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Radical routes to interstellar glycolaldehyde. The possibility of stereoselectivity in gas-phase polymerization reactions involving CH_2O and $^{\bullet}CH_2OH$†

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A previous report that the interstellar molecule glycolaldehyde ($HOCH_2CHO$) can be made from hydroxymethylene (HOCH:) and formaldehyde has been revisited at the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. This reaction competes with the formation of acetic acid and methylformate, molecules which have also been detected in interstellar clouds. Other possible modes of formation of glycolaldehyde by radical/radical reactions have been shown to be viable theoretically as follows:

$$HO^{\bullet} + {}^{\bullet}CH_2CHO \rightarrow HOCH_2CHO \; [\Delta G_r(298\text{ K}) = -303\text{ kJ mol}^{-1}]$$

$$HOCH_2^{\bullet} + {}^{\bullet}CHO \rightarrow HOCH_2CHO \; (-259\text{ kJ mol}^{-1})$$

The species in these two processes are known interstellar molecules. Key radicals $^{\bullet}CH_2CHO$ and $^{\bullet}CH_2OH$ in these sequences have been shown to be stable for the microsecond duration of neutralization/reionization experiments in the dual collision cells of a VG ZAB 2HF mass spectrometer. The polymerization reaction $HOCH_2CH^{\bullet}OH + nCH_2O \rightarrow HOCH_2[CH(OH)]_n{}^{\bullet}CHOH$ ($n = 1$ to 3) has been studied theoretically and shown to be energetically feasible, as is the cyclization reaction of $HOCH_2[(CH_2OH)_4]^{\bullet}CHOH$ (in the presence of one molecule of water at the reacting centre) to form glucose. The probability of such a reaction sequence is small even if polymerization were to occur in interstellar ice containing a significant concentration of CH_2O. The large number of stereoisomers produced by such a reaction sequence makes the formation of a particular sugar, again for example glucose, an inefficient synthesis. The possibility of stereoselectivity occurring during the polymerization was investigated for two diastereoisomers of $HOCH_2[(CHOH)]_2{}^{\bullet}CHOH$. No significant difference was found in the transition state energies for addition of CH_2O to these two diastereoisomers, but a barrier difference of 12 kJ mol^{-1} was found for the H transfer reactions $^{\bullet}OCH_2[(CHOH)]_2CH_2OH \rightarrow HOCH_2[(CHOH)_2{}^{\bullet}CHOH$ of the two diastereoisomers.

Introduction

The question as to whether the building chemicals of life originated from outer space[1] and/or by chemical reactions on prebiotic Earth[2,3] is still a matter of debate.[4,5]

More than 140 neutrals and ions have been identified from spectral lines in interstellar dust clouds, molecular clouds, circumstellar regions surrounding carbon-rich exploded suns and regions of interstellar ice.[6] One of the most interesting current debates concerns the possible identification of the prototypical amino acid glycine ($NH_2CH_2CO_2H$) in interstellar regions (*e.g.* ref. 7), these reports have been challenged.[8] Perhaps the difficulty of detecting glycine is a consequence of the instability of carboxylic acids to withstand ultraviolet and cosmic ray irradiation.[9]

In contrast, the proto two-carbon sugar glycolaldehyde ($HOCH_2CHO$) has been detected in emission towards the Galactic centre source Sagittarius B2(N) by means of multimeter-wave rotational transitions,[10,11] while the reduced analogue ethylene glycol ($HOCH_2CH_2OH$) has been similarly detected towards Sagittarius B2(N-LMH).[12] A preliminary search for the three-carbon sugar glyceraldehyde [$HOCH_2CH(OH)CHO$] toward Sagittarius B2(N) was unsuccessful.[13]

At the time of the identification of interstellar glycolaldehyde it was proposed that glycolaldehyde (and perhaps other sugars) may arise from dimerization of interstellar formaldehyde and that such polymerization reactions may account for the formation of a range of other interstellar molecules including *e.g.* acetic acid and methylformate.[10] A specific scenario proposed for the syntheses of glycolaldehyde and higher sugars from

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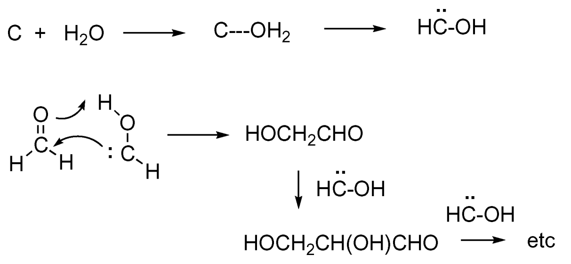
† Electronic supplementary information (ESI) available: Energies and selected geometries of minima and transition states for: the reaction between formaldehyde and hydroxymethylene; nucleophilic attack of water on oxiran-2-ol to form methyl formate; the interconversion of $^{\bullet}CH_2CHO$ to $CH_3{}^{\bullet}CO$; the interconversion of $^{\bullet}CH_2OH$ to $CH_3O^{\bullet}$; the reaction between doublet HCHO and $^{\bullet}CH_2OH$; the reaction between HCHO and $^{\bullet}CH(OH)CH_2OH$. Energies, electronic dipole moments and Cartesian coordinates of minima and transition states for: the glucose cyclization reactions; the glucose/water cyclization reactions; the H transfer reactions of **D** and **F**. H-bonding characteristics changes from reactants to transition states of the H transfer reactions for **C**, **D**, **E** and **F** structures in Scheme 5. See DOI: 10.1039/c0ob00125b

hydroxymethylene (HOCH:) and formaldehyde is shown in Scheme 1.[14–18] Hydroxymethylene has been formed in the laboratory by the reaction of arc-generated carbon with water.[16] The problem with the proposed interstellar synthesis shown in Scheme 1 is with the production of hydroxymethylene, which cannot be formed by the reaction between ground-state triplet carbon (presumably from diamond dust particles in interstellar dust clouds) and water, but can only be formed from "hot" C.[18] So although HOCH: has been shown (by theory) to react directly with formaldehyde without barrier to give glycolaldehyde in an exothermic reaction,[17] an interstellar synthesis (see Scheme 1) involving sequential additions of hydroxymethylene to aldehydes seems a most unlikely scenario.[18] A further mechanistic proposal for the formation of interstellar sugars involves the reaction between formaldehyde and H_3O^+,[19] but the calculated barriers to several transition states in the proposed sequences are appreciable (145–190 kJ mol^{-1}) and suggest such a synthetic sequence to have a low probability. Finally, in the condensed phase, it has been known for nearly 150 years that base-catalysed polymerization of formaldehyde (the formate reaction) can produce up to C_5 sugars, and it has been proposed that apart from the first step of the polymerization, chain extension occurs by the aldol reaction.[20–23]



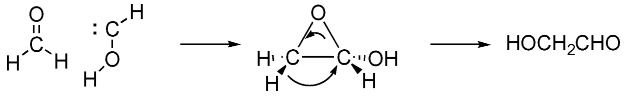
Scheme 1

In this paper, we revisit the hydroxymethylene reaction with formaldehyde and consider, from a joint experimental and theoretical point of view, whether there might be other plausible interstellar syntheses of glycolaldehyde and also perhaps of higher sugars involving radical/radical or radical/neutral reactions.

