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Computational and Experimental Studies on the Mechanism of Formation of Poly(hexahydrotriazine)s and Poly(hemiaminal)s from the Reactions of Amines with Formaldehyde

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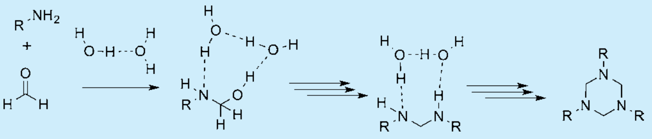
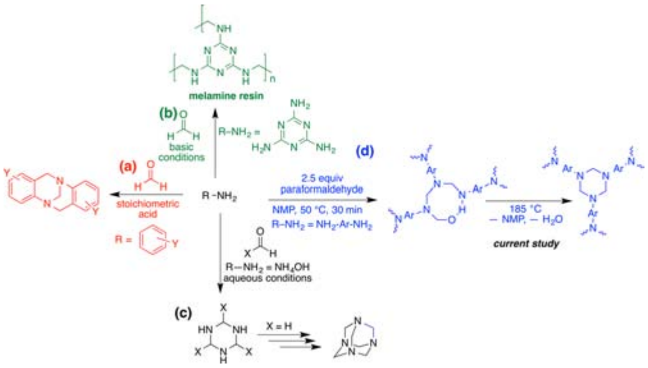
Supporting Information

ABSTRACT: Combined experimental and computational studies have been performed on the mechanism of formation of poly(hexahydrotriazine) and hemiaminal dynamic covalent network (PHT and HDCN) thermosetting polymers from the reactions of diamines with formaldehyde (*Science* **2014**, *344*, 732−735). Results suggest that these polymers are formed by a mechanism involving the water promoted stepwise addition of amines with formaldehyde in preference to dimerization or cyclotrimerization of imine intermediates or self-catalysis by the amine reagents. The predicted mechanism also explains experimentally observed electronic effects for hexahydrotriazine formation.



The condensation of amines with formaldehyde has been widely utilized as a tool for the construction of polymeric materials. However, the types of repeating units formed in these polymerizations are highly dependent on reaction conditions (Scheme 1). For example, Tröger's base analogues are formed by the reaction of anilines with formaldehyde in the presence of strong acids (Scheme 1a).[1,2] By contrast, uncyclized resins are formed by the reaction of formaldehyde with melamine and other aromatic 1,3-diamines, as well as urea, in basic conditions (Scheme 1b).[3] Moreover, heterocyclic hexahydrotriazines may also be formed by the reactions of basic ammonium hydroxide with formaldehyde and other substituted aldehydes (Scheme 1c).[4,5]

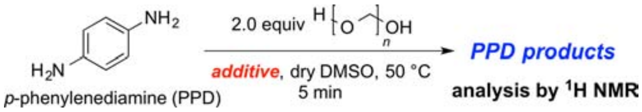
Scheme 1. Reactions of Amines with Aldehydes in Various Reaction Conditions



Inspired by previous work on hexahydrotriazine formation,[6−12] the formation of novel classes of recyclable thermosetting polymers without the use of a strong acid or base by the reactions of diamines with paraformaldehyde (PF) (Scheme 1d) was recently demonstrated.[13] Highly cross-linked hemiaminal dynamic covalent networks, HDCNs, are formed at 50 °C in neutral organic solvents, in which the solvent, hemiaminal intermediates, and water are still present after isolation.[14] Heating the HDCN to 185 °C results in the formation of a polyhexahydrotriazine, PHT, following the loss of water and solvent from the polymer matrix.

Given that the course of these reactions is strongly dependent on pH, an attempt was made to determine whether polymer formation was facilitated by catalysis due to trace formic acid present in PF, or due to proton transfer by water present in the reaction. As shown in Table 1, the addition of 10 or 50 mol % formic acid to the reaction of *p*-phenylenediamine (PPD) with PF resulted in 65% and 50% conversion from starting materials, respectively; however, neither the expected HDCN nor PHT products were formed within this time frame. These conversions are lower than that observed without an additive (>90%

Table 1. Reactions of *p*-Phenylenediamine with Paraformaldehyde in the Presence of Various Additives



additive	conversion from PPD (%)[a]
10 mol % formic acid	65
50 mol % formic acid	50
10 mol % water	90
50 mol % water	94

[a] Percent conversion based on disappearance of aromatic proton signals assigned to PPD.

