Role of the isopropyl group in asymmetric autocatalytic zinc alkylations†

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The amplifying asymmetric autocatalysis discovered by Soai and co-workers is dependent on the unique steric properties of the isopropyl group.

Soai's development of the autocatalytic alkylation of pyrimidinyl aldehydes by $ZnPr^i_2$ has attracted much attention, although a full explanation remains lacking. The reaction is unique, both in the high levels of autoamplification of chirality observed in the secondary alcohol product,[1] and in its ability to elicit absolute asymmetric synthesis.[2] For example, successful autocatalytic turnover is limited to di-isopropyl zinc, and is absent when the Zn-alkyl group is changed to cyclopropyl, cyclopentyl or *tert*-butyl.[3] In previous joint work we have indicated from the reaction kinetics derived by microcalorimetry that the catalytic resting state is a zinc alkoxide dimer,[4] and demonstrated by NMR that this dimer has a square $Zn\text{-}O_2$ core.[5] Crucially, the kinetics and NMR results converge in requiring that homo- and heterochiral dimers are of comparable energy, so that the origin of amplification arises from differential reactivity in favour of the homochiral form. The postulated structure is reaffirmed by DFT calculations.[5,6] This reaction pathway contrasts with asymmetric zinc alkylations with dimeric catalyst resting states. In those cases the monomer is the true catalyst.[7]

We demonstrate herein that the origin of this unique mechanism in Soai's autocatalysis is linked to the bulk of the isopropyl group. It is well known that the apparent size of Pr^i is structure-dependent. In the absence of unfavourable gauche-pentane interactions, Pr^i and Et are of similar size, reflected in their respective *A*-values of 2.21 and 1.79.[8] The presence of gauche pentane (g^+g^-) or longer range H–H repulsions can change the situation, the most familiar example being the preference for hexa-isopropylcyclohexane to exist as the all-axial conformer.[9] A series of papers from Anderson and co-workers analyses the complex relationship between structure and dynamics arising from proximate Pr^i groups.[10]

In earlier work,[6] we reported the DFT-computed energies of a systematic sequence of oligomeric structures including simplified analogues of dimers related to (*R*,*R*)-**2a** and (*R*,*S*)-**2a** (Fig. 1) but based on the formal addition of Me_2Zn to aldehyde **1a**. Our later publication provided a limited number of DFT calculations for the authentic homochiral Pr^i-analogues (*R*,*R*)-**2a** and (*R*,*R*)-**2b**.[5] Further and more extensive computational work has elucidated the role of Pr^i_2Zn. Considering first the $Zn\text{-}O_2$ dimers, a full comparison of both homo- and heterochiral forms **2a** has now been achieved.

This indicates differences from Me_2Zn models,[6] where *syn*- and *anti*-related conformations of the dimer are of comparable energy for both homo- and heterochiral series. The heterochiral isomer has the aryl rings preferentially disposed *anti* to one another with respect to the $Zn\text{-}O_2$ mean plane, in contrast to the preference for *syn*-conformation of the homochiral isomer (Fig. 2).[5] In the course of systematic analysis several conformers were discovered within 2 kcal of the ground-state, for both isomers. The earlier finding from NMR and kinetics that homo- and heterochiral forms are in balanced equilibrium is fully reinforced by these DFT calculations. In addition, the homochiral *syn*-form has a higher dipole moment at μ = 3.11 than the heterochiral *anti*-form at μ = 0.17, pointing to a potential distinction in catalytic reactivity.‡ The structures of the more bulky *tert*-butylzinc derived dimers were computed, and showed a comparable preference for *syn*-homochiral and *anti*-heterochiral conformations. The enthalpy of dimerisation (2 monomer → homochiral dimer) varied from 45 (Me) to 42.5 (Pr^i) to 31.7 (Bu^t) kcal mol^{-1}.

Earlier DFT calculations had identified four closed tetramers whose formation was energetically favourable, but based on *MeZn*-derived structures.[6] These calculations have now been repeated and extended for the relevant Pr^iZn cases, and show a distinct, more complex and more revealing picture (Table 1 and Fig. 3).

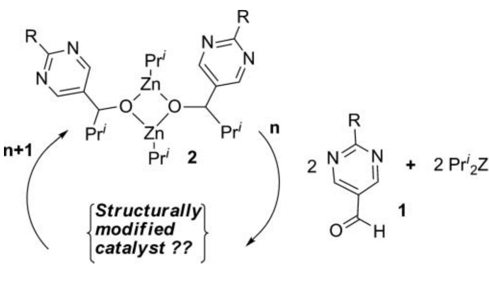

Fig. 1 The NMR-characterised ground state of Zn autocatalysis; **1**, **2** a R = Me, b R = Me_3SiCC.