Results and discussion

1. The hydroxymethylene reaction with formaldehyde

Interstellar glycolaldehyde has been found together with acetic acid and methylformate, and it has been suggested that these three molecules could originate by reactions involving formaldehyde.[10] Even though hydroxymethylene has not been detected in interstellar regions, and it can only be formed from "hot" C (rather than excited triplet C),[18] there are two plausible ways that it can react with formaldehyde. These are (i) the barrierless reaction shown in Scheme 1,[17] and (ii) insertion of HOCH: into the CO double bond of formaldehyde as shown in Scheme 2.[17] A third reaction where carbenoid HOCH: inserts into a CH bond has an appreciable barrier and may be excluded.[17]



Scheme 2

The formation of an oxiran-2-ol intermediate shown in Scheme 2 is of interest as, in principle, it may undergo competitive ring opening reactions to form several interstellar molecules. To investigate this we have revisited the potential surface of the HOCH:/CH_2O system using the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Results are summarized in Fig. 1 and 2 with full details of geometries and energies of intermediates and transition states recorded in Table S1.† All relative energies given in the text and figures are ΔG_r values (at 298 K) in kJ mol^{-1}.

It can be seen in Fig. 1 that HOCH: may react with CH_2O *via* route **A** to form intermediate **1** (+2 kJ mol^{-1}) which converts synchronously through transition state **1/2** (+8 kJ mol^{-1}) to form glycolaldehyde (**2**; −262 kJ mol^{-1}). Species HOCH: may also insert into the carbonyl double bond of formaldehyde over a barrier of +43 kJ mol^{-1} to form oxiran-2-ol (**4**; −181 kJ mol^{-1}). Intermediate **4** may undergo three competitive reactions to form (i) glycolaldehyde (route **B**, −262 kJ mol^{-1}, barrier +34 kJ mol^{-1}), (ii) acetic acid (**5**; −376 kJ mol^{-1}, barrier +93 kJ mol^{-1}), and (iii) methyl formate (**8**; −307 kJ mol^{-1}, maximum barrier +68 kJ mol^{-1}).

Oxirans may be ring opened following or accompanying external nucleophilic attack. Fig. 2 shows the reaction coordinate of the nucleophilic attack of water on oxiran-2-ol to form methyl formate. The oxiran-2-ol is formed with excess energy (−181 kJ mol^{-1}) by the reaction shown in Fig. 1, and an excess energy of +229 kJ mol^{-1} is required to overcome the barriers on the reaction coordinate shown in Fig. 2. The overall reaction to form methyl formate by this route is favourable (−126 kJ mol^{-1}).

The data contained in Fig. 1 and 2 show that (i) glycolaldehyde may be formed directly from complex **1** (H_2CO–HOCH:), formed by reaction between HOCH: and formaldehyde, (ii) glycolaldehyde, acetic acid and methyl formate may, in principle, be formed from an oxiran-2-ol intermediate [produced by insertion of HOCH: into the carbonyl bond of formaldehyde (*cf.* ref. 10)], and (iii) methyl formate may also be formed by the reaction of oxiran-2-ol with water.

2. Other possible interstellar syntheses of glycolaldehyde

Other possible reactions forming glycolaldehyde may involve ionic species or doublet radicals. In this study we are concerned with radical reactions involving molecules already detected in interstellar regions. Three processes that seem plausible are shown in Scheme 3: all reactants and products are known interstellar molecules.[6]

$$HO^{\bullet} + {}^{\bullet}CH_2CHO \rightarrow HOCH_2CHO \quad (1)$$

$$HOCH_2^{\bullet} + {}^{\bullet}CHO \rightarrow HOCH_2CHO \quad (2)$$

$$HOCH_2^{\bullet} + CH_2O \rightarrow HOCH_2CH_2O^{\bullet} \rightarrow HOCH_2CHO + H^{\bullet} \quad (3)$$

Scheme 3

2.1 The HO•/•CH_2CHO addition reaction. Reaction (1) (Scheme 3) is favourable (−303 kJ mol^{-1}) at the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. However, is •CH_2CHO a stable species when energized or does it

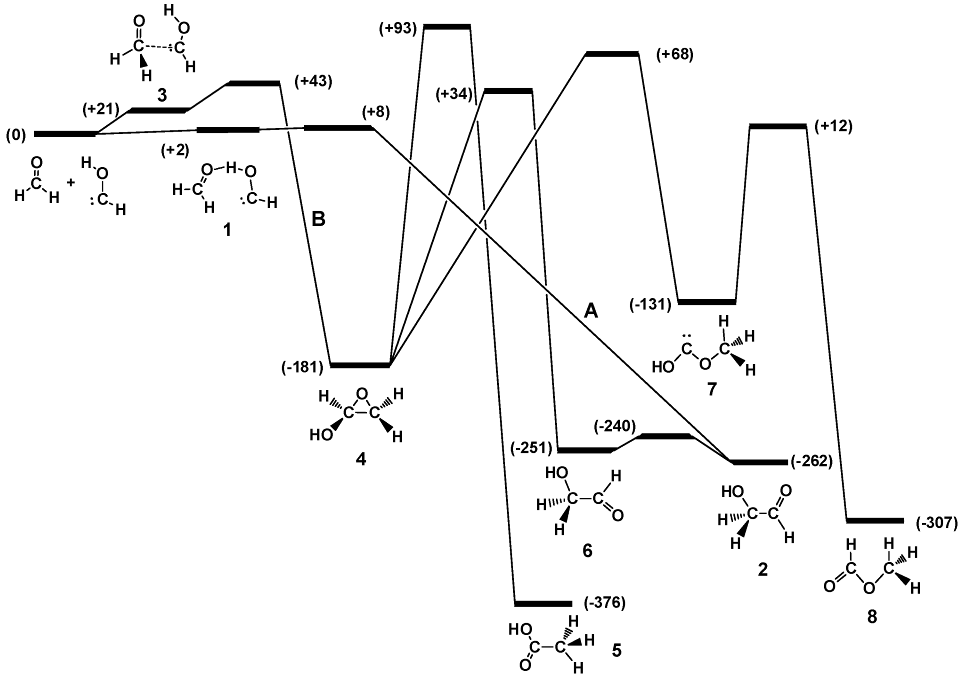


Fig. 1 Reaction coordinate diagram for the reactions between CH_2O and HOCH: to form glycolaldehyde, acetic acid and methyl formate. CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (Δ*G*) in kJ mol^{-1} with respect to reactants (0 kJ mol^{-1}). Details of geometries and energies of minima and transition states are listed in Table S1.†