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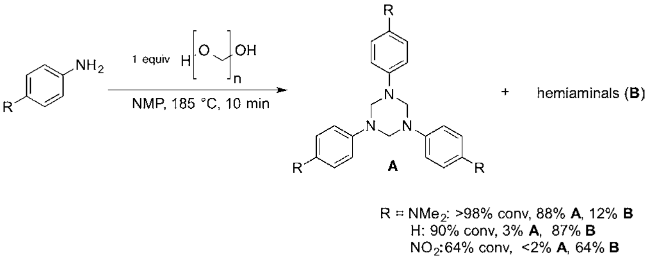
conversion), in which HDCN products were formed. In contrast, conversion was slightly improved by the addition of 50 mol % of water to the reaction mixture during which gelation was evident. These results suggest that HDCN and PHT formation is being hindered by the presence of trace acid. Instead these reactions are likely to be facilitated by proton transfer due to water or the amine reactant.

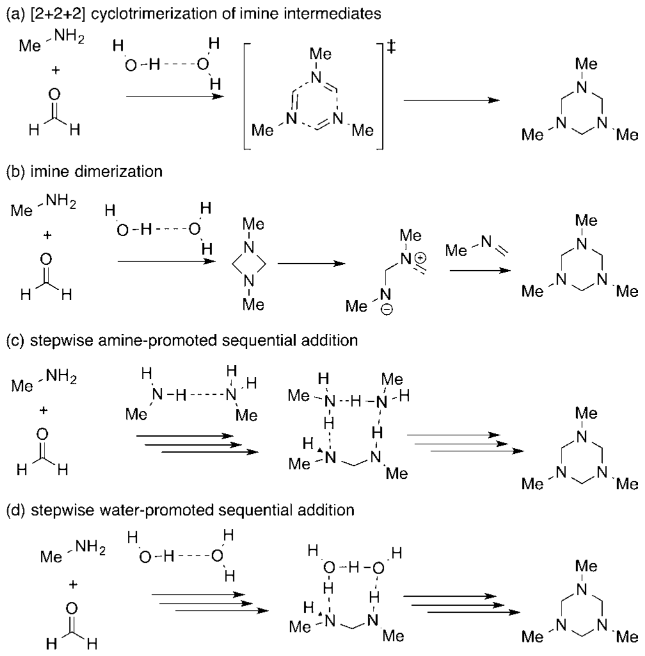
Finally, experiments with variously substituted amines suggest that reactions involving electron-rich amines are faster than those involving electron-poor amines. Reaction of the electron-rich *N*,*N*-dimethyl-*p*-phenylenediamine with PF forms HT in 88% yield at 185 °C after 10 min (Scheme 2) while hemiaminals comprise the remaining products. In contrast, reactions involving the moderately electron-rich aniline and the electron-poor 4-nitroaniline only result in the formation of hemiaminal products (87% and 64% conversion, respectively) and trace amounts of HT (<3% conversion).

Scheme 2. Reactions of Paraformaldehyde with Substituted Anilines



Possible mechanisms for HT formation are shown in Scheme 3 based on these experimental results and previous reports.[10,15,16] First, the previously suggested[5] [2 + 2 + 2] cyclotrimerization of imines initially formed by the reaction of formaldehyde with the primary amine (Scheme 3a) was examined. Imines may also dimerize and form diazetidines,[15] which may then ring-open and react with another imine molecule (Scheme 3b). HTs may also be formed by the amine-promoted sequential addition of amines with formaldehyde (Scheme 3c). Lastly, water molecules may also promote the sequential addition of amines to formaldehyde (Scheme 3d),[11] in which proton transfer is facilitated by trace amounts of water present at the start or generated as a byproduct of imine formation.[16,17]

Scheme 3. Plausible Mechanisms for HT Formation from the Reaction of Formaldehyde with Methylamine As a Model System


