Bis-Aminals of Linear Tetraamines: Kinetic and Thermodynamic Aspects of the Condensation Reaction

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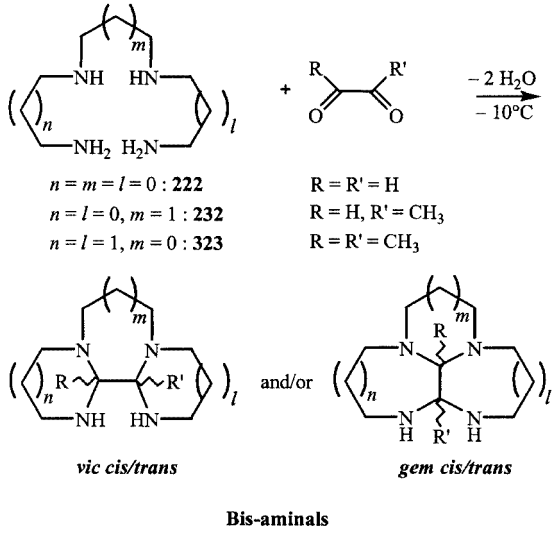
Keywords: Bis-aminals / Amines / Imines / Intermediates / Kinetics

The kinetic and thermodynamic aspects of the condensation reaction of dicarbonyl compounds with linear tetraamines were examined in the light of identification of intermediates and DFT calculations.

Introduction

For a few years now, bis-aminals obtained by condensation of glyoxal or butanedione with linear polyamines[1,2] have been successfully used in the synthesis of polyazacycloalkanes.[3] The bis-aminal bridge acts as an organic template which induces pre-organisation of the tetraamine to favour its subsequent cyclisation. In theory, this condensation reaction should result in multiple stereoisomers according to the *vic*/*gem* insertion of the dicarbonyl reagent and *cis*/*trans* configuration of the resulting bis-aminal bridge. In fact, the reaction is mostly highly selective and leads to only a few isomers;[3b,4] in some cases, the bis-aminal gives rise to an isomerisation process[3a,5] which makes understanding of the reaction sequence more difficult. Finally, the reactivity of this rigidified tetraamine, particularly its ability to react with a bis-electrophile to give macrocyclic intermediates, strongly depends on its configuration.[3b,6] An understanding of this first step, as well as how to control it, are thus essential for subsequent synthesis of macrocyclic tetraamines. These considerations led us to report on a study of the reactivity of linear tetraamines with a variety of substituted dicarbonyl derivatives and to propose a mechanism for the formation of the bis-aminal bridge.



Scheme 1

Results and Discussion

The three tetraamines 1,4,7,10-tetraazadecane (**222**), 1,4,811-tetraazaundecane (**232**) and 1,5,8,12-tetraazadodecane (**323**) were allowed to react with α-dicarbonyl reagents, namely glyoxal, pyruvic aldehyde or butanedione, at −10 °C in ethanol (Scheme 1); once the reaction had been completed, the solvent was carefully removed at −10 °C under reduced pressure. Compared with previously published procedures, this one avoids formation of polymers and gives a good picture of the early state of the reaction before any isomerisation.

Identification of the *vic*/*gem* configuration was obtained from ^{13}C NMR spectroscopic data and the recognition of *cis*/*trans* isomers was deduced from the temperature dependence of the spectra. The *trans* isomer is found to stay rigid[7] whereas the *cis* isomer exhibits a fluxional behaviour consistent with a dynamic process that involves the sequential inversion of the nitrogen atoms and piperazine rings. When needed, for the pyruvic aldehyde derivatives, HMQC, HMBC and COSY sequences were used to elucidate the localisation of the methyl group on the bis-aminal bridge.[8] The results are shown in Table 1.