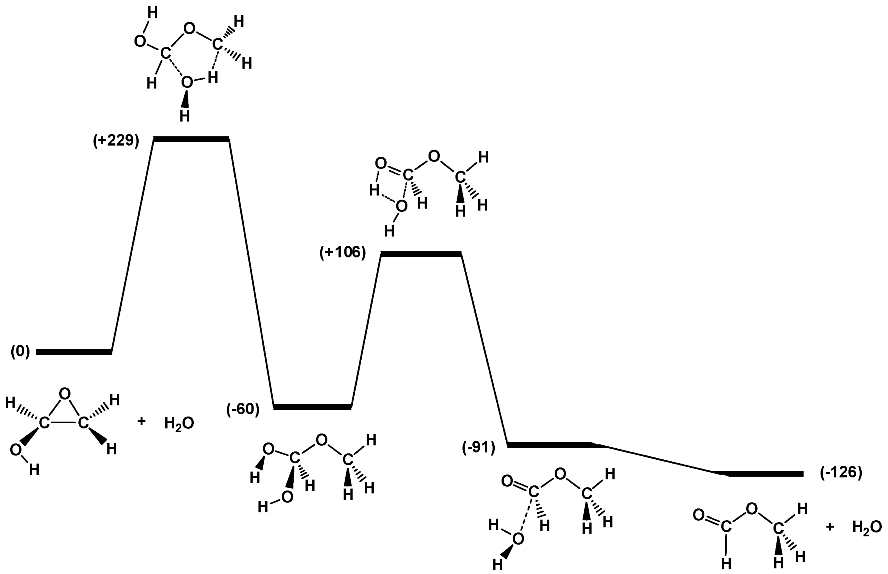


Fig. 2 Reaction coordinate diagram for the reaction between hydroxyoxiran and water to form methyl formate. CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (Δ*G*) in kJ mol^{-1} with respect to reactants (0 kJ mol^{-1}). Details of geometries and energies of minima and transition states are listed in Table S2.†‡

effect H transfer to form the acetyl radical $CH_3{}^{\bullet}CO$ (for a detailed description of the structure of $CH_3{}^{\bullet}CO$ see ref. 24)? The reaction coordinate profile for the interconversion of $^{\bullet}CH_2CHO$ to $CH_3{}^{\bullet}CO$ is shown in Fig. 3, with full details of geometries and energies of minima and the transition state given in Table S3.† The overall reaction is favourable, but there is a barrier of +165 kJ mol^{-1} for the interconversion from $^{\bullet}CH_2CHO$, a value high enough to suggest the stability of both radicals in interstellar media.

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‡ A reviewer has asked if (i) we can determine the reaction coordinate of the reaction between hydroxyoxiran and water to form glycolaldehyde and (ii) compare this with the data available in Fig. 1. Summary results for this reaction were obtained using the level of theory outlined above and are as follows. ΔG_r for the reaction is favourable (−81 kJ mol^{-1}) but Δ$G^{\#}$ (the barrier to the transition state) is +190 kJ mol^{-1}. For the reaction occurring in the absence of water (see Fig. 1), ΔG_r = −81 kJ mol^{-1} and Δ$G^{\#}$ is +215 kJ mol^{-1}. Both reactions are thermodynamically favourable, but kinetically unfavourable.

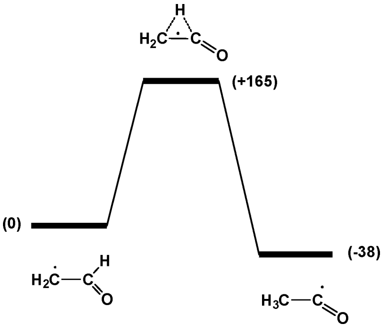


Fig. 3 Reaction coordinate diagram for the interconversion of $^{\bullet}CH_2CHO$ and $CH_3{}^{\bullet}CO$. CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (ΔG) in kJ mol^{-1}. Details of geometries and energies of minima and the transition state are listed in Table S3.†

In order to confirm the stability of $^{\bullet}CH_2CHO$ we have formed the neutral radical in the first collision cell of the tandem collision cell facility of a reverse sector ZAB 2HF mass spectrometer, and have probed the nature of the fragment cations following ionization of the neutral radical in the second collision cell. Radical $^{\bullet}CH_2CHO$ was formed by vertical charge stripping of the enolate anion of acetaldehyde ($^-CH_2CHO$, formed by deprotonation of acetaldehyde in the chemical ionization source of the mass spectrometer). The neutralization/reionization spectrum ($^-NR^+$) (sequential loss of two electrons[25]) of $^-CH_2CHO$ was measured, and this spectrum compared with the charge reversal spectrum ($^-CR^+$) (synchronous loss of two electrons[26]) of the same anion. Any differences between the spectra would be indicative of rearrangement or dissociation of radical $^{\bullet}CH_2CHO$ during the microsecond duration of the $^-NR^+$ experiment.[27] The $^-NR^+$ spectrum of the acetaldehyde enolate anion is shown in Fig. 4. This spectrum is the same within experimental error as the $^-CR^+$ spectrum of the same anion (which has been reported previously[28]), indicating $^{\bullet}CH_2CHO$ to be stable under the experimental conditions used for the charge stripping of the acetaldehyde enolate anion.

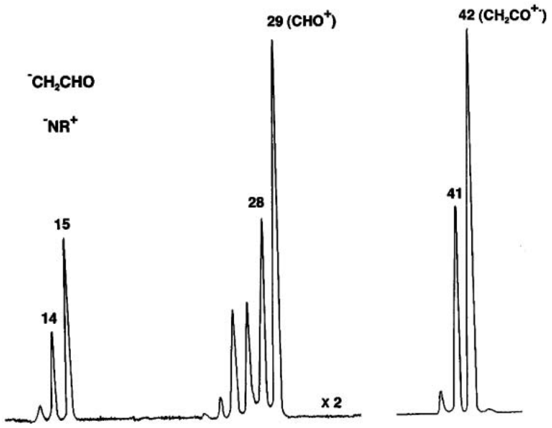


Fig. 4 The neutralization/reionization spectrum ($^-NR^+$) of the acetaldehyde enolate anion ($^-CH_2CHO$). VG ZAB 2HF mass spectrometer. For experimental conditions see Experimental section. For charge reversal ($^-CR^+$) spectrum of $^-CH_2CHO$ see ref. 28.

Thus, theory and experiment suggest that reaction (1) (Scheme 3) is a plausible synthetic route to glycolaldehyde in interstellar regions.

2.2 The $^{\bullet}CH_2OH/^{\bullet}CHO$ addition reaction. Reaction (2) (Scheme 3) is favourable (–259 kJ mol^{-1}) at the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. The formyl radical ($^{\bullet}CHO$) is known to be a stable interstellar molecule,[29] but is $^{\bullet}CH_2OH$ stable when energized or does it effect internal H transfer to form the methoxy radical ($CH_3O^{\bullet}$)? The reaction coordinate profile for the interconversion of $^{\bullet}CH_2OH$ to $CH_3O^{\bullet}$ is shown in Fig. 5, with full details of geometries and energies of minima and the transition state given in Table S4.† The reaction is unfavourable (+34 kJ mol^{-1}) and there is a barrier of +164 kJ mol^{-1} for the interconversion of $^{\bullet}CH_2OH$ to $CH_3O^{\bullet}$, suggestive of the stability of both radicals in interstellar media.

