

tations preclude fusion-gene formation via a simple reciprocal translocation, the discovery by Anderson *et al.* of chromoplexy as the underlying genomic process helps to clarify this. However, that such a high proportion of *EWSRI-FLII* fusions also arise by chromoplexy was not fully appreciated.

Notably, Anderson *et al.* provide evidence to suggest that chromoplexy-associated rearrangements occur simultaneously, presumably in the EWS cell of origin, the nature of which remains unclear. A fascinating question is whether these chromoplexy events can be linked to specific features of three-dimensional chromatin organization and/or of the transcriptional state of chromatin regions involved in chromoplexy rearrangements in this hypothetical cell type, given that they appear to be enriched in early replicating and transcriptionally active genomic regions, which may be prone to breakage as they are exposed during transcription. Gene pairs involved in fusions are often in close proximity in interphase nuclei, regardless of their chromosomal location (5), and this higher-order contiguity can be induced by specific transcription factors (6). A better understanding of the transcriptional regulation of the genes recurrently involved in chromoplexy-derived *EWSRI-FLII* and *EWSRI-ERG* fusions might reveal the cell state or lineage in which EWS arises.

Given the young age of many EWS patients, one may speculate what exogenous or endogenous mutagen could be responsible for such a mutational “burst.” Although radiation is a likely suspect in any disorder involving multiple chromosomal breaks, endogenous mutagens such as transposases and cytidine deaminases have also been linked to complex somatic rearrangements. Could EWS chromoplexy events be linked, for example, to the activity of an aberrantly expressed endogenous transposase such as PiggyBac transposase 5 (PGBD5), which was recently implicated in the genesis of the pathogenic gene rearrangements in childhood malignant rhabdoid tumors (7)? An alternative possibility is a constitutional or acquired DNA repair defect (8). Analysis of the sequence context surrounding chromoplexy breaks may provide clues and potentially point to a therapeutic vulnerability that could be used to treat EWS. Furthermore, perhaps EWS arising from chromoplexy may be responsive to immune checkpoint inhibition, given the preference of chromoplexy events for transcriptionally active regions that should result in multiple fusion transcripts, most of which are likely to be out of frame (except the driver fusion gene). Frameshift alterations represent an especially rich source of neoantigens (9), which can predict response to immune checkpoint inhibition.

Although Anderson *et al.* qualitatively validate a subset of chromoplexy events observed through WGS with spectral karyotype data, a comprehensive bridging of the divide between such large-scale views of chromosome structure and the detailed views of WGS will require the application of long-range WGS approaches using linked-read or proximity-ligation short-read sequencing and long-read sequencing, which uses more expensive and lower-throughput technologies to achieve read lengths that exceed 10 kilobase pairs. The long-range reconstruction of highly rearranged loci can yield insight into both the mutational processes generating complex structural variants and the consequences of these variants on DNA sequences (10).

The findings of Anderson *et al.* raise important clinical questions. The contribution of genetic analysis to the current standard of care for EWS is limited to confirmation of the diagnostic *EWSRI-FLII* or *EWSRI-ERG* fusions. The discovery of genomic patterns associated with subsets of EWSs raises the question of whether additional molecular diagnostic modalities are warranted. If chromoplexy events are important clinical biomarkers for EWS disease aggressiveness, as the authors suggest, their findings may support a new indication for clinical WGS. However, additional analysis of more patient samples will be needed to confirm that the presence of chromoplexy is an independent prognostic predictor in EWS. This is because Anderson *et al.* find that chromoplexy-driven EWS more likely contains tumor protein 53 (*TP53*) mutations. Because *TP53* and stromal antigen 2 (*STAG2*) mutations and genomic complexity have each been associated with more aggressive EWS (11–13), dissecting the contribution of these factors to poor clinical outcomes in chromoplexy-derived EWS will be an important area of future work. More generally, the work of Anderson *et al.* has important clinical implications for the genomic diagnosis of these and other cancers, as well as the expanding biological role of complex rearrangements in cancer evolution. ■

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ORGANOMETALLICS

18 electrons and counting

The bonding rule for transition metal complexes now extends to alkaline earth octacarbonyls