(a) [2+2+2] cyclotrimerization of imine intermediates

(b) imine dimerization

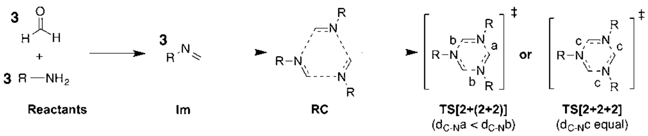
(c) stepwise amine-promoted sequential addition

(d) stepwise water-promoted sequential addition

Detailed computational investigations were performed in GAMESS-US with B3LYP-D3/aug-cc-pVTZ//6-311+G(2d,p) in DMF solvent (as a model for NMP) using the IEF-cPCM method (see Supporting Information for details) on these possible mechanisms to explain why HDCNs are so readily formed in contrast to PHTs, as well as to explain experimentally observed electronic effects.

Interestingly, two types of transition structures (TSs) could be located for cyclotrimerization (Table 2) of imines derived from variously substituted amines. One type of TS corresponds to a concerted, nearly synchronous [2 + 2 + 2] process in which all three C−N bonds are formed to almost the same extent ($d_{C-N}c$ ≈ 2.0−2.1 Å). In the other TSs, termed asynchronous [2 + (2 + 2)] TSs, one C−N bond is almost completely formed ($d_{C-N}a$ ≈ 1.5−1.8 Å) while bonds being formed between the remaining C and N atoms lag far behind ($d_{C-N}b$ ≈ 2.0−3.1 Å). Intrinsic reaction coordinate calculations reveal that both types of TSs are connected to the same reactant complexes (RCs).

Table 2. Free Energies, in kcal/mol, of Key Stationary Points for the Cyclotrimerization of Variously Substituted Imines



R	Im (x3)[a]	RC[b]	TSa[c]	TSb[d]	$\Delta G^{‡,c}$	$\Delta G^{‡,d}$
NO_2	6.3	−7.1	7.9	16.3	15.0	23.4
ester[f]	20.1	6.2	22.6	26.0	15.9	19.3
CN	3.6	−6.1	12.5	12.7	18.6	18.8
−≡−H	−9.0	−18.8	3.2	3.8	22.0	22.6
CF_3	3.9	−7.8	16.0	16.7	23.8	24.5
Ph	−7.8	−24.6	3.9	9.2	28.5	33.8
H	1.8	−4.6	27.4	27.3	31.9	32.1
Me	−21.9	−30.3	5.3	N.D.[e]	35.6	N.D.[e]
NH_2	−44.4	−56.4	−4.6	−10.2	51.8	46.2
OMe	−47.1	−57.7	−2.5	−9.5	55.2	48.2

[a] The combined free energy for the reaction 3 amine + 3 formaldehyde → 3 imine. [b] Reactant complex. [c] [2 + (2 + 2)]. [d] [2 + 2 + 2]. [e] Transition structure not determined. [f] CO_2Me.

Barriers for asynchronous [2 + (2 + 2)] cycloadditions are approximately equal to, or in a few cases lower than (by about 4−8 kcal/mol), corresponding barriers for synchronous [2 + 2 + 2] transition structures (Table 2). Cyclotrimerizations involving amines substituted by the electron-rich methoxy and amino functional groups are the notable exceptions to this trend; barriers for the asynchronous [2 + (2 + 2)] cyclotrimerization are 6−7 kcal/mol higher than barriers for the synchronous [2 + 2 + 2] process.

Significantly, reactivity trends in Table 2 indicate that the barriers for the cyclotrimerization of imines formed from electron-deficient amines are lower than those for reactions involving electron-rich amines. This is primarily due to the fact