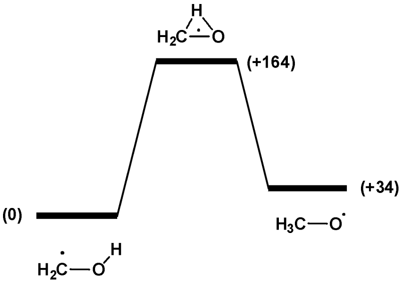


Fig. 5 Reaction coordinate diagram for the interconversion of $^{\bullet}CH_2OH$ to $CH_3O^{\bullet}$. CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (ΔG) in kJ mol^{-1}. Details of geometries and energies of minima and transition state are listed in Table S4.†

In this system, the stability of $CH_3O^{\bullet}$ was examined by comparing the $^-NR^+$ and $^-CR^+$ spectra of the methoxide anion (formed by deprotonation of methanol in the source of the mass spectrometer). In contrast, the radical $^{\bullet}CH_2OH$ cannot be made by charge stripping of $^-CH_2OH$ because this anion is unstable with respect to its radical (*i.e.* the electron affinity of $^{\bullet}CH_2OH$ is negative).[30] So in this case the neutral was made by electron attachment to $CH_2{=}^+OH$ (formed by dissociation of the ethanol radical cation), and the two spectra to be compared are the collision induced MS/MS of the cation and the $^+NR^+$ spectrum. The $^+NR^+$ spectrum of $CH_2{=}^+OH$ and the $^-NR^+$ spectrum of CH_3O^- are shown in Fig. 6 and 7 and are very different, reflecting the differences in structures of the two neutrals. However the CID

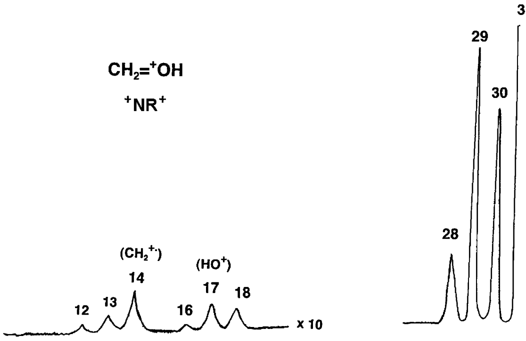
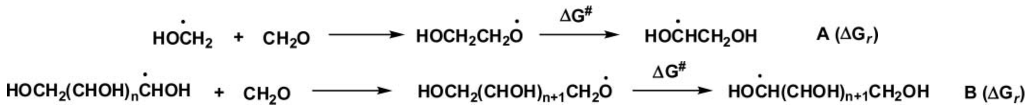


Fig. 6 The neutralization/reionization spectrum ($^+NR^+$) of $CH_2{=}^+OH$. VG ZAB 2HF mass spectrometer. For experimental conditions see Experimental section.

Table 1 ΔG data for further additions of CH_2O and H transfer reactions calculated at MP2/6-31+G(d) level of theory[a]



$$HO\dot{C}H_2 + CH_2O \longrightarrow HOCH_2CH_2\dot{O} \xrightarrow{\Delta G^\#} HO\dot{C}HCH_2OH \quad A\ (\Delta G_r)$$

$$HOCH_2(CHOH)_n\dot{C}HOH + CH_2O \longrightarrow HOCH_2(CHOH)_{n+1}CH_2\dot{O} \xrightarrow{\Delta G^\#} HO\dot{C}H(CHOH)_{n+1}CH_2OH \quad B\ (\Delta G_r)$$

A or B (*n*)		$\Delta G^\#$ (H transfer, kJ mol^{-1})	ΔG_r (kJ mol^{-1})
A		+133 (1,3)	−22
B	(*n* = 0)	+96 (1,4)	−16
	(*n* = 1)	+56 (1,5)	−21
	(*n* = 2)	+69 (1,6)	−58
	(*n* = 3)[b]	+73 (1,7)	−95

[a] The level of theory used for all of these calculations [MP2/6-31+G(d)] [including A and B (*n* = 0)] is different from that used in Fig. 8 and 9 because of the comparison with the larger systems considered here. [b] When *n* = 4, the $\Delta G^\#$ value is +92 kJ mol^{-1} for the corresponding 1,8 H transfer: this means that the conversion of the open chain structure to the C_7 cyclic sugar will be kinetically less favourable than formation of the more stable glucose.

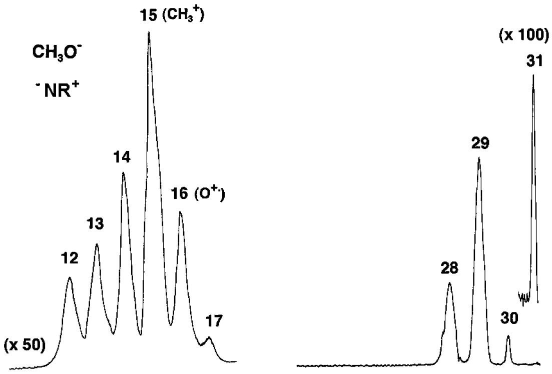


Fig. 7 The neutralization/reionization spectrum ($^-NR^+$) of CH_3O^-. VG ZAB 2HF mass spectrometer. For experimental conditions see Experimental section.

MS/MS and $^+NR^+$ of $CH_2{=}^+OH$ are similar within experimental error, as are the $^-CR^+$ and $^-NR^+$ spectra of CH_3O^- (CID MS/MS and $^-CR^+$ data are not included here (but see ref. 30)).

We conclude that reaction 2 (Scheme 3) is a plausible interstellar synthesis of glycolaldehyde.

2.3 The $^\bullet CH_2OH/CH_2O$ addition reaction.

Reaction 3 (Scheme 3) is different from those considered above, because the initial adduct formed is at a different oxidation level than those discussed above, and must lose a hydrogen atom in order to produce glycolaldehyde. But the initial adduct is at the correct oxidation level to effect a chain-extension sequence with formaldehyde and we will return to this aspect below. It has been shown above that $^\bullet CH_2OH$ is stable for the microsecond duration of the NR process studied in the mass spectrometer, and the radical is therefore an appropriate reactant for this process.

The reaction coordinate profile [at the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory] for the reaction between doublet $^\bullet CH_2OH$ and CH_2O is shown in Fig. 8, with structural and energy data for all minima and transition states shown in Fig. 8 collected in Table S5.† The two reactants combine to form H-bonded intermediate **9** (+12 kJ mol^{-1}), with subsequent C–C bond formation giving $HOCH_2CH_2O^\bullet$ (**10**; +13 kJ mol^{-1}) followed by H loss to produce $HOCH_2CHO$ in an unfavourable reaction (+71 kJ mol^{-1}).