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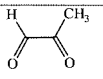
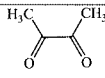
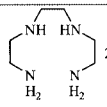
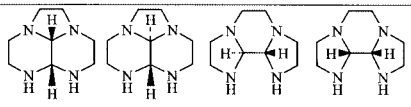
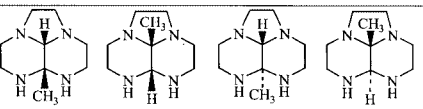
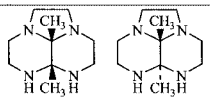
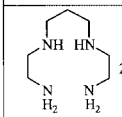
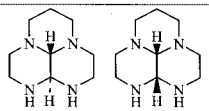
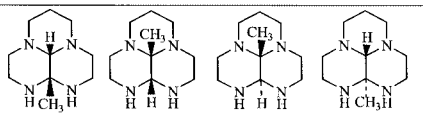
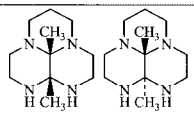
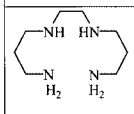
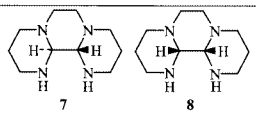
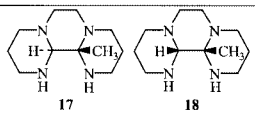
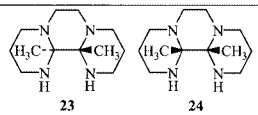
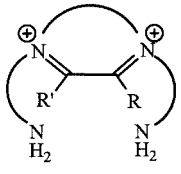
Table 1. Bis-aminals obtained at −10 °C and 80 °C; E_r = relative energies of formation of the isomers (DFT/B3LYP/ 6−31G**) in kcal/mol

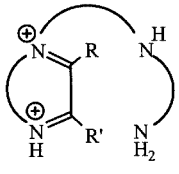
Entries			
 222			
	1 2 3 4	9 10 11 12	19 20
A: % (−10 °C)	0 0 80 20	100 0 0 0	100 0
B: % (80 °C)	71 11 14 4	100 0 0 0	100 0
C: E_r	0 4.80 7.47 8.49	0 2.27 5.00 10.43	0 12.23
 232			
	5 6	13 14 15 16	21 22
A: % (−10 °C)	0 100	90 10 0 0	100 0
B: % (80 °C)	100 0	90 10 0 0	100 0
C: E_r	0 2.12	0 5.26 6.29 3.27	0 0.44
 323			
	7 8	17 18	23 24
A: % (−10 °C)	30 70	75 25	25 75
B: % (80 °C)	90 10	75 25	25 75
C: E_r	0 4.21	0 7.46	0 5.22

These data show, firstly, that only a few of the expected compounds were actually obtained. Seven-membered cycles are not produced and the formation of rings with a maximum of six members appears to constitute the driving force of the reaction. Moreover, for the bis-aminals resulting from glyoxal condensation, refluxing for several hours in ethanol caused some isomerisations to occur, converting the kinetic adducts observed at −10 °C into the thermodynamic ones (Table 1, entries A and B). With pyruvic aldehyde and butanedione, one may wonder about the kinetic or thermodynamic nature of the observed bis-aminals, even in the lack of a clear isomerisation process over the same temperature range. For this purpose, the calculation of energies of formation of these bis-aminals offers a clue and the corresponding DFT energies are reported in Table 1 (entries C). These data indicate that, with pyruvic aldehyde, the most stable isomer is always predominantly reached. With butanedione, such general behaviour is not observed, as condensation with the tetraamine **323** mainly leads to the less stable bis-aminal, whatever the reaction temperature. The energies of formation of the bis-aminals cannot, therefore, constitute the only criterion capable of accounting for the reaction stereoselectivity. With this aim in view, we thus studied in detail the mechanism involved in formation of bis-aminals.

