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PAPER

Can cytosine, thymine and uracil be formed in interstellar regions? A theoretical study†

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This theoretical study investigates possible synthetic routes to cytosine, uracil and thymine in the gas phase from precursor molecules that have been detected in interstellar media. Studies at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory suggest that: The reactions between :CCCNH and :CCCO with monosolvated urea may constitute viable interstellar syntheses of cytosine and uracil. No low energy equilibration between cytosine and uracil has been demonstrated. The interaction of :CH_2 with the 5 C–H bond of uracil may form thymine in an energetically favourable reaction, but competing reactions where :CH_2 reacts with double bonds and other CH and NH bonds of uracil, reduce the effectiveness of this synthesis. The reaction between the hydrated propional enolate anion and isocyanic acid may produce thymine, in a reaction sequence where $\Delta G_{\text{reaction}}$(298 K) is –22 kJ mol^{-1} and the maximum energy requirement (barrier to the first transition state) is only 47 kJ mol^{-1}.

Introduction

One of the major ongoing questions in science is whether biomolecules were originally produced terrestrially or extraterrestrially. Aristotle considered that life originated on a 'cosmic' rather than a terrestrial level because of the then considered five primary elements and because he thought that "cells" came to Earth from external sources.[1] This question was readdressed by Hoyle and colleagues in the 1950s: they proposed that biological molecules could originate from interstellar regions.[2,3] There seems no doubt that the pyrimidine and purine nucleobases could have been formed on prebiotic earth (see below).[4,5] However, the possibility that they could be formed extraterrestrially must also be considered since some biomolecules and their precursors have been detected in circumstellar envelopes, interstellar molecular clouds, interstellar ice, comets and meteorites. Examples of biologically important molecules detected extraterrestrially in, for example molecular clouds, range from the glycine precursor amino acetonitrile (NH_2CH_2CN)[6] and the proto sugar glycolaldehyde ($HOCH_2CHO$),[7,8] to possible pyrimidine and purine base precursors like HCN,[9] HNCO,[10] NCCCH,[11] $HCONH_2$[12] and NH_2CONH_2[13] (see also Table 1).

There are adequate scientific data now available to confirm that the three pyrimidine bases cytosine, thymine and uracil (together with the purines adenine and guanine) could have been formed on prebiotic earth.[e.g. 14–34] This could have occurred in a number of ways, for example, from hydrogen cyanide oligomers,[15] from formaldehyde and formic acid mixtures with hydrogen cyanide,[14] from cyanoacetylene and cyanate,[17] from a mixture of carbon dioxide, methane, nitrogen and water (to form thymine),[19] from formaldehyde and hydrazine,[20] with carbon monoxide and ammonia (for cytosine),[21] and with formamide to form all three pyrimidine bases.[21] Some of these reactions have been shown to occur more readily if the precursor molecules are adsorbed on clays or similar materials.[22–27] Hydrothermal formation of nucleobases has been reported in detail for formaldehyde and hydrogen cyanide mixtures.[28] Finally, there has been considerable debate as to whether cyanoacetylene or cyanoacetaldehyde is the more appropriate/likely pyrimidine base precursor in solution.[29–33]

It is of interest to compare these possible prebiotic syntheses with the sophisticated procedures by which cytosine, uracil and thymine (and their phosphate derivatives) are biosynthesised today. Cytosine and uracil are formed by enzymic reactions involving carbamoyl phosphate and aspartate, while the extra methyl group of thymine is inserted by the reaction of uracil monophosphate with thymidylate synthase and methylene tetrafolate.

Less data are available concerning possible interstellar syntheses of cytosine, uracil and thymine. There have been no reports of the identification of these nucleobases in interstellar regions by infrared or microwave spectroscopy, but uracil has been detected in both the Murchison and Orgueil meteorites.[35,36] The carbon isotope ratios for uracil from the Murchison meteorite indicate a non-terrestrial origin.[37] It has been shown that pyrimidine/ice/water mixtures when irradiated with UV photons, form several products including uracil, and this has been proposed as a possible

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† Electronic supplementary information (ESI) available: Fig. S1-hydrolysis of HNCO. Fig. S2-Woodward Hoffmann diagrams. The tunnelling procedure with Figs. S3–S6. Tables S1 to S8-geometries and energies of all species shown in Fig. 1–7 and Figs S7a and S8. CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. See DOI: 10.1039/c1ob06352a

Table 1 Interstellar molecules[a] (cumulenes and heterocumulenes are shown in bold letters)

Diatomic
AlCl, AlF, AlO, **CC**, CH, CH^+, CF^+, CN, CN^-, CO, CO^+, CP, CS, CSi, FeO, HCl, HF, H_2, HN, HO, HS, KCl, LiF, MgH^+, N_2, NO, NP, NS, NSi, NaCl, NaI, O_2, OP, OS, OS^+, OSi, SH, SSi.

Triatomic
AlNC, AlOH, **C_3**, **C_2H**, CH_2, **C_2O**, CO_2, **C_2P**, **C_2S**, *cyclo*-C_2Si, HCN, HCO, HCO^+, HCP, HCS, HCS^+, HDO, H_3^+, HNC, HN_2^+, HNO, H_2D^+, HD_2^+, H_2N, H_2O, H_2S, HOC^+, KCN, MgCN, MgNC, NaCN, NaOH, N_2O, OCN^-, OCS, O_3, SO_2, SiCN, SiNC.

4-atomic
CH_2O, CH_2S, C_2H_2, **C_2HN**, CH_2N, **C_3H**, ***cyclo*C_3H**, **C_3N**, **C_3O**, **C_3S**, **C_3Si**, CH_3, **C_4**, $HCNH^+$, HCNO, HNCO, HNCS, HSCN, $HOCO^+$, H_3O^+, H_2O_2, NH_3.

5-atomic
CH_4, CH_2CN, CH_2CO, CH_2NC, CH_2NH, CH_2OH^+, **C_3H_2**, ***cyclo*C_3H_2**, **HC_2CN**, **HC_2NC**, **C_3NH**, HC_3N, **C_4H**, **C_4H^-**, **C_4Si**, **C_5**, HCO_2H, HCOCN, NH_2CN, SiH_4.

6-atomic
C_2H_4, CH_2CHO, CH_2CNH, *cyclo*C_3H_2O, CH_3CN, CH_3NC, CH_3OH, CH_3SH, C_3H_2N, **C_4H_2**, **C_4HN**, **C_5H**, **C_5N^-**, HC_2CNH^+, $HCONH_2$, NH_2CHO.

