Calcium control and $InsP_4$

SIR — In their paper on page 162 of this issue[1], Bird *et al.* claim to demonstrate that inositol trisphosphate ($Ins(1,4,5)P_3$) alone can account for calcium-ion entry in stimulated cells, with no need for a contribution from the tetrakisphosphate $Ins(1,3,4,5)P_4$. But the reported experiments do not actually address the issue of the physiological role of $Ins(1,3,4,5)P_4$ *in vivo*. What the authors do show is that introducing high doses of $Ins(1,4,5)P_3$ or $Ins(2,4,5)P_3$ as a bolus into cells can cause calcium-ion entry, an observation that has been made by others in several experimental systems (see ref. 2 for review).

Under another experimental paradigm very similar to that of Bird *et al.*, $Ins(1,4,5)P_3$ did not cause calcium-ion entry, but needed help from $Ins(1,3,4,5)P_4$ (ref. 3). This phenomenon may, of course, be an artefact (an explanation implicit in the paper by Bird *et al.*), but if this is so, is it likely to be a quantitative distortion of an existing mechanism or a new phenomenon created *de novo* by experimental conditions?

Credulity in the latter alternative is stretched to the limit by the observation that the clear requirement for $Ins(1,3,4,5)P_4$ could not be substituted by $Ins(1,4,5)P_3$, $Ins(1,3,4)P_3$, $Ins(2,4,5)P_3$, $InsPS_3$, or $Ins(1,3,4,5,6)P_5$, all at concentrations five- or more-fold than the fully effective dose of $Ins(1,3,4,5)P_4$ (ref. 4), a pharmacology which matches an $InsP_4$-binding protein found in many tissues[5]. These data show clearly that $Ins(1,3,4,5)P_4$ can control calcium entry, and suggest that if this phenomenon is an artefact, it is one of degree only. Moreover, if, as Bird *et al.* claim, $(1,4,5,)P_3$ is responsible for everything in an intact cell *in vivo*, where is the selective pressure for $Ins(1,3,4,5)P_4$ (and its receptor) to evolve and remain in existence for hundreds of millions of years?

If experimental artefacts are indeed distorting the picture, I suggest that there is a more plausible alternative for their nature in the possibility that the receptors for $Ins(1,4,5)P_3$ and $Ins(1,3,4,5)P_4$ interact, and their dissociation causes calcium entry[2,6]. *In vivo*, this dissociation would be promoted by the ligands ($InsP_3$ and $InsP_4$), but any experimental manoeuvre that separates these two proteins will cause calcium entry irrespective of the presence of $Ins(1,3,4,5)P_4$. Thus one need propose only that various experimental regimes influence quantitatively the interaction between two allosteric proteins to reconcile the apparent contradictions.

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1. Bird, G. S. J., Rossier, M. F., Hughes, A. R., Shears, S. B., Armstrong, D. L. & Putney, J. W. Jr *Nature* **352**,162–165, (1991).
2. Irvine, R. F. *Bioessays* (in the press).
3. Morris, A. P., Gallacher, D. V. Irvine, R. F. & Petersen, O. H. *Nature* **330**, 653–655 (1987).
4. Changya, L., Gallacher, D. V., Irvine R. F., Potter, B. V. L. & Petersen, O. H. *J. Membr. Biol.* **109**, 85–93 (1989).
5. Theibert, A. B. *et al. Proc. natn. Acad. Sci. U.S.A.* **83**, 3165–3169 (1991).
6. Irvine, R F. *FEBS Lett.* **263**, 5–9 (1991).

Induced molecule self-organization

SIR — In his comment[1] in News and Views on our work on the encapsulation of anionic guests in inorganic host molecules, Mitchell wondered whether the vanadium oxide host shells we synthesized exist without the encapsulated species. In answer, we have no evidence that they do. We find the encapsulation is due to a new type of self-organization process leading to unusual weak repulsive interactions in molecular species and to novel topological structures.

With the self-assembly process, almost any hollow sphere (cluster shell) can be generated, depending on size, shape and charge of the encapsulated anionic species X (the template), by using square-pyramids (of OVO_4; Fig. 1) as the repeating building block. The central anion is responsible for the architecture of the system, determining the number of linked units as well as their type of linking. A new and typical example is $[H(VO)_{18}O_{26}(NO_3)]^{10-}$ (Fig. 2) with an ellipsoidal structure, which has NO_3^- as the encapsulated ion.