The first step of the nucleophilic addition of amines to aldehydes or ketones leads to an imine or an iminium ion, depending on the primary or secondary nature of the amine concerned. The formation of the aminal function is the consequence of the addition of a second amine on the sp^2 carbon atom. With dicarbonyl reagents and tetraamine substrates, one can assume the prior formation of six-membered, cyclic diiminium species (Scheme 2). To obtain evidence of these intermediates, the condensation step was performed in the presence of sodium borohydride, in order to trap the diiminium species, which were found to be variously-substituted piperazines. The data reported in Table 2 allow us to draw an important conclusion: *the fast formation of a six-membered diiminium ring constitutes the first step of the reaction*. Moreover, the position of the CH aminal on the rigidifying bridge (Table 1) indicates that the ketone function has a higher affinity for a primary amine than for a secondary one, whereas the aldehyde function reacts faster with the latter.[9] This last point was confirmed by a



Structure 1

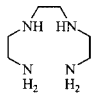
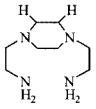
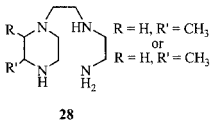
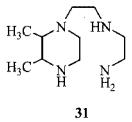
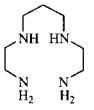
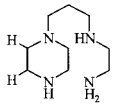
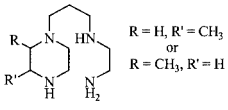
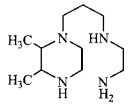
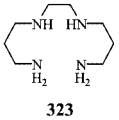
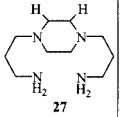
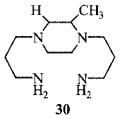
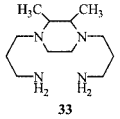


Structure 2

Scheme 2

competitive condensation of glyoxal and butanedione on the tetraamine **323**, which led exclusively to the glyoxal-derived bis-aminal.

Table 2. Piperazine rings trapped by reductive amination of diiminium intermediates

			
 **222**	 **25**	 **28**	 **31**
 **232**	 **26**	 **29**	 **32**
 **323**	 **27**	 **30**	 **33**

As a matter of fact, the reaction of glyoxal with tetraamines **222** and **323** involves the two secondary amine functions; the insertion of this dicarbonyl compound is central (Scheme 2, structure 1). However, with tetraamine **232**, the demand for the formation of a six-membered ring requires the use of a primary amine, and therefore the insertion of the glyoxal is lateral (Scheme 2, structure 2).

A primary nitrogen is always implied whenever butanedione is allowed to react with tetraamines **222** and **232**; however, the same constraint on the building of the six-membered cycle imposes the involvement of the two secondary nitrogens of the tetraamine **323**.

Pyruvic aldehyde constitutes an interesting combination of the previous principles: the reaction of the ketone moiety with the primary amine and that of the aldehyde with the secondary amine constitute the favoured way, which leads to a lateral diiminium ring with tetraamines **222** and **232**. With tetraamine **323**, again, the only solution to achieve the six-membered cycle implies the use of the two secondary amines.

The formation of the diiminium intermediate is followed by the subsequent addition of the two remaining nitrogens on the sp^2 carbons; its evolution governs the reaction stereoselectivity. According to the central/lateral location of the diiminium ring, two different cases have to be considered.

Firstly, when the diiminium is lateral, the two remaining nitrogen atoms are borne by a unique pendant arm. Their approach on the same side of the average plane of the ring is greatly favoured; the main ensuing adduct is the *gem-cis* one (Figure 1). The kinetic bis-aminals obtained from tetraamine **232**, like those resulting from the condensation of **222** with butanedione and pyruvic aldehyde, conform to this mechanism.

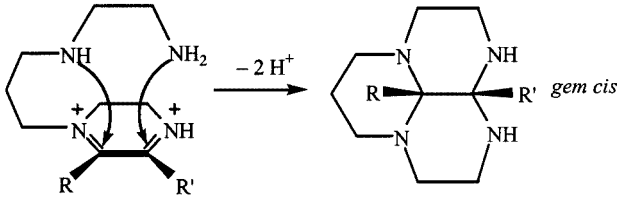
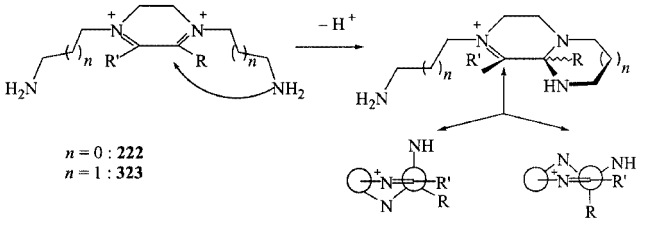