7-atomic
cycloC_2H_4O, CH_2CHCN, CH_2CHOH, CH_3CHO, CH_3NH_2, CH_3C_2H, **HC_4CN**, **C_6H**, **C_6H^-**.

8-atomic
CH_2OHCHO, CH_2CHCHO, **CH_2CCHCN**, CH_3CO_2H, **CH_3C_2CN**, **C_6H_2**, **C_7H**, HCO_2CH_3, NH_2CONH_2, NH_2CH_2CN.

9-atomic
CH_3CH_2CN, CH_3CH_2OH, CH_3CHCH_2, CH_3CONH_2, CH_3OCH_3, **CH_3C_4H**, **C_7HN**, **C_8H**, **C_8H^-**.

10 or more atoms
CH_3CH_2CHO, CH_3COCH_3, **CH_3C_4CN**, $HOCH_2CH_2OH$, **CH_3C_6H**, **HC_8CN**, $HCO_2C_2H_5$, *n*C_3H_7CN, C_6H_6, $HOCH_2COCH_2OH$, **$HC_{10}CN$**, **$HC_{11}N$**, $C_{14}H_{10}$, C_{60}, C_{70}.

Deuterated molecules
HD, H_2D^+, HD_2^+, HDO, D_2O, DCN, DCO, DNC, N_2D^+, NH_2D, NHD_2, ND_3, HDCO, D_2CO, CH_2DC_2H, CH_3C_2D.

Molecules reported but not confirmed
HOCN, $NH_2CH_2CO_2H$, $CO(CH_2OH)_2$, $C_2H_5COCH_3$, $C_{10}H_8^+$, SiH, PH_3.

[a] This list was compiled from data listed in: http://www.astro.uni-koeln.de/cdms/molecules http://www.astrochymist.org/astrochymist_ism.html http://en.wikipedia.org/wiki/List_of_molecules_in_interstellar_space, also ref. 43.

interstellar synthesis.[38,39] This seems intuitively unlikely, if for no other reason than pyrimidine has not been detected as an interstellar molecule.[40] Finally, it has been suggested that uracil may not be stable in interstellar regions,[41] or under conditions where the temperature is elevated above 400 °C.[42]

This paper considers whether it is theoretically possible to form cytosine, uracil and thymine from precursor molecules which have already been detected in interstellar regions.

Results and discussion

Reactions discussed in this article may occur on dust particles containing condensed water ice, or small or large pieces of water ice in dark and dense molecular clouds (temperature usually *ca.* 5–20 K in the cloud centre). Less likely reaction regions are interstellar water-ice systems, *e.g.* water-ice comets (heated to ≥100 K by ultraviolet radiation) or other water-ice systems (*e.g.* the water-ice rings of Saturn are *ca.* 240 K). Dense molecular clouds contain some 10^6 molecules cm^{-3}, and are turbulent with major heating by ultraviolet radiation and the stellar wind penetrating the outside of the cloud. For example, a near ultraviolet photon of wavelength 193 nm is equivalent to an energy of 620 kJ mol^{-1}. The centre of a dense molecular cloud is likely to be opaque to ultraviolet radiation, but can still be heated by high energy collision events of dust or ice particles with cosmic rays, gamma radiation, and secondary electrons from cosmic rays.[44–48] Reactions considered in this article are thermodynamically favourable ($\Delta G_{\text{reaction}}$ is negative), but have barriers to the transition state of the rate-determining step of each reaction. Reaction coordinate profiles were calculated at 298 K (see Figs and Supporting information†) and at 0 K (see Supporting information†).

1. Cytosine and uracil

Molecules so far identified in interstellar regions using infrared and/or microwave spectroscopy are listed in Table 1. Which of these molecules could be used to construct cytosine and uracil in interstellar molecular clouds or interstellar ice regions? Likely reactions in interstellar regions could involve heterocumulenes. Cumulenes and heterocumulenes comprise some 30% of all detected interstellar molecules: many of these are particularly reactive species, some are electron deficient carbenoid systems. Certain of these, for example, :CCCNH[49–51] and :CCCO[52] might be used as building blocks for the formation of cytosine and uracil. Alternatively, interstellar molecules containing the nitrile group could be possibilities: for example, cyanoacetylene and cyanoacetaldehyde have already been proposed as precursor molecules in prebiotic syntheses of pyrimidine nucleobases.[29–33] Perhaps they may also be precursors in interstellar regions?

1.1 The reactions of CCCNH and CCCO with urea. A simple method to form cytosine could involve a two-body reaction between the interstellar molecules CCCNH[49–51] and urea.[13] The mechanism by which this process is proposed to occur is shown in Fig. 1a. The first step involves the carbene centre of :CCCNH interacting with an NH_2 of urea to form an NC bond and transfer H to the carbene site to form intermediate **2**. This intermediate then effects intramolecular nucleophilic attack at the electrophilic CCCNH carbon with accompanying H transfer to the central carbon to yield cytosine. The second step of this reaction is synchronous; there is no low-energy process involving nucleophilic attack followed by proton transfer. The analogous reaction between CCCO[52] and urea[13] to form uracil does not occur. The reaction coordinate profile of this system (Fig. 1b) is different