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† Electronic supplementary information (ESI) available: Full author listing for Gaussian03; Table of computed enthalpies; Cartesian coordinates of the structures (in Ångstroms); Further calculations on favoured conformers of the homo- and heterochiral dimer. See DOI: 10.1039/b705978g

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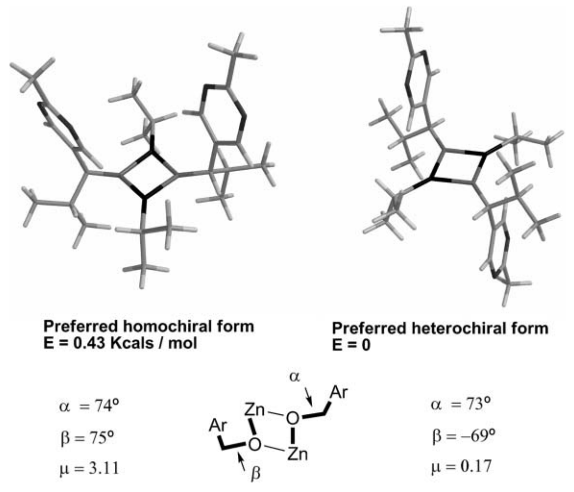


Fig. 2 The preferred conformers of the homochiral and heterochiral zinc dimers **2a**. DFT minimizations were carried out at the B3LYP/6-31-G(d) level from multiple starting points and in each case at least four conformers exist within 2.5 kcal mol^{-1} of these structures. Full details including further ONIOM calculations are contained in the Supplementary Information.†

Table 1 Binding enthalpies of tetrameric structures (B3LYP/6-31g(d)) in comparison to dimers, referenced to *n* isolated monomeric Zn alkoxides. [MeZn structures from ref. 6]

Entry[a]	Structure	Binding energy (Me) kcal mol^{-1}	Binding energy (*i*-Pr) kcal mol^{-1}	Binding energy (relative to 2 × precursor dimer)
1C	Me cube all-(*R*)	129.51		39.53
2C	Pr^i cube all-(*S*)		91.68	7.46
3C	Me cube (*RRSS*)	129.58		40.86
4C	Pr^i cube (*RRSS*)		91.86	6.78
1L	Me ladder all-(*S*)	110.81		20.83
2L	Pr^i ladder all-(*S*)		80.88	−3.34
1B	Me barrel all-(*R*)	128.95		38.97
2B	Pr^i barrel all-(*R*)		104.8	20.58
1M	Me SMS all-(*S*)	116.02		26.04
2M	Pr^i SMS all-(*S*)		101.03	17.11

[a] C = cube, L = ladder, B = barrel, M = (square-macrocycle-square (SMS)).

Alkylzinc alkoxides normally associate to form stable cubic tetramers; for this reason in conventional Zn-based asymmetric alkylations this tetrameric product normally plays no further part in the reaction.[7] In the present case computation of cubic structures derived from the Pr^i-dimer assembly initially led to minimum energy structures with severe non-bonding H–H interactions, both for all-(*S*) and (*R*,*R*,*S*,*S*) cubic tetramers. The derived structures were then subjected to a conformational minimization search (MMFF, Spartan04) with frozen atomic coordinates for the Zn-O core. Two distinct lower-energy conformers were identified for each isomer and used as the starting points for further DFT full minimisation, giving the data recorded in Table 1. It is clear that the problem of steric crowding in cubic tetramers remains; there are still more than 10 pairs of remote H–H contacts between 1.9–2.3 Å. Overall, most of the >40 kcal mol^{-1} enthalpic advantage of the {2 dimer → tetramer} process is lost on changing from methylzinc to isopropylzinc-derived structures, because of the increased steric strain.[11] Severe crowding in the cube tetramer is demonstrated by the space-filling model of Fig. 3.

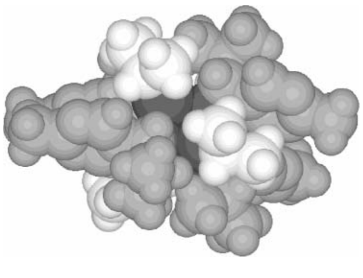


Fig. 3 Space-filling view of the cube structure showing crowding of $ZnPr^i$ (white) and $OCH(Pr^i)Ar$ (grey) residues.

The remaining Zn-O_2 square-based tetramers are all more strained in the *i*-Pr than in the Me series. For the former series, the ladder (Fig. 4) is less stable than two isolated monomers. The macro-isomer (SMS) is only modestly more strained in the *i*-Pr series, and lacks severe H–H interactions (2 contacts below 2.3 Å). Forming the barrel isomer by making two additional Zn–N bonds is only very marginally advantageous, for several reasons. The caps are distorted away from the preferred rhomboidal geometry, there are several short contacts and in particular the shorter HH-distances within the cavity are <1.9 Å. All of these factors contraindicate formation of this otherwise appealing structure.