Figure 1. Lateral diiminium evolution

Secondly, when the diiminium is central, the two remaining nitrogen atoms are borne by the two independent pendant arms. This situation is found when the tetraamine **222** reacts with glyoxal as well as in the condensation of the tetraamine **323** with each dicarbonyl derivative. The attack of the first primary amine leads to an iminium-aminal constituted by two fused six-membered rings, for which two arrangements around the sp^3 aminal carbon have to be considered. In these two situations, the hydrogen (for glyoxal and/or pyruvic aldehyde) or methyl (for pyruvic aldehyde and/or butanedione) bonded to the sp^3 aminal carbon can occupy an axial or equatorial position. These two conformations were optimised at the DFT/B3LYP/6−31G** level in each case (Figure 2). For the iminium-aminal derived from condensation of tetraamine **222** and glyoxal, the two conformations where the hydrogen atom lies either in a pseudo-equatorial (**34**) or a pseudo-axial position (**35**) are isoenergetic, which means that the hydrogen and nitrogen atoms occupy almost equivalent positions. These two geometries are characterised by a staggered configuration about the $C_{(sp2)}-C_{am}$ bond. In the iminium-aminal ring the bond between the positively charged sp^2 nitrogen and a vicinal sp^3 carbon is lengthened, relative to the normal C−N bond. These considerations illustrate structural anomeric effects.[10] For the iminium-aminal derived from tetraamine **323** and glyoxal or butanedione, the most stable conformation exhibits an axial hydrogen atom or methyl group (**37** and **41** respectively) with, in each case, a staggered configuration about the $C_{(sp2)}-C_{am}$ bond. Finally, the iminium-



$n = 0$, R = R' = H	**34**: – 533.861084 ua	**35**: – 533.861075 ua
$n = 1$, R = R' = H	**36**: – 612.501848 ua	**37**: – 612.507361 ua
$n = 1$, R = H, R' = CH_3	**38**: – 651.829569 ua	**39**: – 651.823800 ua
$n = 1$, R = R' = CH_3	**40**: – 691.140056 ua	**41**: –691.144545 ua

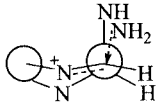
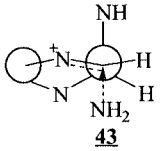
Figure 2. Central diiminium evolution. The energies of formation of iminium-aminal intermediates are given in Hartrees [1 Ha (a.u.): 627.509 kcal/mol]

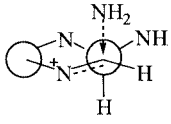
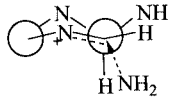
aminal considered in the reaction of tetraamine **323** and pyruvic aldehyde is the one in which the aldehyde function was the first to react, as shown by the competitive condensation experiment previously described; the corresponding hydrogen atom then occupies the equatorial position on the sp^3 aminal carbon (**38**).

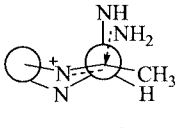
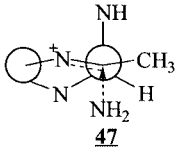
In all these intermediates, the faces of the last sp^2 iminium-aminal carbon atom are now diastereotopic and make different the approaches of the last nitrogen atom located on the remaining pendant arm. To shed light on the stereoselectivity of the last nucleophile addition, we carried out DFT calculations to locate transitions states of the last cyclisation step; the distances calculated for the incipient C···N(H_2) bond are reported in Table 3. The calculated geometries are characterised by a partial pyramidalisation of the iminium carbon accompanied by lengthening of the imine bond in the transition state; the central six-membered ring presents a half-chair conformation. For the **222** tetraamine, in the transition states **42** and **43** leading to the *vic-cis* and *vic-trans* bis-aminals respectively, the strains imposed by the presence of a five-membered ring result in the eclipse of the iminium double bond by the C−N bond of the aminal carbon. The subsequent approach of the nitrogen lone pair preferentially takes place on the less hindered side of the iminium carbon (transition state **43**) and the energetic barrier calculated for this transition state is lower than the one calculated for transition state **42** (ΔE = 2.03 kcal/mol, Table 3). Consequently, the *trans* transition state is more accessible and the final ring-closure leads to the kinetic *trans* bis-aminal, which is consistent with the major compound obtained at −10 °C.