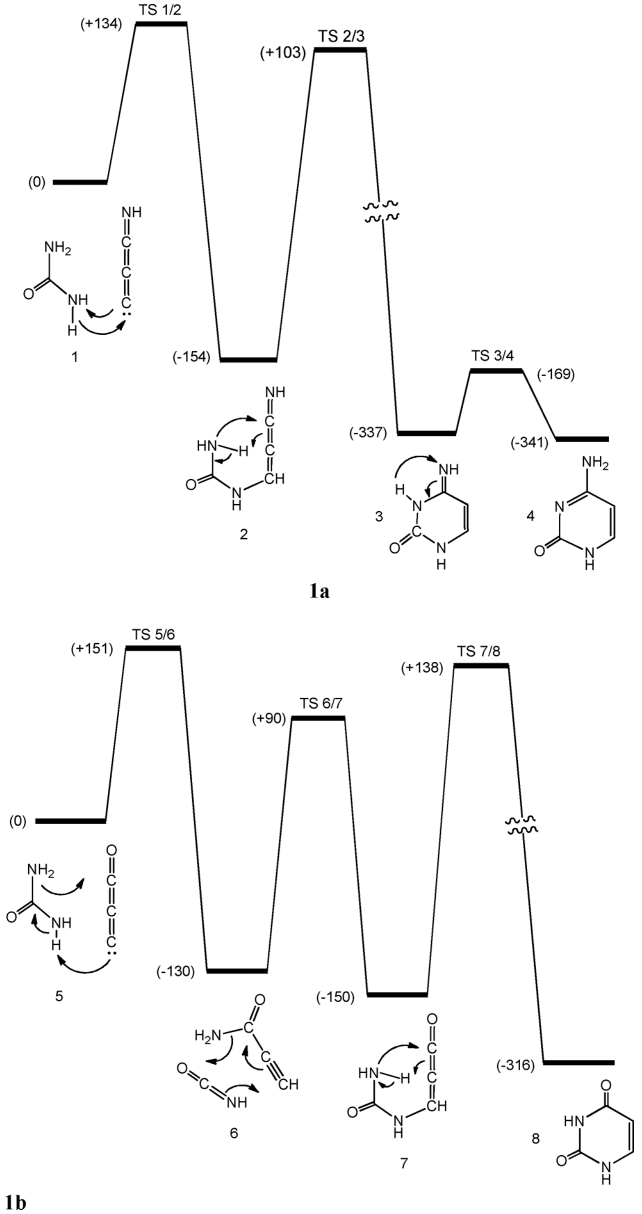

Fig. 1 Reaction coordinate diagrams for the condensation of (a) CCCNH and (b) CCCO with urea. CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. Δ*G* energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Tables S1a and S1b†.

from that shown in Fig. 1a. This reaction is both unusual and counter intuitive, with the carbene centre adding a H from one NH_2, while the other amino group of urea attaches to the carbonyl carbon of CCCO to form a complex between isocyanic acid and propiolamide (**6**). This intermediate rearranges to **7** which then undergoes a synchronous reaction analogous to that shown in step two of Fig. 1a. Relative free energies (Δ*G*) in kJ mol^{-1} calculated at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory are shown in Fig. 1a and 1b. Structures and energies of all minima and transition states shown in Fig. 1a and 1b are recorded in Supporting information Tables S1a and S1b†.

For the reactions shown in Fig. 1 to be effective as interstellar syntheses, they need to be as efficient as possible from both kinetic and thermodynamic points of view. Although $\Delta G_{\text{reaction}}$ values for each sequence are favourable, the barriers to the highest energy transition states are quite significant which make these reactions kinetically unfavourable. How might the barriers to the transition states for the rate determining step in each reaction coordinate system be reduced? The first possibility is if the rate determining steps of these processes occur with H tunnelling at low temperatures: the second is if the reactions are carried out on interstellar ice, where the possibility of solvation of a reactant might reduce the barrier to the transition state in the rate determining step of each reaction.

Recently, in seminal investigations, Schreiner and colleagues[53] reported that the carbenoid systems :CROH (R = H, CH_3) convert intramolecularly to the more stable isomer RCHO at temperatures close to absolute zero. The rate determining step of this reaction involves carbene interaction with the OH bond, with hydrogen tunnelling effectively "reducing" the energy barrier to the transition state. The first, and rate-determining steps of the reactions shown in Fig. 1a and 1b involve the intermolecular interaction of a carbene moiety with an NH bond of urea: perhaps hydrogen tunnelling will assist this process? The tunnelling computations used in this investigation are explained in detail in the Supporting information section†. Two different methods (Eckart and WKB) [54–57] were used for this study. The processes investigated here (the first steps in Fig. 1a and 1b), have extremely low tunnelling corrected rate constants at low temperature (see Supplementary information Fig. S4 and Fig. S6†), *e.g.*, ~10^{-40} s^{-1} (k_{WKB}) at 125 K for Fig. 1a, and ~10^{-32} s^{-1} (k_{WKB}) at 150 K for Fig. 1b. These figures indicate that the tunnelling effect is negligible for the first step of the reactions shown in Fig. 1a and 1b.

There have been studies reported where gas-phase reaction coordinates (like those shown in Fig. 1a and 1b) have been modified by addition of solvent molecules (usually water) to a reactant in order to change the barrier to the transition state in the rate determining step of that reaction.[*e.g.* 58] We have carried out extensive computational investigations using such models for the reaction coordinate profiles shown in Fig. 1a and 1b. One to three molecules of water solvated to urea have been investigated: only the simplest systems of relevance are described here. Consider the reactions of :CCCNH and :CCCO with monosolvated urea [$NH_2C({=}O)NH_2$ (H_2O)]. There are a number of positions where a water molecule may be attached to urea and a number of ways it may interact within the reacting system. The first reaction possibilities are shown in Fig. 2a and 2b (full structure and energy data are given in Supporting information Tables S2a and S2b†). The first step of each reaction is equivalent to those shown in Fig. 1a and 1b. Solvated urea is less reactive in the carbene addition steps with barriers in the first rate-determining steps being increased over those shown in Fig. 1a and 1b. In contrast, subsequent steps in Fig. 2a and 2b are more facile than the equivalent steps shown in Fig. 1a and 1b.

A very different scenario is shown in Fig. 3a and 3b. The barriers to all steps in these reaction sequences are now significantly smaller than those shown in Fig. 1a and 1b, with the mechanisms of the processes different from those of Fig. 1 and 2. The reaction sequences shown in Fig. 3a and 3b are similar and surprisingly complex. Structures and energies of all species are recorded in Supporting information Tables S3a and S3b†. Consider Fig. 3a as illustrative. The carbene centre interacts with the water moiety