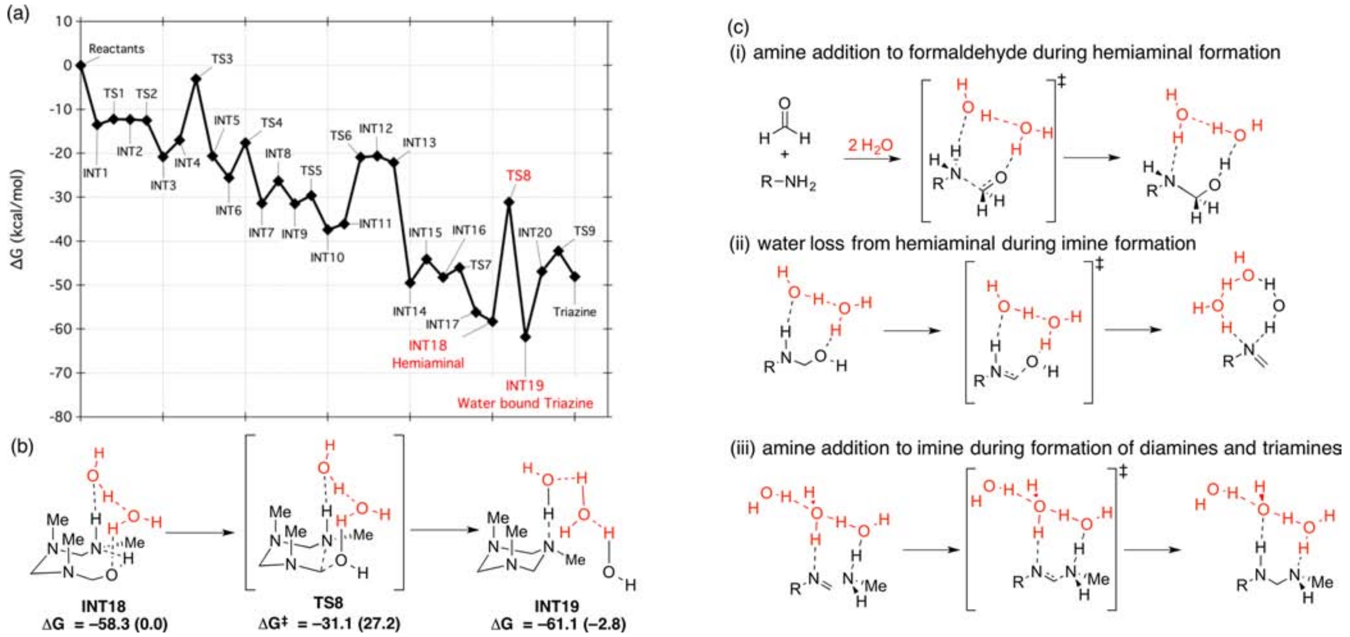


Figure 1. (a) Free energy profile for the water-promoted formation of HT. (b) Transformation of hemiaminal intermediate INT18 into the water-bound HT via TS8. Free energies (relative free energies, in parentheses) are shown in kcal/mol. (c) Generalized depiction of the three main types of transformations occurring during stepwise, water-promoted HT formation.

that electron-deficient amines form less stable imines (and therefore less stable reactant complexes), which more readily access the TSs. These trends are inconsistent with experimental observations (Scheme 2). Consequently, mechanisms that invoke HT formation via [2 + 2 + 2] cyclotrimerization were disregarded.

Transition structures could not be located for the methylamine self-catalyzed addition to formaldehyde; presumably due to the fact that self-catalysis would necessarily involve proton transfer from the amine cocatalyst to formaldehyde, a process disfavored by the weakly acidic amines.

The mechanism for the formation of HT due to sequential addition of methylamine and formaldehyde was examined in substantial detail. The free energy profile shown in Figure 1a shows that many intermediates and transition structures are formed during the course of HT formation. The three types of transformations exhibited throughout the entire process may be summarized as follows (Figure 1c): (i) amine addition to formaldehyde during formation of hemiaminal intermediates, (ii) water loss from the hemiaminal during formation of imine intermediates, and (iii) amine addition to the imine during formation of the diamine and triamine intermediates. Transition structures for all of these transformations involve C−N formation or C−O bond breaking concomitant with protonation or deprotonation of the amine or formaldehyde reactants facilitated by hydrogen-bonding water molecules. Barriers for hemiaminal formation are typically smaller than 4 kcal/mol, while barriers for diamine or triamine formation are typically less than 8 kcal/mol. In contrast, barriers for water loss and imine formation are greater than 17 kcal/mol. These observations are in agreement with previous theoretical studies.[16,17]

Formation of the water-bound HT from the hemiaminal, i.e. INT18 → TS8 → INT19 (Figure 1b), involves initial proton transfer from one of the bound water molecules to the hydroxyl group present in the hemiaminal. Subsequent water loss triggers spontaneous cyclization and formation of the water-bound HT, INT19. This transformation possesses the largest barrier observed for the entire free energy surface, 27.2 kcal/mol, which is in agreement with experiments showing that high temperatures are required to form PHTs from the HDCNs.