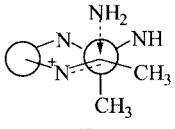
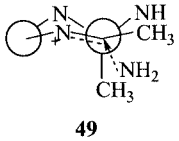
For the tetraamine **323**, the transition states which lead to the *vic-cis* bis-aminals **44**, **46**, **48**, are constituted by two six-membered fused rings and present a staggered arrangement with respect to the partially pyramidalised carbon atom, as expected for reactive conformations in nucleophilic additions. These situations are greatly favoured, as no bond becomes eclipsed during the iminium carbon pyramidalisation.[11,12] As expected, the nucleophilic NH_2 attack is nonperpendicular and the N(H_2)CC angle was found to be around 105°. In these conformations, the trajectory of the nucleophilic attack is *syn* to the C_{am}−NH bond. In the transition states **45**, **47** and **49**, the nucleophilic attack occurs *anti* to the NH moiety and the calculated geometries show that the free amine function approaches at an angle of around 102°. The comparison of the energetic barriers indicates that the favoured attack leads to the formation of the *cis* products with glyoxal and butanedione, whereas the

Table 3. Transition states for the last cyclisation step (DFT/ B3LYP/6−31G**); activation energies are relative to the reactants (iminium-aminals)

Tetraamine: **222**	 42	 **43**
E_{act} (kcal·mol^{-1})	10.19	8.16
$d_{C...NH2}$ (Å)	1.98	1.99
$d_{C=N}$ (Å)	1.34	1.34
N–CC angle of attack	112.35	107.16

Tetraamine: **323**	 **44**	 **45**
E_{act} (kcal·mol^{-1})	0.97	3.23
$d_{C...NH2}$ (Å)	2.04	2.00
$d_{C=N}$ (Å)	1.33	1.34
NCC angle of attack	105.19	102.37

Tetraamine: **323**	 **46**	 **47**
E_{act} (kcal·mol^{-1})	10.64	5.10
$d_{C...NH2}$ (Å)	1.98	1.97
$d_{C=N}$ (Å)	1.35	1.35
NCC angle of attack	106.14	99.50

Tetraamine: **323**	 **48**	 **49**
E_{act} (kcal·mol^{-1})	6.38	26.93
$d_{C...NH2}$	1.99	1.98
$d_{C=N}$	1.36	1.35
NCC angle of attack	103.89	103.75

trans compound is preferentially reached with pyruvic aldehyde. This is in good agreement with experimental results for the bis-aminals derived from tetraamine **323**; it therefore means that the mixtures observed at −10 °C correspond to a kinetic situation. The model shows that the nucleophilic attack occurs *anti* to the axial substituent of the aminal carbon, regardless of whether this substituent is a hydrogen atom or a methyl or amino group. This situation corresponds to an NH_2 moiety approach assisted by the σ* orbital, antiperiplanar to the incipient bond,[13,14] that is, σ^*_{CN} orbital for transition states **43** and **47** and σ^*_{CH} or σ^*_{CC} orbitals for transition states **44** and **48**. Thus, the stereoselectivity of this last cyclisation step is conditioned to the preferential geometry of the iminium-aminals. The disposition of the aminal carbon substituents and the rigidity of these intermediates impose the direction of the nucleophilic approach towards the best orientated σ*orbital, as in the Cram cyclic model.[15]