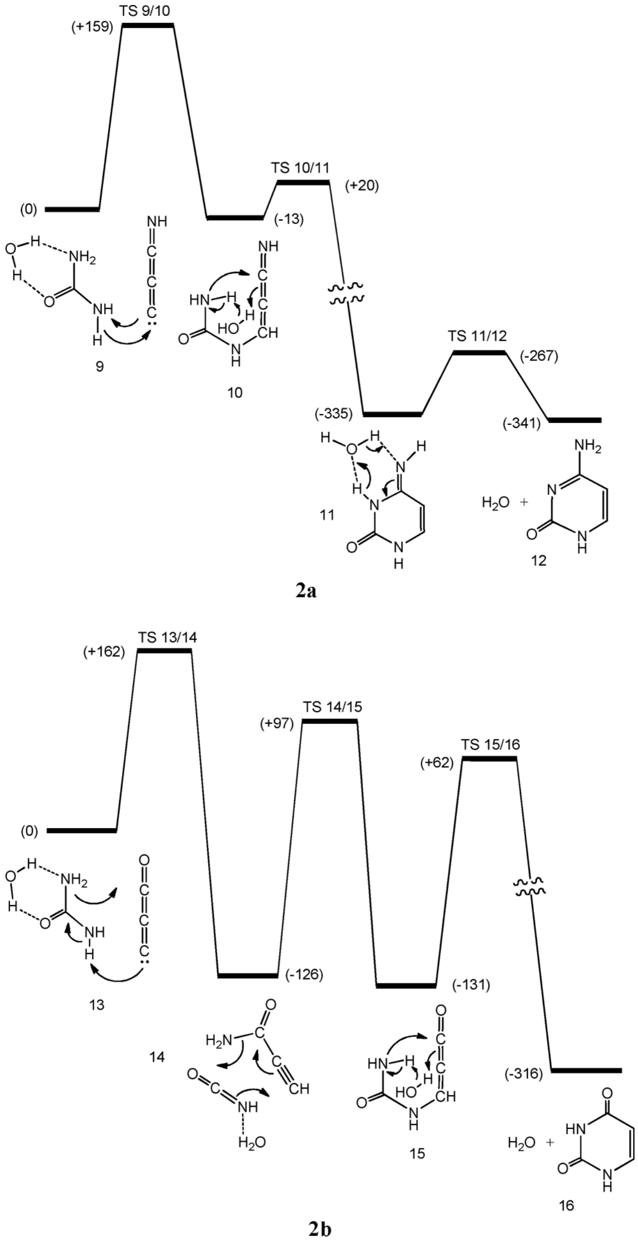

Fig. 2 Reaction coordinate diagrams for the condensation of (a) CCCNH and (b) CCCO with mono solvated urea (route 1). CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. ΔG energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Tables S2a and S2b†.

of urea monohydrate accompanied by cyclisation in the rate determining first step of the reaction to produce key reactive intermediate **19**. The nature of the HOMO of this unusual intermediate suggests dipolar character (see Supporting information Fig. S9†): the dipolar valence bond structure of **19** is drawn in Fig. 3a. Cyclisation accompanied by synchronous protonation and deprotonation involving the water molecule forms reactive intermediate **20** which effects facile H transfer to **21**. Nitrogen inversion within **21** followed by repositioning of the water molecule forms **3** which undergoes the final six-centred H transfer to form cytosine. $\Delta G_{\text{reaction}}$ (−341 kJ mol^{-1}) is very favourable with the barrier of the first and rate determining step of only +73 kJ mol^{-1}.

The uracil synthesis shown in Fig. 3b is similar to the cytosine synthesis except that uracil does not require the final H transfer (*cf.* Fig. 3a and 3b).

The processes shown in Fig. 3 are kinetically more favourable than those summarised in Fig. 1 and 2, and would *seem to constitute viable interstellar syntheses from available starting materials*.‡ However, these reaction sequences initially involve three body reactions (water, urea and *e.g.* :CCCNH): the probability of the occurrence of these is smaller than the two-body reactions shown in Fig. 1, even if the reactions are taking place on the surface of interstellar ice, or attached to carbon or silicate dust particles (with condensed water ice on the dust particles) in dense molecular clouds.

1.2 The formation of cytosine from cyanoacetylene and cyanoacetaldehyde.

Cyanoacetylene[60] is a known interstellar molecule and cyanoacetaldehyde is a degradation product of cyanoacetylene.[61] They have been proposed as precursors to cytosine in prebiotic syntheses on earth,[29–33] and cyanoacetylene has been proposed as a precursor to extraterrestrial pyrimidines,[62] and there has been debate as to which of the two is the more likely precursor.[29–33] Additions of cyanoacetylene or cyanoacetaldehyde to urea, should, at least theoretically, yield cytosine with $\Delta G_{\text{reaction}}$ of some −150 kJ mol^{-1} or less. However, the rate determining steps of these processes have barriers of ≥200 kJ mol^{-1}, and as such are not favourable interstellar processes (data not included here).

In Fig. 4 and 5 are shown specific examples of addition reactions of urea–water monosolvates with cyanoacetylene and cyanoacetaldehyde respectively. Full details of energies and structures are listed in Supporting information Tables S4 and S5†. Both sequences have favourable $\Delta G_{\text{reaction}}$ values, but maximum barriers of 170–250 kJ mol^{-1} make the processes less favourable than those shown in Fig. 3. The mechanism of the urea/cyanoacetaldehyde (water) process is particularly interesting, with the water molecule involved directly in reactions in every step, namely protonation/deprotonation (step 1), anti-elimination of water (rate determining step 2), protonation/deprotonation (step 3) and proton transfer (step 4).

1.3 The interconversion of uracil and cytosine.

It would seem a prerequisite for the utilisation of the five RNA/DNA bases as genetic markers that they should be stable and not degradable in solution, yet there have been many reports of nucleic acid damage involving deamination of cytosine.[63–65] Cytosine deamination in biological media is a slow process, and a genetic assay for this process was reported in 1990.[66] A number of specific reports of the deamination of cytosine are available, and a selection of these follows: deamination with sodium bisulfite,[67] metal mediated deamination[68] and nitric oxide deamination.[69] Various computational studies have considered the deamination of cytosine.[70–73] The proposed formation of uracil (Fig. 3b) involves the use of :CCCO, a species which occurs in relatively high abundance in some molecular clouds.[49] The proposed formation of cytosine requires :CCCNH, a species not as available as :CCCO since

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‡ Hydrolysis of urea by one molecule of water is not likely to compete with the reactions shown in Fig. 3. Urea does hydrolyse slowly in water (as solvent) to form ammonia and carbamic acid: the carbamic acid is unstable and decomposes to ammonia and carbon dioxide. Urea can be hydrolysed, for example in soils, with the extracellular enzyme urease acting as a catalyst: even so, the reaction can be slow.[59]