Characteristic of this type of species is the rather large separation between negatively charged centres (here O . . . O) due to very weak (repulsive) forces, never before reported. The weak repulsive interactions can also allow unusually high 'coordination numbers' as high as 24 (see below; the highest known conventional coordination number is 12)[2]. These types of weak interactions are probably important in the poorly understood mechanism of anion exchange through membranes which occurs very rapidly.

Interesting topological considerations should also be mentioned. By linking 18

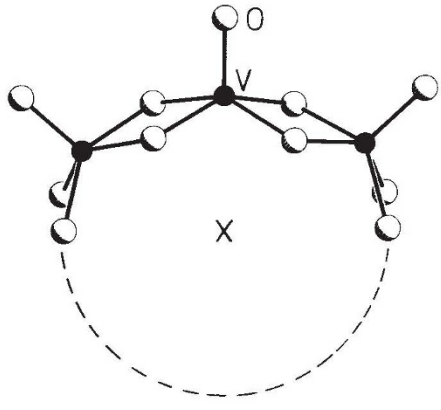

FIG. 1 Building molecular shells from OVO_4 tetrahedra.

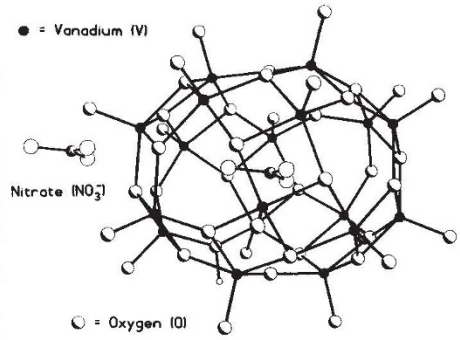

FIG. 2 The new inclusion species $[H(VO)_{18}O_{26}(NO_3)]^{10-}$, prepared by R. Rohlfing in our group. Notable in the structure is the large distance between the O atoms in shell and in the central anion, 280 picometres. With a more highly charged anion, such as CO_3^{2-}, the interaction with the V^{n+} centres in the shell is increased and the separation becomes less.

tetragonal OVO_4 pyramids, spherical hollow spheres, $[(VO)_{18}O_{24}(X)]^{n-}$, spanned by 24 O atoms can be generated[3]. Depending on the anion X the O atoms of the cluster shell with the same stoichiometry can either adapt the form of one of the 13 archimedean solids (the rhombicuboctahedron with 18 squares and 8 triangles) or the mysterious so-called fourteenth archimedean solid (or pseudo-rhombicuboctahedron). These cluster shells can be transformed into each other by rotating the upper hemisphere of the cluster by 45°.

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1. Mitchell, P. C. H. *Nature* **348**, 15–16 (1990).
2. Wells, A. F. *Structural Inorganic Chemistry* (Clarendon, Oxford, 1989).
3. Müller, A., Penk, M., Rohlfing, R., Krickemeyer, E. & Döring, J. *Angew. Chem. Int. Edn. Eng.* **29**, 926–927 (1990).

SIR — Although we were flattered to have our research cited in Mitchell's News and Views article[1] on new guest–host chemistry, the article may have left the mistaken impression that purely inorganic analogues of organic crowns and cryptands were hitherto unknown.

Inorganic crowns and cryptands have been investigated for at least 15 years. Interest was sparked initially by the biological activity of the sodium cryptate $[NaW_{21}Sb_9O_{86}]^{18-}$ (ref. 2), a species that has subsequently achieved notoriety as HPA23 in AIDS therapy. Larger, crown-shaped cryptands have been reported more recently: $[P_5W_{30}O_{110}]^{15-}$ (ref. 3); $[As_4W_{40}O_{140}]^{28-}$ (ref. 4) and $[P_8W_{48}O_{184}]^{40-}$ (ref. 5). The last two species have multiple cation binding sites in the interiors of their crown structures; the $[As_4W_{40}O_{140}]^{28-}$ cryptand even displays allosteric binding effects.

Inorganic complexes containing encapsulated anions were first characterized by Keggin[6] in 1933. Today, the number of inor-