Conclusion

Analysis of the condensation reaction of various dicarbonyl compounds with linear tetraamines revealed that, of all the possible stereoisomers, only a few were obtained. Under reductive amination conditions a variety of substituted piperazines were isolated, which means that fast formation of a diiminium intermediate is initially involved. After this first six-membered ring was established, the next cyclisation steps were modelled and the results were consistent with kinetic control of the subsequent attack. Moreover, computed transition states provided a model for understanding the stereoselectivity of the condensation reaction. They suggest that the last nucleophilic attack happened preferentially *anti* to the axial group of the first formed aminal carbon. It led to either *cis* or *trans* bis-aminals, depending on the dicarbonyl compound and tetraamine. Finally, via the isomerisations that occurred with glyoxal bis-aminals, the kinetic adducts were converted into thermodynamic ones.

Experimental Section

General Procedure for the Synthesis of Bis-aminals: A solution of the dicarbonyl derivative (2 mmol) in ethanol (5 mL) was added slowly to a solution of the tetraamine (2 mmol) in ethanol (5 mL) at −10 °C. After 2 h of vigorous stirring, the solvent was evaporated at the same temperature and, where necessary, the residue was purified by extraction with toluene (three times, 5 mL each) and dried under vacuum.

Bis-aminals Derived from Glyoxal

Bis-aminals Obtained by Condensation with Triethylenetetraamine (222): Colourless oil, quantitative. **Isomer 1:** ^{13}C NMR ($CDCl_3$): δ = 42.9, 47.9, 50.2 (N*C*H_2N), 65.6, 76.0 (N*C*N) ppm. **Isomer 2:** ^{13}C NMR ($CDCl_3$): δ = 45.7, 50.5, 51.3 (N*C*H_2N), 71.7, 88.9 (N*C*N) ppm. **Isomer 3:** ^{13}C NMR ($CDCl_3$): δ = 43.6, 48.1, 50.8 (N*C*H_2N), 79.5 (N*C*N) ppm. **Isomer 4:** ^{13}C NMR ($CDCl_3$): δ = 45.7, 50.5, 51.3 (N*C*H_2N), 72.2 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 169.3 $[M + H]^+$.

Bis-aminals Obtained by Condensation with *N*,*N*′-Bis(2-aminoethyl)-1,3-propanediamine (232): Colourless oil, 95%. **Isomer 5:** ^{13}C NMR ($CDCl_3$): δ = 23.8 ($NCH_2CH_2CH_2N$), 43.3, 53.4, 54.5 (N*C*H_2N), 70.9, 87.7 (N*C*N) ppm. **Isomer 6:** ^{13}C NMR ($CDCl_3$): δ = 19.2 ($NCH_2CH_2CH_2N$), 40.2, 46.2, 46.4, 55.3, 56.1, 57.2 (N*C*H_2N), 67.9, 77.5 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 183.3 $[M + H]^+$.

Bis-aminals Obtained by Condensation with *N*,*N*′-Bis(3-aminopropyl)ethylenediamine (323): White powder, 95%. **Isomer 7:** ^{13}C NMR ($CDCl_3$): δ =25.4 ($NCH_2CH_2CH_2N$), 43.8, 51.5, 53.6 (N*C*H_2N), 78.1 (N*C*N) ppm. **Isomer 8:** ^{13}C NMR ($CDCl_3$): δ = 28.8, 32.6 ($NCH_2CH_2CH_2N$), 39.6, 39.8, 44.3, 47.0, 48.6, 51.8, 53.8 (N*C*H_2N), 76.4, 78.3 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 197.3 $[M + H]^+$.

Bis-aminals Derived from Pyruvic Aldehyde

Bis-aminal 9: Brown oil, 68%. ^{13}C NMR ($CDCl_3$): δ = 25.2 (CH_3), 39.6, 42.2, 48.2, 48.8, 50.2, 50.8 (N*C*H_2N), 64.7 [N*C*(CH_3)N], 80.2 [N*C*(H)N] ppm. ESI-MS (MeOH): *m*/*z* = 183.3 $[M + H]^+$.