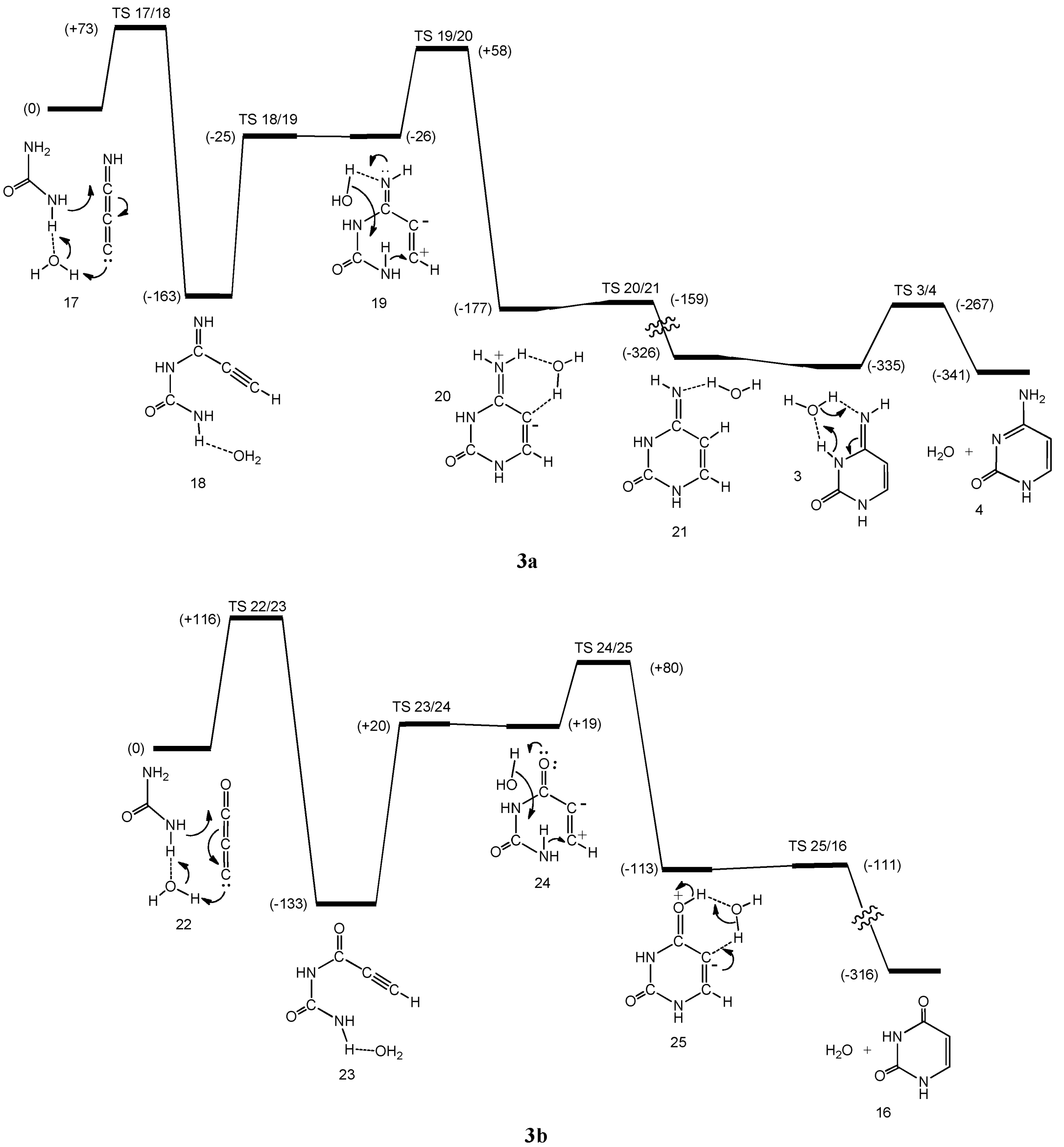


Fig. 3 Reaction coordinate diagrams for the condensation of (a) CCCNH and (b) CCCO with mono solvated urea (route 2). CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. ΔG energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition state see Supporting information Tables S3a and S3b†.

when energised, :CCCNH may rearrange to the more stable isomer HCCCN.[52] Any facile gas-phase conversion of uracil to cytosine could therefore be of significance. Extensive *ab initio* calculations have been carried out for reversible conversion of uracil to cytosine using both varying numbers of water molecules and the H_2O/OH^- system.[70–73] The highest energy transition states in these processes range from +130 to +220 kJ mol^{-1}, values which limit the interstellar applicability of these reactions.

We have extended the theoretical investigation of a possible uracil/cytosine interconversion using neutrals, radicals and anions derived from ammonia. The lowest energy process has an energy requirement of +108 kJ mol^{-1}. This process is shown in Fig. 6; full details of energies and geometries of all species in Fig. 6 are listed in Supporting information Table S6†. However the uracil tautomer involved in this reaction lies 42 kJ mol^{-1} above the usual keto tautomer of uracil and interconversion of the two (using one molecule of water to assist the proton transfer) involves a barrier of 82 kJ mol^{-1} to access the six-centred transition state (from the keto tautomer of uracil). *Thus there appears to be no simple and low-energy process available in interstellar regions to provide a viable interconversion of uracil to cytosine.*

2 Possible interstellar syntheses of thymine?

To devise a viable interstellar synthesis of thymine is challenging because of the presence of the methyl substituent. Either this methyl group must be added late in the synthesis [*e.g.* in the reaction between methylene (:CH_2) and uracil], or it must be present on one of the precursor molecules. In solution, methylene can be generated in a number of ways, for example by photolysis of diazomethane, with methylene often reacting in an indiscriminate manner by competitive interaction with single and double bonds.

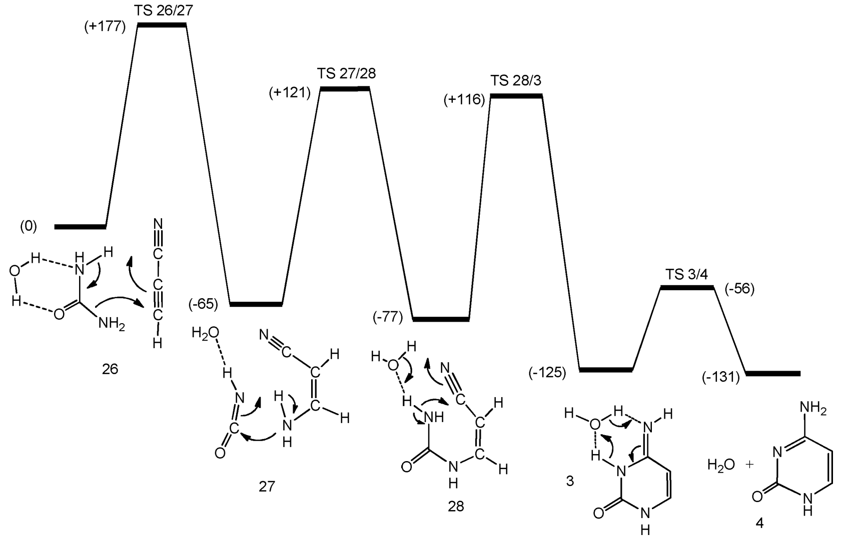


Fig. 4 Reaction coordinate diagram for the reaction of cyanoacetylene with monosolvated urea. CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. ΔG energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Table S4†.