2.4 A free radical/CH_2O polymerization process?

A formaldehyde polymerization process to form a C_6 sugar like glucose in interstellar molecular clouds seems counter-intuitive, but is a reaction sequence of this type energetically feasible? The polymerization reaction involving aldehydes and HOCH: described earlier is a very unlikely scenario in interstellar regions because each step involves addition of hydroxymethylene, a species which can only be formed from 'hot' carbon.[18] A reaction sequence initiated as shown in Fig. 8, where adduct **10** undergoes 1,3 H transfer (barrier to transition state **10/11** is +133 kJ mol^{-1}) to form $HOCH_2{}^\bullet CHOH$ (**11**) which can then add a second CH_2O to yield **12**, which then undergoes (i) $H^\bullet$ loss to form $HOCH_2CH(OH)CHO$ (**13**), and (ii) internal 1,4 H transfer to give $HO^\bullet CHCH(OH)CH_2OH$ (**14**) (see Fig. 9, and Table S6†). Data pertaining to reactions with additional units of CH_2O are listed in Table 1. The least favourable step in this polymerization sequence is the 1,3 H transfer in Fig. 8 which has a barrier of +133 kJ mol^{-1}. The corresponding 1,4 H transfer in Fig. 9 has a barrier of +99 kJ mol^{-1} to surmount transition state **12/14**.§

The ΔG_r (free energy of the defined reaction) and $\Delta G^\#$ (free energy to the transition state for the particular H transfer process) for those processes shown in Fig. 8 and 9, and for the subsequent additions of CH_2O to **14** (Fig. 9) are listed in Table 1. The reactions considered are defined by equations **A** and **B** (*n* = 0–3) in Table 1. The level of theory used to compute the data shown in Table 1 was MP2/6-31+G(d), because the increasing size of the open-chain systems precluded the use of the level of theory used earlier [*i.e.* CCSD/6-311+G(3df,2p)//MP2/6-311++G(3df,2p)]. The data contained in Table 1 show that *as the individual CH_2O additions proceed, increasing the number of CH(OH) units in the open-chain sugar is energetically favourable, provided that the excess energy of CH_2O addition is retained throughout the condensation cycle.*

The major barrier to this formaldehyde polymerization cycle is the 1,3 H rearrangement which occurs following the first addition of formaldehyde (+133 kJ mol^{-1}, Fig. 8). Perhaps there is a more energetically favourable method of forming intermediate **11**

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§ A reviewer has asked which of the many stable conformers we chose to use for an individual step in a reaction pathway. For the processes described in Fig. 1, 2, 3, 5 and 8 we have used the most stable conformer in each case. For the reactions of the more complex systems shown in Table 1 and Fig. 9–12, the conformer used is the one that minimises the barrier to the transition state for that particular reaction step. IRC calculations confirm that a transition state is connected to the chosen reactant.

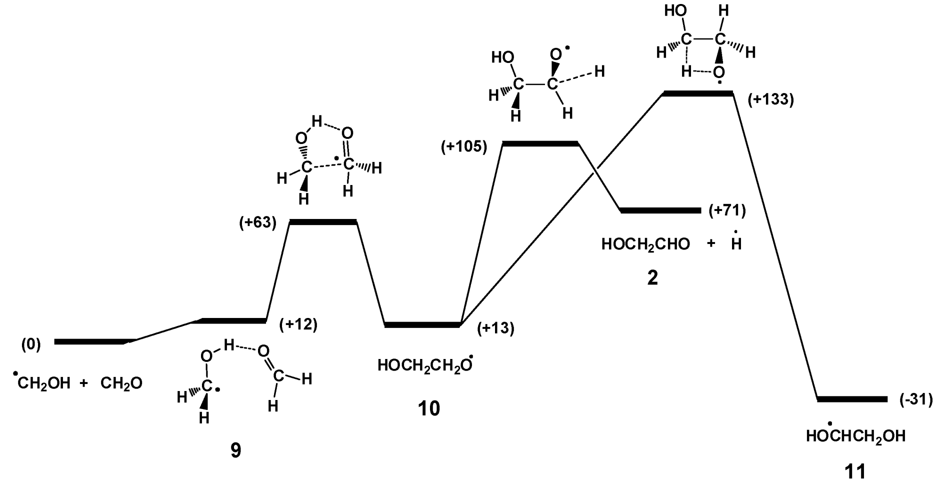


Fig. 8 Reaction coordinate diagram for the reactions between $^{\bullet}CH_2OH$ and CH_2O to give glycolaldehyde (**2**) and $HOCH_2{}^{\bullet}CHOH$ (**10**). CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (ΔG) in kJ mol^{-1}. Details of geometries and energies of minima and transition states are listed in Table S5.†

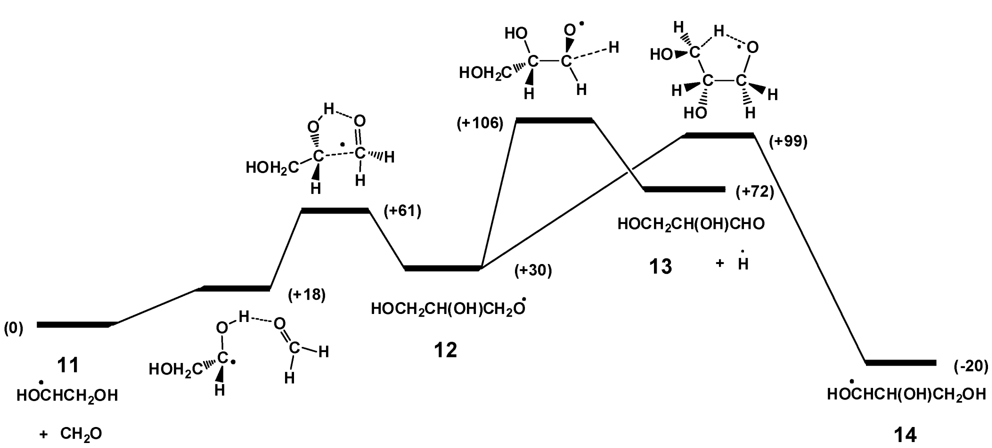


Fig. 9 Reaction coordinate diagram for the reactions between $HOCH_2{}^{\bullet}CHOH$ (**10**) and CH_2O to give glyceraldehyde (**13**) and $HOCH_2CH(OH){}^{\bullet}CHOH$ (**14**). CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. Relative energies (ΔG) in kJ mol^{-1}. Details of geometries and energies of minima and transition states are listed in Table S6.†

($HOCH_2{}^{\bullet}CHOH$; Fig. 8)? In principle, intermediate **11** is available from the known interstellar molecule ethylene glycol, by loss of a hydrogen atom (perhaps following cosmic ray irradiation, *cf.* ref. 31), or by abstraction of a hydrogen atom by a radical, *e.g.* $H^{\bullet}$ or $HO^{\bullet}$.

Reactions 4 to 7 (Scheme 4) have been studied at the CCSD/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory. The energy required for each process is indicated in Scheme 4. Formation of $HOCH_2{}^{\bullet}CHOH$ from ethylene glycol by reaction with the hydroxyl radical (equation 6) is energetically plausible, and condensation between this species and formaldehyde could effect the reactions shown in Fig. 9, together with the chain extension cycle outlined above in Table 1.