Taken together, these considerations make the SMS-form the most likely tetrameric species. It would be a likely end-product in a (dimer + 2 RCHO + 2 R_2Zn) mechanistic pathway.[14] This structure notably retains the trigonal coordinatively unsaturated Zn geometry, previously argued to be an important aspect of autocatalysis,[4,5] that is supported by the preferred *monomeric* structure of conventional Zn asymmetric alkylation catalysts.

Even at 0 °C with the efficient ethynylpyrimidines like **1b** and **2b**, the observed degree of autoamplification of e.e. is substantially higher than predicted by the dimer model.[1b]§ The possible involvement of higher oligomers than the dimer in Zn autocatalysis is also raised by the observation of high catalytic activity at −25 °C.[15] At this temperature we observe that *unsymmetrical* higher oligomers are evident, even dominant, in the ^1H NMR spectrum.[16] The complexity of the low temperature spectrum indicates more than one species is present, with the RT aromatic singlet splitting into complex multiple signals and the Me_3Si– singlet showing at least

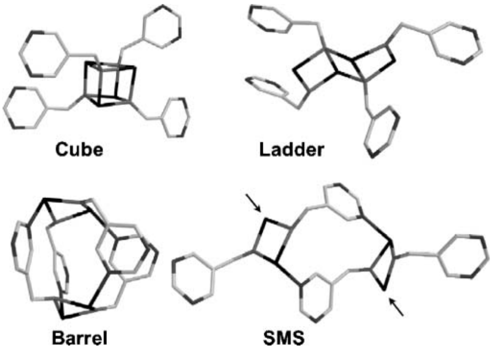


Fig. 4 Minimum energy structures (Table 1) of the four closed tetramers. Pr^i-groups and 2-Me substituents have been removed for clarity. Arrows indicate coordinatively unsaturated trigonal zinc sites in the square-macrocycle-square tetramer.

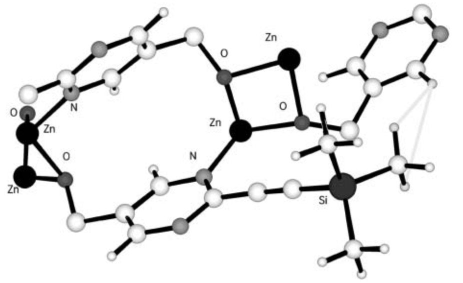
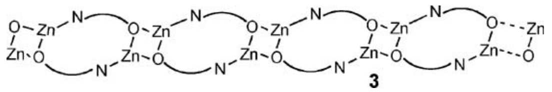


Fig. 5 How the macrocyclic tetramer (SMS) may demonstrate a long-range SiMe_3–HCAr NOESY effect. Entry 2M was modified to incorporate the 4-Me_3SiCC substituent and reminimized at PM3 level.

five daughter signals at 208 K. The 2D EXSY spectrum at this temperature indicates pairwise relationships between several Ar signals, indicating restricted rotation of some arenes. There is also a clear NOE relationship between some Ar-*H* (but not C*H*O) and the $(CH_3)_3$Si protons. In the monomer, the relevant inter-proton distance is 7.3 Å. The only simple way for these remote protons to experience NOE contact (<4 Å) is for the silyl group to be part of a bridging pyrimidine, as in the SMS tetramer, and the aryl group in contact to be part of a terminal pyrimidine. This is sketched in Fig. 5.

These studies have already defined two distinct roles for the *i*-Pr group. We postulate the possibility of a third role. A striking feature of the Soai autocatalysis system is that chirality can be induced and amplified by a vast range of seemingly unconnected chiral additives. These range from single enantiomer chiral crystals (quartz, sodium chlorate),[17] to conventional functional organic compounds and including hydrocarbons with quaternary asymmetric centres and also isotopically chiral (R_1R_2CHD) alcohols.[18] These cases resemble the absolute asymmetric synthesis observed in the Soai system in the absence of any initiating source of asymmetry,[2] but with control of the stereochemical outcome by the addend. An autocatalytic reaction may be triggered in a predictable way by vanishingly low enantiomer excesses in the reactant or by enantioselective photoreaction of the pyrimidinyl alcohol with polarised light.[19] Asymmetric induction must first arise in and then be propagated from a locally ordered nanoscale environment, and such processes are poorly understood.[20] The SMS-tetramer retains two trigonal Zn centres that are potential catalytic sites and thus can lead to linear oligomerization. Ordered oligomeric fragments like **3** propagated from the SMS-tetramer, and formed in local association with the chiral additive, could initiate the autocatalytic process. Indeed, once the initiation process provides a modest excess of one hand, established statistical mechanisms for amplification will lead to the observed predominance of the same enantiomer.[21]



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Notes and references

‡ The dipole moment of the preferred 4-TMS-alkynyl analogue μ = 2.98 debye.

§ For example, the TMS-ethynyl case shows amplification from 8.4% e.e. to 74.2% e.e. in 5 turnovers (ref. 1*b*). A dimer model predicts 42% e.e. under these conditions. More highly oligomeric homochiral catalysts give correspondingly higher levels of amplification, based on our model.[4]

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