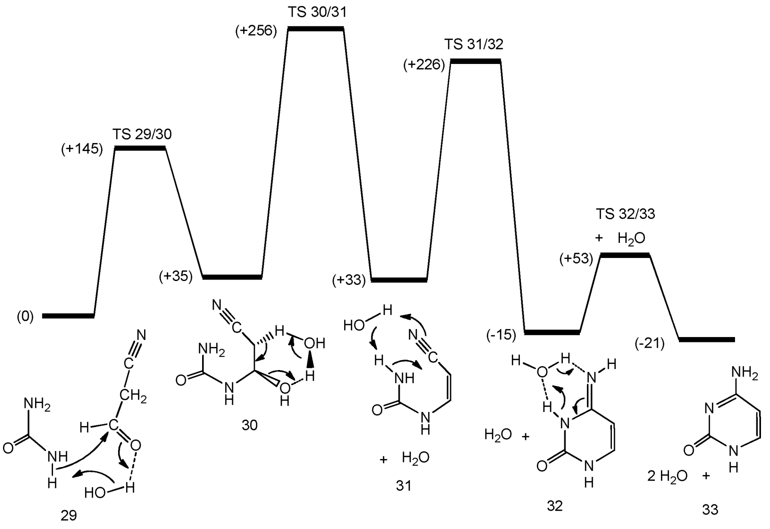


Fig. 5 Reaction coordinate diagram for the reaction between monosolvated cyanoacetaldehyde and urea. CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. ΔG energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Table S5.1.3 The interconversion of uracil and cytosine†.

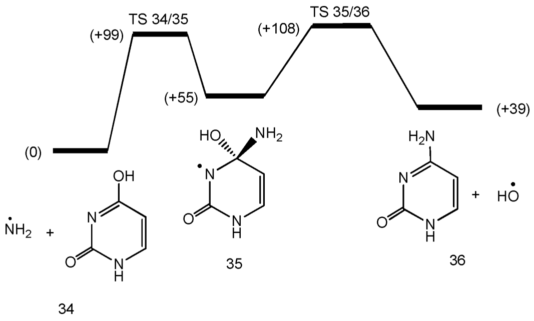
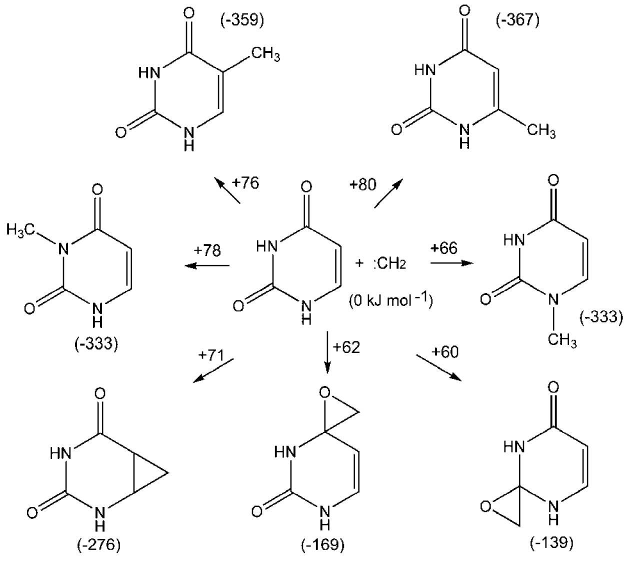


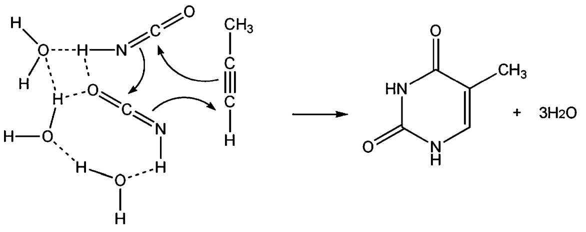
Fig. 6 Reaction coordinate diagram for the reaction between the enol form of uracil and NH_2 to form cytosine. CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. ΔG energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Table S6†.

How will uracil and methylene react in the gas phase? The results of calculations at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory are shown in Scheme 1. All the reactions shown are energetically feasible, with those forming thymine and 1-methyluracil being the most kinetically favoured. However, the multiple processes which may occur mask the specific reaction between methylene and uracil to form thymine, thus this process does not constitute an efficient interstellar synthesis of thymine.

The only other identified interstellar molecules that might, in principle, act as precursors of the methyl group of thymine are propyne (CH_3C_2H)[74,75] and propional (CH_3CH_2CHO),[76] neither of which is a reactive carbenoid system. The simplest process would be the synchronous reaction between one molecule of propyne and two of isocyanic acid,[10] but calculations at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory fail to



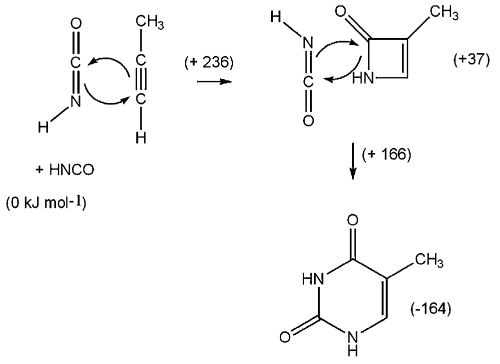
Scheme 1



Scheme 2

find any transition state for this process. Addition of three molecules of water to the two isocyanic acid molecules leads to the reaction shown in Scheme 2. $\Delta G_{\mathrm{reaction}}$ for this process is favourable (–228 kJ mol^{-1}) but the barrier to the transition state is unfavourable (+188 kJ mol^{-1}). Another unfavourable aspect of this process is that isocyanic acid can be hydrolysed in the presence of water to form carbon dioxide and ammonia. The lowest energy profile of the reaction of isocyanic acid with one molecule of water has $\Delta G_{\mathrm{reaction}}$ = –98 kJ mol^{-1} with a barrier of +204 kJ mol^{-1} for the first and rate determining step (the addition of H_2O across the C=N bond of HNCO) [see Supporting information Fig. S1, CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory†]. This hydrolysis may compete with the process shown in Scheme 2.§

A stepwise process was uncovered while searching the CH_3C_2H/2 HNCO potential surface. This is shown in Scheme 3.



Scheme 3

The process is novel, involving two four centre cyclisation processes. The overall process is favourable ($\Delta G_{\mathrm{reaction}}$ = –164 kJ mol^{-1}) but the first cyclisation step has a high energy demand; the barrier to the transition state is +236 kJ mol^{-1}.