$HOCH_2CH_2OH \rightarrow HOCH_2{}^{\bullet}CHOH + H^{\bullet}$ (+ 381 kJ mol^{-1}) (4)

$HOCH_2CH_2OH \rightarrow HOCH_2CH_2O^{\bullet} + H^{\bullet}$ (+ 426) (5)

$HOCH_2CH_2OH + HO^{\bullet} \rightarrow HOCH_2{}^{\bullet}CHOH + H_2O$ (- 99) (6)

$HOCH_2CH_2OH + HO^{\bullet} \rightarrow HOCH_2CH_2O^{\bullet} + H_2O$ (- 55) (7)

Scheme 4

The polymerization reactions discussed above may be possible theoretically, but the probability of forming, say, a C_6 sugar by such processes is small in an interstellar dust cloud, even if the initial $^{\bullet}CH_2OH$ radical is anchored to a dust particle with a significant concentration of formaldehyde nearby. Perhaps such a polymerization process could occur on or within interstellar ice, for example in comets where there may be significant relative quantities of ice-bound formaldehyde.[32] In this context, organic compounds found in the Murchison meteorite are of interest and may have been formed by polymerization of formaldehyde under alkaline conditions.[33] Whether these were formed prior to or during entry into the earth's atmosphere is not known. A range of reduced and oxidized open chain sugars were identified, including ethylene glycol ($HOCH_2CH_2OH$), dihydroxyacetone [$HOCH_2C({=}O)CH_2OH$], glycerol [$HOCH_2CH(OH)CH_2OH$] and glyceric acid [$HOCH_2CH(OH)CO_2H$], together with much smaller amounts of C_4, C_5 and C_6 polyols and polyol-carboxylic acids (sugars may undergo conversion to carboxylic acids in alkaline conditions (ref. 34 and *cf.* ref. 20–23). It was argued that these molecules could not be formed following contamination of the meteorite with earth-borne micro-organisms, since under such conditions, the formation of C_5 and C_6 sugars should have been predominant. Earlier studies,[35,36] of the possible presence of sugars in (pre-Murchison) meteorites identified mixtures of C_5 and C_6 sugars.

Formaldehyde polymerization in interstellar regions is an interesting proposal, because the biosynthesis of, for example, glucose and ribose on earth is now quite different from this. Glucose (the particular stereoisomer produced by enzymic catalytic reactions) and oxygen are the products of photosynthesis in plants and some prokaryotes, with the evolution of aerobic life awaiting a suitable concentration of oxygen in the atmosphere. In animals and fungi, glucose is also formed by breakdown of glycogen; in plants the breakdown substrate is starch. Finally, in animals, glucose is synthesized in the liver and kidneys from non-carbohydrate intermediates, such as pyruvate and glycerol, by a process known as gluconeogenesis. There are a number of ways that C_5 sugars (*e.g.* ribose) may be biosynthesised; the most common is the pentose phosphate pathway which involves four enzymically catalysed steps starting from glucose-6-phosphate.[37] However, the possibility of an RNA world (ref. 38 and *cf.* ref. 39) requires ribose being available on prebiotic earth, perhaps by formaldehyde polymerization, a proposal which has been challenged.[40]

2.5 Possible gas phase formation of the cyclic sugar glucose?

The energetics of the conversion of open-chain to cyclic glucose have been the subject of theoretical studies at a number of different levels of theory.[41–43] Formation of the cyclic species is favourable, but the energy to the transition state is of the order of 160 kJ mol^{-1}. The reaction energetics were also probed with the addition of one to three molecules of water near the reaction centre; addition of one molecule of water reduces the barrier to the transition state from *ca.* 160 to 80 kJ mol^{-1}.

Our system is different from that considered above because it commences with the appropriate C_6 stereoisomer of $HOCH_2(CHOH)_4{}^{\bullet}CHOH$ (**15**). Possible reaction sequences determined at the MP2/6-31+(d) level of theory are shown in Fig. 10 (see also Table S7†). Loss of $H^{\bullet}$ from **15** can occur initially to form open-chain glucose **17** (barrier +107 kJ mol^{-1}) which then cyclises to glucose (**16**, β anomer shown) (overall reaction −14 kJ mol^{-1}; barrier to transition state +159 kJ mol^{-1} from **17**). The process from **17** is the same as that described earlier.[41–43] The second process shown in Fig. 10 involves a synchronous cyclization/H loss from **15** to yield cyclic product **16**. This process has a barrier to transition state **15**/[**16+H**$^{\bullet}$] of +181 kJ mol^{-1}.

Both of the reactions shown in Fig. 10 need significant excess energy to surmount transition states **15**/[**16+H**$^{\bullet}$] and **17**/**16**. If the cyclization occurs in an interstellar ice environment, addition of one molecule of water at the reaction centre should be feasible. This scenario is shown in Fig. 11 (see also Table S8†) and is comparable with computational data obtained previously[41–43] Following formation of **17** (Fig. 10 and 11), addition of one molecule of water allows formation of transition state [**17+H$_2$O**]/**18** (+84 kJ mol^{-1}; Fig. 11), yielding the β anomer of glucose in a catalytic reaction favourable by −46 kJ mol^{-1}.¶

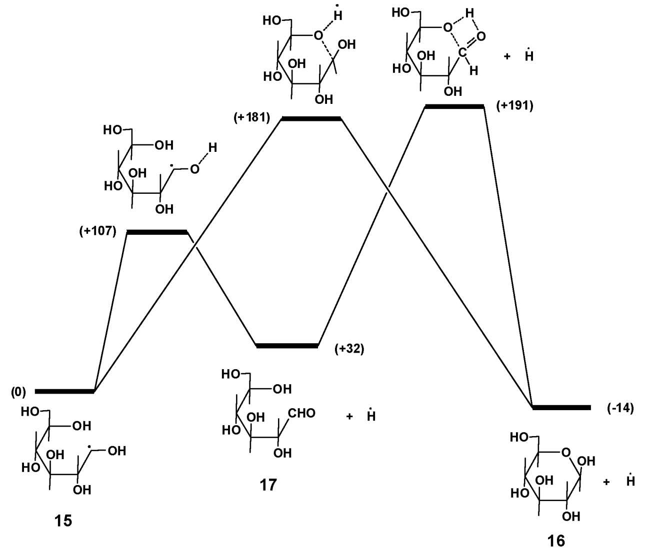


Fig. 10 Reaction coordinate diagram for the glucose cyclization reactions. MP2/6-31+G(d) level of theory. Relative energies (Δ*G*) in kJ mol^{-1}. Details of geometries and energies of minima and transition state are listed in Table S7.†

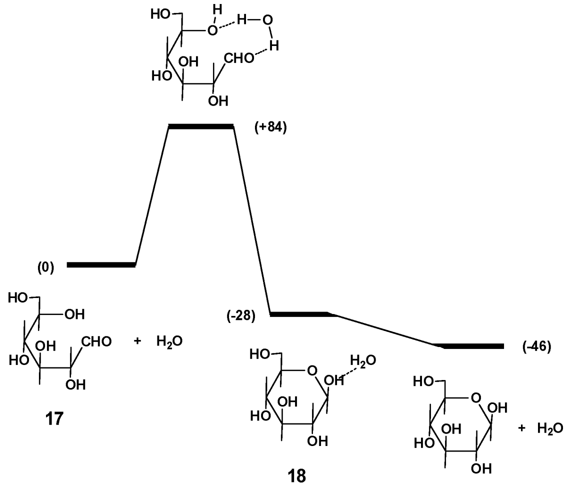


Fig. 11 Reaction coordinate diagram for the glucose/water cyclization reaction. MP2/6-31+G(d) level of theory. Relative energies (Δ*G*) in kJ mol^{-1}. Details of geometries and energies of minima and transition states are listed in Table S8.†

