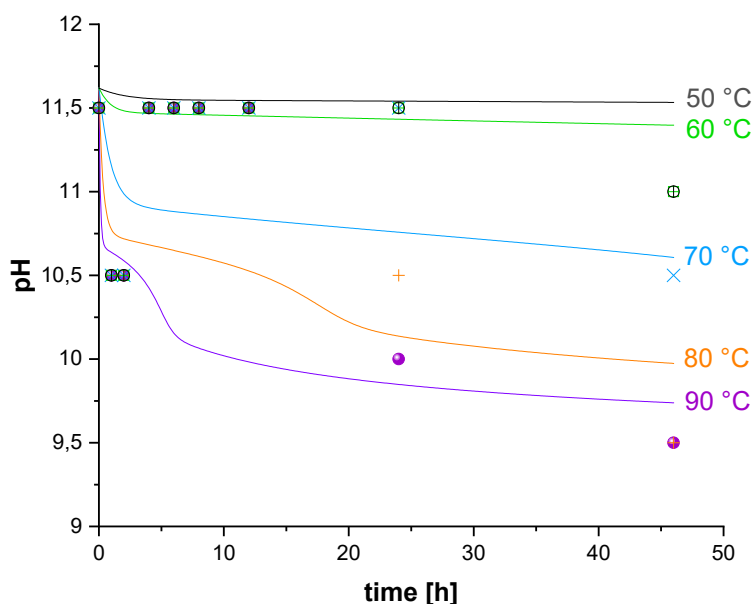


Figure S25. Time dependent pH variation as a function of reaction temperature. The reactions were conducted with 5%v/v of ethanolamine in H_2O/D_2O with a 6-fold excess of urea (ethanolamine : urea = 1:6). The fitted lines correspond to the results of the kinetic modelling (See section 3.5).

Section S10. ^{13}C NMR spectra

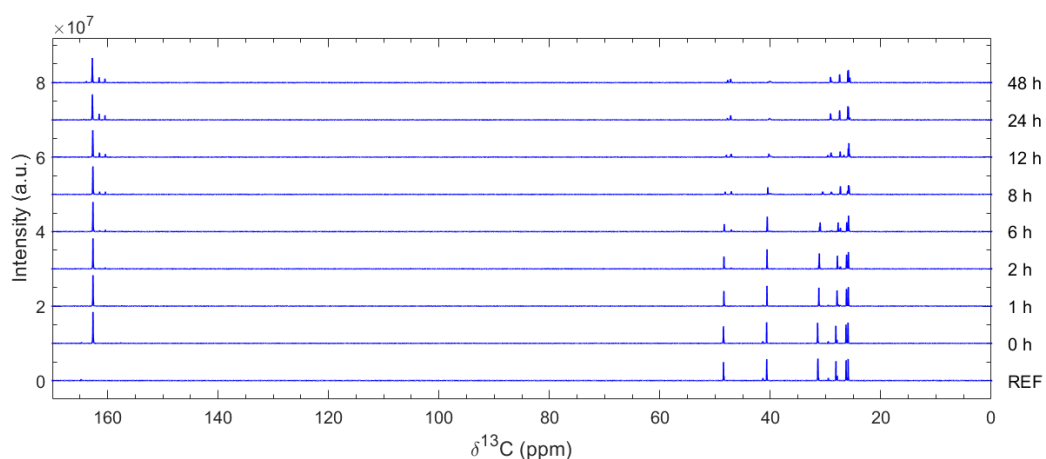


Figure S26. ^{13}C NMR spectra of the possible reaction products of bis-(hexamethylene)triamine with urea. The reaction was conducted at 80 °C with 5%v/v of bis-(hexamethylene)triamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 18-fold urea excess with respect to the urea:amine ratio, corresponding to (bis-(hexamethylene)triamine:urea 1:18).