Woodward and Hoffmann proposed that a ground-state pericyclic change is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is odd, where $(4q+2)_s$ and $(4r)_a$ refer to suprafacial (4*q*+2)-electron and antarafacial (4*r*)-electron components, respectively.[77] In the case of the reaction shown in Scheme 3, the HOMO of the transition state of the first step is displayed in Supporting information Fig. S2a†. There is a radical centre located on the O atom of HNCO, which takes little part in the reaction. The frontier orbitals are the p orbitals of the two middle C atoms of CH_3CCH plus N and C atoms of HNCO with opposite algebraic sign overlap. The first step of the reaction is thermally forbidden, since it involves an even number of electron pairs (2 pairs of π electrons, 1 pair from HNCO and 1 pair from CH_3C_2H) with 2 antarafacial components. This is in accord with the high barrier calculated for this step (+236 kJ mol^{-1}). The HOMO of the intermediate from the first step is shown in Supporting information Fig. S2b†, with the addition of another molecule of HNCO involving 2 pairs of electrons and 1 antarafacial component, indicating a thermally allowed reaction. However, the frontier orbital distributed on the reacting C atom in step two is small, resulting in the barrier for the second step being significant (+129 kJ mol^{-1}).

Adding one or two molecules of water to the isocyanic acid reactants shown in Scheme 3 increases the energies to both transition states together with the probability of some hydrolysis of HNCO. Thus the interactions between propyne and isocyanic acid are not appropriate interstellar reactions.

The results of the theoretical calculations described above suggest that propyne is not a likely precursor to thymine, which means that only propional (CH_3CH_2CHO) now remains to be investigated. In order to be a thymine precursor, propional needs to be modified to have both electrophilic (on the carbonyl carbon) and nucleophilic or radical reaction centres (on the central carbon). Either radical $CH_3{}^{\bullet}CHCHO$ or the enolate anion ($CH_3{}^{-}CHCHO$) is required. Neither of these species has yet been reported in interstellar media but $CH_3{}^{\bullet}CHCHO$ may be formed by reaction of propional with a radical, *e.g.* $H^{\bullet}$, $HO^{\bullet}$ or $NH_2{}^{\bullet}$ (*cf.* Table 1). Calculations at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory indicate that reaction of propional with $HO^{\bullet}$ gives both ${}^{\bullet}CH_2CH_2CHO$ and $CH_3{}^{\bullet}CHCHO$, with the

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§ Intuitively, the barrier of +204 kJ mol^{-1} for the rate-determining addition of water in this gas phase reaction seems high, because HNCO is readily hydrolysed in water. However the condensed phase reaction is different (from the gas-phase process), since it is carried out in water, a polar solvent with a high dielectric solvent (ε_{H_2O} = 78). When water is used as solvent, the high dielectric constant of that solvent reduces the Coulombic attraction within a transition state involving charge separation, reducing the energy barrier required to surmount that transition state. In accord with this proposal, when HNCO is allowed to react with two molecules of water, the barrier to the transition state reduces from +204 to +152 kJ mol^{-1} at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory. Thus the hydrolysis of HNCO will compete with the cyclisation process shown in Scheme 2 as the number of water molecules attached to HNCO increases.

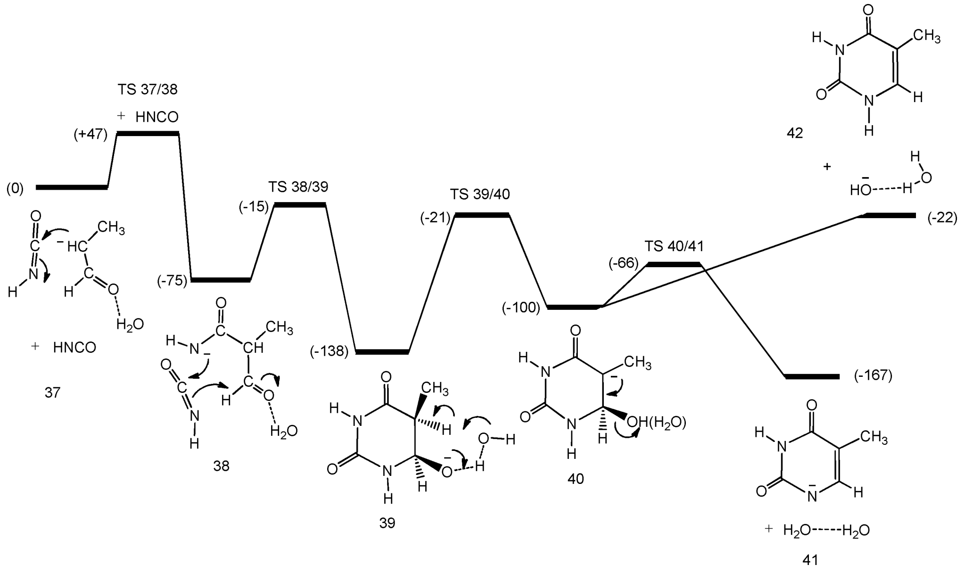

Fig. 7 Reaction coordinate diagram for the reaction between the mono hydrated propional enolate anion and two molecules of isocyanic acid to produce thymine. Δ*G* energies in kJ mol^{-1}. For full details of energies and geometries of minima and transition states see Supporting information Table S7†. The reaction $CH_3CH_2CHO + HO^- \rightarrow CH_3{}^-CHCHO(H_2O)$ is favourable [$\Delta G_{reaction} = -142$ kJ mol^{-1} at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory].

former formed in the higher yield (data not provided). We have not investigated the radical system further.

In contrast, the enolate anion can be formed exclusively by the reaction of propional with a powerful gas-phase base, *e.g.* HO^- (from interstellar ice or NaOH[78]) or a cumulene anion C_nH^- [(n = 2, 4, 6);[79] for example, the ΔG^o_{acid} values of acetylene (precursor of C_2H^-) and propional (precursor of $CH_3{}^-CHCHO$) are 1529 and 1504 kJ mol^{-1} respectively),[80,¶] thus the acetylide anion will deprotonate propional. Enolate anions of this type have not, to date, been identified in interstellar environments, but there is no reason why they should not be present, particularly in view of the recent detection of a range of cumulene anions.[79,82–89] A reaction coordinate diagram for the reaction between the monosolvated propional enolate anion and two molecules of isocyanic acid is shown in Fig. 7, with details of the energies and geometries of all structures (in Fig. 7), listed in Supplementary information Table S7†.