Bis-aminals 13 (90%) and 14 (10%): Yellow oil, quantitative. **Isomer 13:** ^{13}C NMR ($CDCl_3$): δ = 11.7 ($NCH_2CH_2CH_2N$), 18.2 (CH_3), 37.8, 41.3, 43.5, 52.0, 53.8, 55.2 (N*C*H_2N), 63.8 [N*C*(CH_3)N], 79.9 [N*C*(H)N] ppm. **Isomer 14:** ^{13}C NMR ($CDCl_3$): δ = 11.7 ($NCH_2CH_2CH_2N$), 18.2 (CH_3), 38.5, 43.7, 45.1, 45.6, 48.0, 49.7 (N*C*H_2N), 69.4 [N*C*(CH_3)N], 70.9 [N*C*(H)N] ppm. ESI-MS (MeOH): *m*/*z* = 197.3 $[M + H]^+$.

Bis-aminals 17 and 18: Yellow oil, 85%. **Isomer 17 (75%):** ^{13}C NMR ($CDCl_3$): δ = 7.4 (CH_3), 26.6, 27.2, ($NCH_2CH_2CH_2N$), 39.1, 45.5, 47.5, 49.2, 53.8, 55.5 (N*C*H_2N), 70.1 [N*C*(H)N], 85.0 [N*C*(CH_3)N] ppm. **Isomer 18 (25%):** ^{13}C NMR ($CDCl_3$): δ = 10.3 (CH_3), 17.4, 20.2, ($NCH_2CH_2CH_2N$), 38.6, 42.6, 43.5, 44.5, 46.1, 54.2 (N*C*H_2N), 69.6 [N*C*(H)N], 84.3 [N*C*(CH_3)N] ppm. ESI-MS (MeOH): *m*/*z* = 211.3 $[M + H]^+$.

Bis-aminals Derived from Butanedione

Bis-aminal 19: Beige powder, 90%. ^{13}C NMR ($CDCl_3$): δ = 12.2, 23.6 (CH_3), 40.5, 47.7, 47.7 (N*C*H_2N), 67.7, 76.6 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 197.3 $[M + H]^+$.

Bis-aminal 21: Beige powder, 95%. ^{13}C NMR ($CDCl_3$): δ = 11.5, 19.0 (CH_3), 24.3 ($NCH_2CH_2CH_2N$), 39.9, 42.7, 46.3, 47.7, 49.7, 51.9 (N*C*H_2N), 68.9, 74.0 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 211.4 $[M + H]^+$.

Bis-aminals 23 and 24: Brown oil, 95%. **Isomer 23 (25%):** ^{13}C NMR ($CDCl_3$): δ = 6.8 (CH_3), 27.0, ($NCH_2CH_2CH_2N$), 39.6, 48.6, 50.0 (N*C*H_2N), 73.8 (N*C*N) ppm. **Isomer 24 (75%):** ^{13}C NMR ($CDCl_3$): δ = 7.8, 17.6 (CH_3), 17.8, 29.4, ($NCH_2CH_2CH_2N$), 39.8, 40.2, 44.8, 46.9, 49.3, 50.2 (N*C*H_2N), 72.2, 73.2 (N*C*N) ppm. ESI-MS (MeOH): *m*/*z* = 225.4 $[M + H]^+$.

General Procedure for Isomerisations: The bis-aminals obtained by condensation of each tetraamine with glyoxal, that is, respectively, a mixture of isomers **3** and **4**, the compound **6** and a mixture of isomers **7** and **8**, were heated at 80 °C in ethanol for twelve hours. The proportions of the resulting mixtures are reported in Table 1.