The mechanism and computed free energies for imine dimerization are shown in Figure 2. Dimer formation proceeds through a low-lying reactant complex, RC22, which is 19 kcal/mol more stable than the amine and formaldehyde reactants. The free energy barrier for imine dimerization in the transition structure, TS22, is 50 kcal/mol with respect to RC22. This barrier is prohibitively large and is also at least 23 kcal/mol larger than that computed for HT formation via the water-promoted stepwise reaction of an amine and formaldehyde.

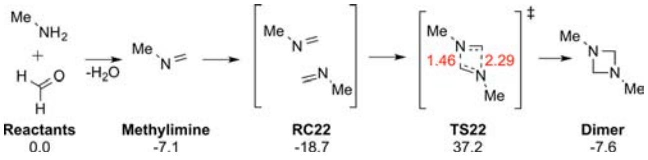


Figure 2. Structures, predicted energies, and partial bond distances (shown in red) for *N*-methylimine dimerization.

Finally, the reaction of trifluoromethylamine with formaldehyde was examined to determine why electron-deficient amines are considerably less reactive than the analogous electron-rich amines in these reactions as shown in Scheme 2. The barrier for initial formation of the first hemiaminal, INT2, is 19.3 kcal/mol, about 17 kcal/mol larger than that required to form the analogous hemiaminal in the reaction of methylamine with formaldehyde (Figure 3). Similarly, the barrier for imine formation is 23.5 kcal/mol with respect to the low-lying hemiaminal intermediate, which is 8 kcal/mol larger than the analogous process involving methylamine. Examination of the electrostatic potential (ESP) charge on the nitrogen atom reveals that it becomes more positive on going from INT1-F to TS1-F which is disfavored by the presence of the attached electron-withdrawing trifluoromethyl group, in agreement with experi-

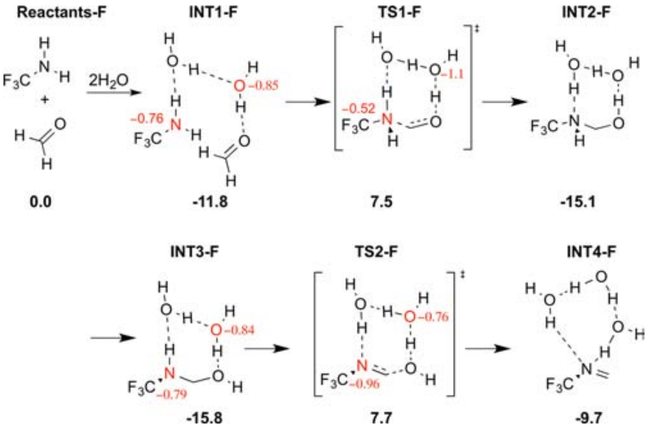


Figure 3. Structures, energies, and selected electrostatic potentials (shown in red) for the water-promoted reaction of formaldehyde with trifluoromethylamine.

ments. In a similar vein, the charge on the oxygen atom on one of the H-bonded water molecules becomes more positive on going from INT3-F to TS2-F as it transfers a proton to the leaving hydroxyl group that was attached to the hemiaminal, which is disfavored due to the intrinsic electronegativity of oxygen, in agreement with experiments.

In conclusion, combined experimental and computational investigations have been used to explore various mechanisms for the formation of hemiaminals and HTs as models for HDCN and PHT formation from the reactions of amines with formaldehyde. These investigations have revealed that mechanisms involving water-promoted sequential condensations are preferred to mechanisms involving the amine-promoted addition of amines with formaldehyde or imine dimerization or cyclotrimerization. The results also readily explain the greater reactivities of electron-rich amines in these reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, ^{1}H NMR spectra, B3LYP coordinates and energies, and full reference list. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Note that, in contrast to refs 4−5, the reactions of substituted amines with aldehydes do not form PHTs in our hands. Instead, the reactions stop after formation of the imine.

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