The reaction sequence shown in Fig. 7 is favourable ($\Delta G_{reaction}$ = –22 kJ mol^{-1}) while the barrier for the rate-determining step is only 47 kJ mol^{-1}. At no stage does the molecule of water attach to isocyanic acid, so competitive hydrolysis of isocyanic acid is not an issue. The initial cyclic intermediate has two chiral centres and four diastereoisomers. Two of the diastereoisomers may have the H and "OH" to be eliminated *anti* to each other, all four diastereoisomers may have them in *gauche* orientations, while the two diastereoisomers that cannot have the two substituents *anti*, may have them *eclipsed*. The particular conformer of the chosen diastereoisomer **39** shown in Fig. 7 has the H and "OH" (to be eliminated) *gauche* to each other and the elimination reaction is stepwise, proceeding through carbanion intermediate **40**. This *gauche* elimination shows two possible pathways to products; namely, to form (a) thymine and $[HO^-(H_2O)]$ [$\Delta G_{reaction}$ = –22 kJ mol^{-1}] and (b) the thymine anion plus $(H_2O)_2$ [$\Delta G_{reaction}$ = –167 kJ mol^{-1}]. These processes may occur for all four of the diastereoisomers.[‖] Two diastereoisomers can have the H and "OH" eclipsed giving a planar six centre state: the other two diastereoisomers can have the H and "OH" *anti* to each other. The *gauche* elimination is shown in Fig. 7, with the *anti* and *eclipsed* (*planar*) eliminations represented in Supporting information Figs. S7a and S8† respectively (full details of structures and energies are listed in Supporting information Tables S7a and S8†). The three processes are energetically favourable interstellar syntheses of thymine: the lowest energy elimination is that involving *eclipsed* substituents (planar six-centred transition state) by 38 kJ mol^{-1}.

Initially, these are three-body reactions. Even if the reactions occur on the surface of interstellar 'dust', the probability of the reaction occurring is low.

The temperature of the calculation

All reaction coordinate profiles shown in the Figures were calculated at 298 K. The Supplementary information section also contains data for reaction coordinate profiles calculated at 0 K.† A reviewer has suggested that it might be more appropriate to show the 0 K (rather than 298 K) calculations in the Figures. That would be misleading for two reasons. First, the reactions cannot occur at 0 K unless there is an H-tunnelling factor (which has not been demonstrated). Second, the representation of processes at 0 K show the reactions to be significantly more kinetically favourable

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[¶] Blanksby[81] suggested that cumulene anions should be present in interstellar regions because of the high electron affinities of the neutral cumulenes. Only recently have such anions been identified in space.[79,82–89]

[‖] When the reaction profile of the analogous system using the propional enolate anion solvated with two molecules of water is investigated, the corresponding intermediate to **40** decomposes solely to thymine (**42**) plus $[HO^-(H_2O)_2]$. Under these conditions, $[HO^-(H_2O)_2]$ does not deprotonate thymine to form the thymine anion.

than those at 298 K and this is arguably too optimistic a statement to make for these reactions. At 0 K, [$\Delta G = \Delta H$], so, in general, the barriers to the transition states of the rate determining steps are reduced, even though $\Delta G_{\text{reactions}}$ values at 0 K, although still negative, are less favourable. Consider the detail. For Fig. 1a, 1b, 2a, 2b, 3a, 3b, 4, 5, 6 and 7, the barriers to each rate determining step at 0 K are reduced by 47, 45, 76, 80, 58, 85, 78, 99, 42 and 40 kJ mol^{-1} respectively from those calculated at 298 K. $\Delta G_{\text{reaction}}$ values are still favourable but less negative in all cases than those calculated at 298 K. To take two examples, the favourable processes shown in Fig. 3a and 7 (at 298 K) are close to barrierless at 0 K [Fig. 3a (barrier 15 kJ mol^{-1}) and Fig. 7 (barrier 7 kJ mol^{-1}).

We do not know the temperature at which each of the described reactions might occur in particular regions of molecular clouds; greater than 100 K in some cases would seem possible, but presumably less than 298 K. The data shown in the Figures (at 298 K) give more realistic insights of the likelihood of a particular reaction than those recorded at 0 K.

Conclusions

Theoretical studies at the CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory suggest that:

1. The reactions between :CCCNH and :CCCO with monohydrated urea may constitute viable interstellar syntheses of cytosine and uracil.
2. The reactions of NCC_2H and $NCCH_2CHO$ with water and urea can, in theory, produce cytosine, but the energy requirements for these reactions are high.
3. No low energy equilibration between uracil and cytosine has been demonstrated.
4. The insertion of :CH_2 into the 5 C–H bond of uracil forms thymine in an energetically favourable reaction. However, competing reactions where :CH_2 interacts with double bonds and other CH and NH bonds of uracil mask the effectiveness of this thymine synthesis.
5. The reaction between the mono solvated propional enolate anion and isocyanic acid should produce thymine. $\Delta G_{\text{reaction}}$ is –22 kJ mol^{-1} and the maximum energy requirement (barrier to the transition state in the rate-determining step) is + 47 kJ mol^{-1}; *this may be a possible route to thymine in interstellar media.*

Theoretical methods

Geometry optimisations were carried out at the B3LYP/6-311++G(d,p) level of theory,[90] within the GAUSSIAN 09 suite of programs.[91] Stationary points were characterised as either minima (no imaginary frequencies) or transition states (one imaginary frequency) by calculation of the frequencies using analytical gradient procedures. The minima connected by a given transition structure were confirmed by intrinsic reaction coordinate (IRC) calculations.[92] The calculated frequencies were also used to determine zero-point vibrational energies. More accurate energies for the B3LYP geometries were determined using the using CCSD(T) method[93] together with the 6-311++G(d,p) basis set, including zero-point vibrational energies (ZPVEs) correction (unscaled). Reaction coordinate profiles referred to in the text or a figure are calculated at 298 K. Reaction coordinate profiles calculated at 0 K are recorded as Supporting information†. In some cases (*i.e.*, tunnelling effect) other levels of theory were used: when this was done it is specifically mentioned in the text.

The tunnelling corrected rate constants for the first steps in Fig. 1a and 1b was evaluated by the WKB (Wentzel–Kramers–Brillouin) method within a reaction-path Hamiltonian model by multiplying the classical rate at which the reactant hits the reaction barrier by the quantum mechanical transmission probability.[54,55] In comparison, the tunnelling contributions to the rate constant were also estimated using the Eckart method, in which the cross-section of the potential energy surface is fitted with the Eckart potential.[56,57] Full details (including comparisons) of the two methods (together with Figs. S3–S6) and the results of the calculations for the rate determining steps of the processes shown in Fig. 1a and 1b are contained as Supplementary information†.

All calculations were carried out using eResearch [the South Australian Partnership for Advanced Computing (SAPAC) Facility], and the Australian Partnership for Advanced Computing (APAC) [Australian National University (Canberra)] facilities.

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