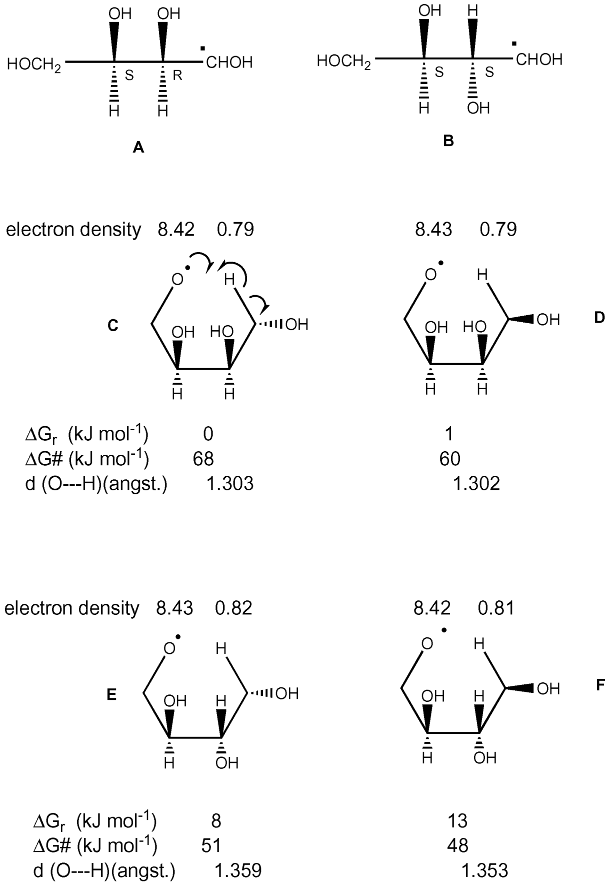
2.6 Stereoselectivity of CH_2O polymerization processes?

There is a further complication with the formaldehyde polymerization process. Although there is no chiral C in **2** or **10** (Fig. 8), there are in **13** and **14** (Fig. 9) leading to two enantiomers of each structure. Further addition of formaldehyde will lead to a number of diastereoisomers: addition of formaldehyde to the two enantiomers of **14** to form a C_4 system will lead to four isomers; to C_5, eight isomers; and to a C_6 system, 16 isomers. Only one of these sixteen isomers will form glucose as shown in Fig. 11. The formation of many stereoisomers of which only one will give the required cyclic product is clearly an inefficient synthetic pathway.

Perhaps there is some stereoselectivity in the formation of particular open chain stereoisomers; this could be particularly important if these reactions are controlled by kinetics in interstellar regions.

¶ Note that the relative energies in Fig. 10 and 11 are not directly comparable, because the 0 kJ mol^{-1} references in the two figures are different.

It has been shown that in the formation of the C_3, C_4, C_5 and C_6 open chain structures, *either the initial condensation step or the H transfer is rate determining*. The condensation step involves the attack of the essentially planar carbon-centred radical above and below the plane of the formaldehyde molecule. For the reaction of (**10**) with formaldehyde to give (**12**) (Fig. 9), there is no kinetic advantage in attack at one rather than the other face of formaldehyde, so both enantiomers should be formed equally. The situation concerning addition of formaldehyde to two diastereoisomers may be different. It is not an option to calculate the reaction coordinates of addition of formaldehyde to all diastereoisomers in the chain extension reactions, so we will concentrate on the particular cases shown in Scheme 5. The transition state barriers for **A** and **B** reacting with formaldehyde differ by only 2 kJ mol^{-1} (at the MP2/6-311+G(d) level of theory; data not provided). This difference is small, and cannot be taken to indicate whether the kinetics of either **A** or **B** with formaldehyde is the more favoured.



Scheme 5

The H transfer from the two enantiomers of (**12**) should give the two isomers of (**14**) (Fig. 9) in equal amounts. The analogous H transfer reaction of diastereoisomer **A** can occur *via* **C** or **D**, since there is a choice of two Hs that may transfer to the oxygen radical centre (see Scheme 5). Similarly, diastereoisomer **B** may effect H transfer through either **E** or **F**. Calculation of the reaction coordinates of these four processes have been carried out at the MP2/6-311+G(d) level of theory, with reactions **D** and **F** examined at MP2, X3LYP and BMK levels of theory using the same 6-311+G(d) basis set in each case. The differences in transition state energies of the H transfer reactions of **D** and **F** using the three computational systems are 12 kJ mol^{-1} (MP2), 11 kJ mol^{-1} (X3LYP) and 11 kJ mol^{-1} (BMK). The close correspondence of these results led us to use only MP2 for the other systems. Pertinent data are summarized in Scheme 5, an example of the differences in reaction profiles is shown for **D** and **F** in Fig. 12, while full energy and geometry data are listed in Table S9.†

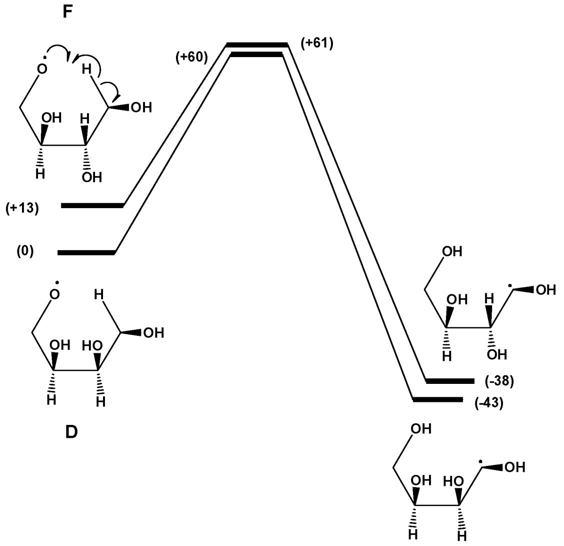


Fig. 12 Reaction coordinate diagram for the H transfer reactions of **D** and **F** (see Scheme 5). MP2/6-311+G(d) level of theory. Relative energies (ΔG) in kJ mol^{-1}. Details of geometries and energies of minima and transition state are listed in Table S9.†

In selecting **A** and **B** (Scheme 5) for study, only one configurational change was invoked, that of the carbon adjacent to the carbon bearing the transferring H. For each of **C** to **F**, the reacting conformer was chosen to be as close in structure as possible to the nearly planar transition state for the H transfer process. IRC calculations connect the translation state and reactant in each case. The relative free energies of the reactants of **C** to **F** are, at least in part, a consequence of H bonding which may occur between hydroxyl groups (Scheme 5 and Fig. 12). The relative energies of the reactants of **C** and **D** are similar (1 kJ mol^{-1}), and between **E** and **F** (5 kJ mol^{-1}). In contrast, there are larger differences between **C** and **E** (8 kJ mol^{-1}) and **D** and **F** (12 kJ mol^{-1}).