General Procedure for Reductive Aminations: A solution of the dicarbonyl derivative (2 mmol) in ethanol (5 mL) was slowly added to a mixture of the tetraamine (2 mmol) and sodium borohydride

(10 equiv.) in ethanol (5 mL) at −10 °C. After 2 h of vigorous stirring, the reaction was quenched by addition of HCl (4 N) and the ethanol was evaporated. The acidic aqueous phase was washed with dichloromethane (3 × 20 mL), neutralised with NaOH (4 N), then washed with dichloromethane (3 × 20 cm^3). The organic phase was dried with Na_2SO_4 for one hour, then filtered. The solvent was evaporated and the residue was dried under vacuum. The products, a mixture of the starting tetraamines and piperazines **25** to **33**, were obtained as colourless oils.

Compounds Obtained with Glyoxal

Compound 25: ^{13}C NMR ($CDCl_3$): δ = 38.8, 53.3 (2), 61.2 (NCH_2N) ppm. ESI-MS for $C_8H_{20}N_4$ (MeOH): *m/z* = 173.2 [M + H]$^+$.

Compound 26: ^{13}C NMR ($CDCl_3$): δ = 26.9 ($NCH_2CH_2CH_2N$), 41.7, 46.1 (2), 48.4, 52.5, 54.6 (2), 57.3 (NCH_2N) ppm. ESI-MS for $C_9H_{22}N_4$ (MeOH): *m/z* = 187.3 [M + H]$^+$.

Compound 27: ^{13}C NMR ($CDCl_3$): δ = 30.3 ($NCH_2CH_2CH_2N$), 40.6, 53.1 (2), 56.3 (NCH_2N) ppm. ESI-MS for $C_{10}H_{24}N_4$ (MeOH): *m/z* = 204.4 [M + H]$^+$.

Compounds Obtained with Pyruvic Aldehyde

Compound 28: ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 42.3, 46.8, 49.3, 50.2, 52.5, 57.5, 65.5, 67.9 (NCH_2N) ppm. ESI-MS for $C_9H_{22}N_4$ (MeOH): *m/z* = 187.3 [M + H]$^+$.

Compound 29: ^{13}C NMR ($CDCl_3$): δ = 19.5 ($NCH_2CH_2CH_2N$), 25.4 (CH_3), 40.1, 45.7, 48.2, 50.7, 53.0, 57.0, 60.8 (NCH_2N) ppm. ESI-MS for $C_{10}H_{24}N_4$ (MeOH): *m/z* = 201.2 [M + H]$^+$.

Compound 30: ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3) 29.1, 29.5 ($NCH_2CH_2CH_2N$), 40.8 (2), 51.3 (2), 53.5, 55.0, 56.4 (2) (NCH_2N) ppm. ESI-MS for $C_{11}H_{26}N_4$ (MeOH): *m/z* = 215.3 [M + H]$^+$.

Compounds Obtained with Butanedione

Compound 31: ^{13}C NMR ($CDCl_3$): δ = 23.0 (2) (CH_3), 41.7, 47.0, 48.8 (2), 49.2, 49.4, 49.7, 52.4 (NCH_2N) ppm. ESI-MS for $C_{10}H_{24}N_4$ (MeOH): *m/z* = 201.4 [M + H]$^+$.

Compound 32: ^{13}C NMR ($CDCl_3$): δ = 24.5 (2) (CH_3), 25.0 (2) ($NCH_2CH_2CH_2N$), 37.7, 41.8, 49.7, 52.6 (2), 53.5, 56.9, 58.1 (NCH_2N) ppm. ESI-MS for $C_{11}H_{26}N_4$ (MeOH): *m/z* = 214.4 [M + H]$^+$.

Compound 33: ^{13}C NMR ($CDCl_3$): δ = 19.2 (CH_3), 24.0 ($NCH_2CH_2CH_2N$), 37.4, 49.2, 56.4, 57.6 (NCH_2N) ppm. ESI-MS for $C_{12}H_{28}N_4$ (MeOH): *m/z* = 229.4 [M + H]$^+$.

Computational Methods

All structures were computed by using hybrid density functional theory (B3LYP) and the 6−31G** basic set, as implemented in Gaussian 98.[16] All gas-phase minima and transition states were characterised by frequency analysis. The correlation between the calculated transition states, the reactants and the products was checked with the IRC (Reverse/ Forward) option.

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