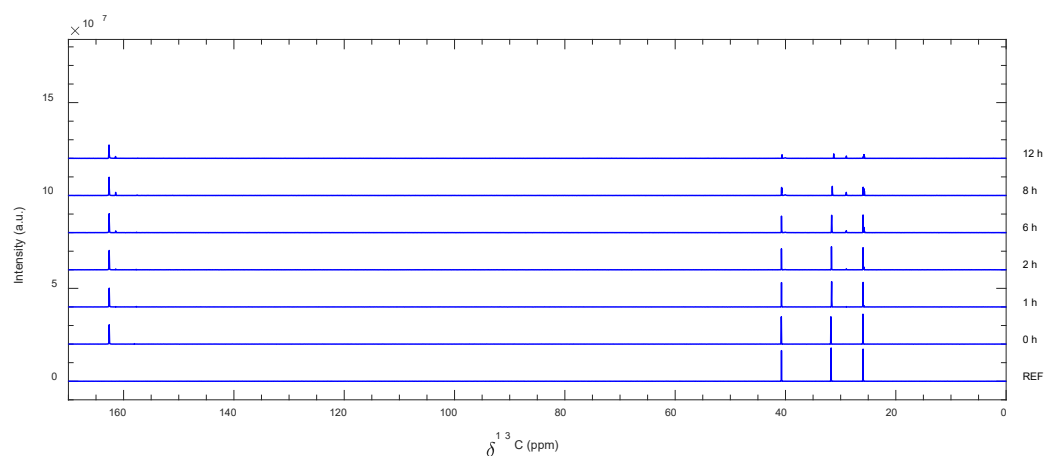


Figure S27. ^{13}C NMR spectra of the products of hexamethylenediamine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of hexamethylenediamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 12-fold urea excess (hexamethylenediamine:urea 1:12).

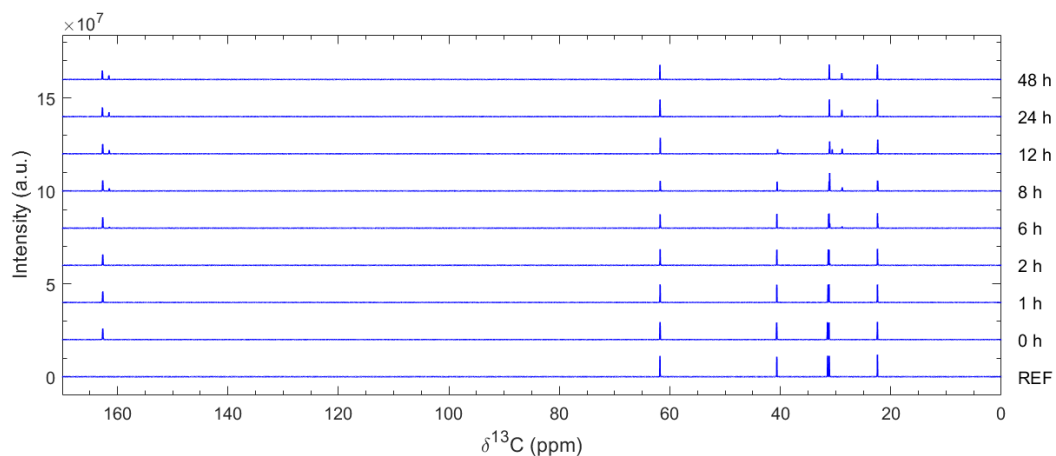


Figure S 28. ^{13}C NMR spectra and numbering of positions of the possible reaction products of 5-amino-1-pentanol after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of 5-amino-1-pentanol in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 6-fold urea excess (5-amino-1-pentanol:urea 1:6).

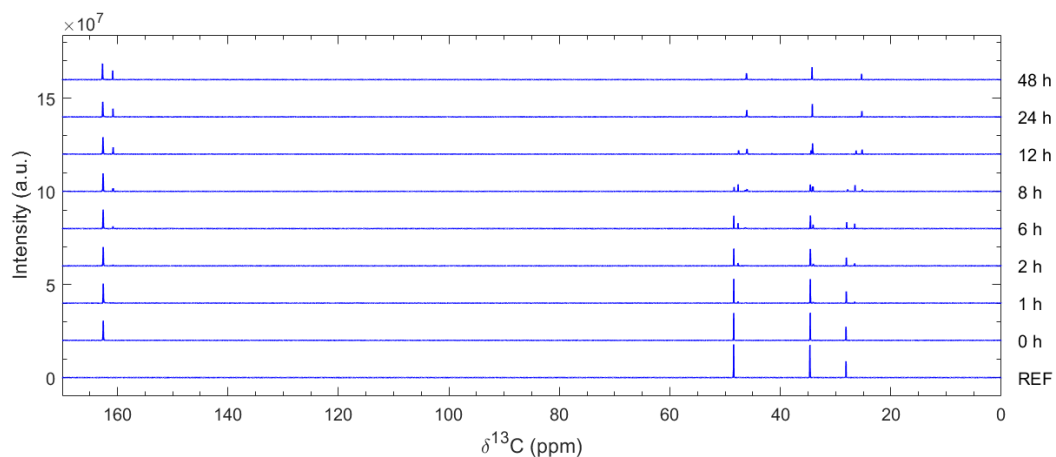


Figure S29. ^{13}C NMR spectra of the possible reaction products of *N,N'*-dimethyl-1,3-propanediamine after reaction with urea. The reaction was conducted at 80 °C with 5%v/v of *N,N'*-dimethyl-1,3-propanediamine in $\text{H}_2\text{O}/\text{D}_2\text{O}$ and with a 12-fold urea excess (*N,N'*-dimethyl-1,3-propanediamine:urea 1:12).

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