There are differences in the barriers to the transition states of all four systems; namely **C** (+68 kJ mol^{-1}) > **D** (+60 kJ mol^{-1}) > **E** (+51 kJ mol^{-1}) > **F** (+48 kJ mol^{-1}). The computational data show that the barrier to the transition state is smaller when the extent of H bonding change from reactant to transition state is minimised. In the cases of **E** and **F**, there are essentially no H bonding changes in going from reactant to transition state, whereas H bond weakening from reactant to transition state is appreciable for **C** and less so for **D** (see Table S10†). The other important feature is the electron densities on the transferring H and the recipient O in reactants. These are also recorded in Scheme 5. The electron densities on O are similar for **C** to **F**. However, the electron densities on the transferring Hs are larger for **E** and **F** than for **C** and **D**, in accord with the lower barriers to the transition states for **E** and **F** than **C** and **D**.‖ Thus, differing configurations of the substituents around a central carbon of **A** and **B**, together with the electron densities on the transferring H in the transition states (for **C** to **F**) are important in determining the relative barrier to the transition state for each H transfer step.

Conclusions

(i) The reactions between hydroxymethylene and formaldehyde can produce glycolaldehyde, acetic acid and methyl formate. All calculations at the CCSD(T)/6-311++G(3df,2p)//MP2/6-311++G(3df,2p) level of theory.

(ii) A combination of experiment and theory indicate that the radical reactions (a) and (b) should constitute viable syntheses of glycolaldehyde.

$$HO^{\bullet} + {}^{\bullet}CH_2CHO \rightarrow HOCH_2CHO \quad (a)$$

$$HOCH_2^{\bullet} + {}^{\bullet}CHO \rightarrow HOCH_2CHO \quad (b)$$

$$HOCH_2^{\bullet} + CH_2O \rightarrow HOCH_2CH_2O^{\bullet} \rightarrow HOCH_2CHO + H^{\bullet} \quad (c)$$

(iii) A theoretical study shows that $HOCH_2{}^{\bullet}CHOH$ [formed as shown in (c) above] can react with successive molecules of CH_2O with accompanying H transfer in each additive step to form $HOCH_2[CH(OH)]_{n+1}{}^{\bullet}CHOH$ ($n = 1$–3). Such a sequence is feasible energetically from a theoretical viewpoint but the probability of sequential additions of CH_2O would be very small, even if, for example, the reaction sequence occurred in interstellar ice which contained a significant concentration of CH_2O.

(iv) The polymerization reaction described above would produce a number of diastereoisomers (*e.g.* 16 when $n = 3$) and thus be an inefficient synthesis of a particular isomer (*e.g.* glucose). However, it has been shown for the particular diastereoisomers shown in Scheme 5 that the H transfer reaction has a barrier which depends on (i) the relative arrangements of the hydroxy substituents in reactant and transition state, and (ii) the electron density on the transferring hydrogen in the transition step. Thus, there may be diastereoisomeric control in a polymerization step where the reaction is kinetically controlled, and where the H transfer step is rate determining.

Experimental section

Mass spectrometric methods

The experiments were performed using a two-sector modified VG ZAB 2HF mass spectrometer with **BE** configuration, where **B** and **E** represent magnetic and electric sectors, respectively. The precursor ions $CH_2{=}^{+}OH$ and CH_3O^- were formed in the chemical ionization source by respective loss of $H^{\bullet}$ from the methanol molecular cation and by the reaction of methanol with HO^- (from H_2O). Source conditions were as follows: source temperature 100 °C, repeller voltage –0.5 V, ion extraction voltage 7 kV, mass resolution $m/\Delta m \geq 1500$. For the formation of $CH_2{=}^{+}OH$, methanol was added through the septum inlet (unheated) to give a pressure of 10^{-5} Torr measured in the source housing. For the formation of CH_3O^-, a mixture of water and methanol (1 : 1) is then introduced through the septum inlet (unheated) to give a constant pressure of 10^{-4} Torr in the source housing. The estimated pressure in the ion source is 10^{-1} Torr. Collision induced (CID) spectra were determined using the magnetic sector to select the parent ion, utilising oxygen as the collision gas in the first collision cell following the magnetic sector. The pressure of oxygen in the first cell was maintained such that 80% of the parent ion beam was transmitted through the cell. This corresponds to an average of 1.1–1.2 collisions per ion.[48] Product anion peaks resulting from CID processes were recorded by scanning the electric sector.

Neutralization/reionization spectra ($^{+}NR^{+}$ or $^{-}NR^{+}$)[25] were performed for mass selected anions utilizing the dual collision cells located between the magnetic and electric sectors. Neutralization of cations or anions was effected by collisional electron attachment or detachment using O_2 at 80% transmission (of the ion beam) as collision gas in the first collision cell, while reionization to cations was achieved by collision of neutrals with O_2 (80% transmission) in the second collision cell. To detect a reionization signal due to the parent neutral, the neutral species must be stable for the one microsecond timeframe of this experiment. Charge reversal ($^{-}CR^{+}$) spectra[26] were recorded using single-collision conditions in collision cell 1 (O_2, 80% transmission of main beam). Comparison of $^{-}CR^{+}$ and $^{-}NR^{+}$ (or CID and $^{+}NR^{+}$) data for a given parent anion provides information concerning the neutral formed from the parent anion: see ref. 27 for a description of this procedure.

Theoretical methods

Second-order Møller-Plesset perturbation theory[49] (MP2) in conjunction with a large basis set is normally used for systems containing weakly bonded correlation effects.[50–52] Therefore, for most of the calculations for this investigation, the MP2 method was chosen to carry out optimizations, using the split-valence 6-311++G(3df,2p) basis set[53] within the GAUSSIAN 03 suite of programs.[54] Stationary points were characterized 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.[55] More accurate energies for the MP2 geometries were determined using CCSD(T) procedure together[56] with the 6-311++G(3df,2p) basis set, including zero-point vibrational energies (ZPVEs) correction (unscaled). In some cases other levels of theory (X3LYP[57] and BMK[58]) were used: when this was done it is specifically mentioned in the text. 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.

‖ Electron density calculations using different methods often give different absolute values.[44] Because of this we have calculated electron densities of H and O (see Scheme 5) by the AIM,[45] NBO,[46] and Mulliken[47] methods. The three methods give different absolute values in each instance, but the relative trends are the same in all cases. The values listed in Scheme 5 are NBO electron densities. The following values were obtained (order AIM, NBO and Mulliken): **C** [O (8.36, 8.42, 8.16); H (0.40, 0.79, 0.68)]; **D** [O (8.87, 8.43, 8.17); H (0.24, 0.79, 0.68); **E** [O (8.54, 8.43, 8.18); H (0.82, 0.82, 0.69)]; **F** [O (8.18, 8.42,8.17); H (0.57, 0.81, 0.69)].

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