By P. B. Armentrout

The “octet rule” is based on the stability afforded to species with closed-shell electron configurations like the noble gases. Simple “second-row” compounds like methane, ammonia, and water have eight electrons surrounding the central atom, as do their third-row analogs (silane, phosphine, and hydrogen sulfide). For atoms in the fourth row of the periodic table and beyond (principal quantum number designated by n), the single ns ,

“Intriguingly...the $M(\text{CO})_8$ species do not actually have a singlet spin state... [r]ather...a triplet spin state...”

three np , and five $(n - 1)d$ orbitals must be filled with two electrons per orbital, resulting in an analogous “18-electron” rule for a closed shell. This simple electron counting guides inorganic chemists working with transition metals in predicting stable compounds, just as the octet rule guides organic chemists working with carbon. For example, the stable transition metal carbonyls $\text{Cr}(\text{CO})_6$, $\text{Fe}(\text{CO})_5$, and $\text{Ni}(\text{CO})_4$, as well as heavier homologs, can be formed, indicating that CO is a two-electron donor. Metals with an odd number of valence electrons must double up with a metal-metal bond, so $\text{Mn}_2(\text{CO})_{10}$ and $\text{Co}_2(\text{CO})_8$ form in order to satisfy the 18-electron rule. On page 912 of this issue, Wu *et al.* (1) demonstrate that the 18-electron guiding principle is not only limited to transition metals but can also be extended to nearby elements, the alkaline earths.

Alkaline earth metals (Ms; Be, Mg, Ca, Sr, and Ba) have a valence electron configuration of ns^2 and generally form two covalent bonds

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with other elements, for example, MgO and BaBr₂. Grignard reagents RMgX, where R is generally an alkyl group and X is a halide, are common reagents in organic and organometallic synthesis. In solution, alkaline earths are readily oxidized and normally found in their +2 oxidation state. Surprisingly, Wu *et al.* show that the octacarbonyls of the heavier alkaline earths—Ca, Sr, and Ba—can be formed in the neutral state as a consequence of surrounding the two-electron M atoms with another 16 electrons.

Metal carbonyls have been known since the late 19th century (2) and are used as starting materials for transition metal compounds in organic synthesis and as catalysts in hydroformylation. At a fundamental level, metal

electron-counting procedure noted above, in which the CO ligand donates its pair of electrons into an empty orbital on the metal, provides one binding motif, called σ donation (after the symmetry of the bond being formed; see the figure, right). Because the HOMO is largely a nonbonding orbital on CO, σ -bond donation does not greatly affect the C=O stretching frequency (3).

However, CO ligands are actually more promiscuous in their binding. The lowest unoccupied molecular orbitals (LUMOs) on CO are the two antibonding π^* orbitals (see the figure, left). Transition metals can utilize electrons in d orbitals with the same π symmetry to augment the binding to the CO ligand, in essence, forming a sec-

absorptions at 1987, 1995, and 2014 cm⁻¹ for saturated carbonyl complexes of Ca, Sr, and Ba, respectively, as well as other absorptions for smaller complexes. Because only a single C=O stretching frequency was observed, the absorbing species must have high symmetry, assigned as cubic O_h for M(CO)₈.

These frequencies indicate that substantial backbonding occurs that gradually decreases with increasing metal size. Backbonding is critical in the formation of these complexes. The approach of CO to one of the Ms should entail a repulsive interaction between the occupied *ns*² orbital on the M and the HOMO of CO. To avoid this difficulty, the Ms must empty seven valence orbitals [one *ns*, three *np*, and three of the (*n* - 1)d orbitals], which permits strong σ donor bonds with the CO ligands. The eighth “bonding” orbital needed for eight ligands is purely ligand based and has a_{2u} symmetry (a type for which there is no atomic orbital on the M). The two M valence electrons then occupy the remaining two (*n* - 1)d orbitals (having e_g symmetry), which augment the bonding by backbonding interactions, as demonstrated by the C=O stretching frequencies measured.

Intriguingly, because these two orbitals are isoenergetic, the M(CO)₈ species do not actually have a singlet spin state in which all the electrons are paired (which one ordinarily associates with stable 18-electron complexes). Rather, each of the two (*n* - 1)d orbitals contains a single electron, yielding a triplet spin state, as confirmed by quantum chemical calculations. Wu *et al.* also examined the cationic analogs of M(CO)₈ complexes in the gas phase. Evidence for a saturated M(CO)₈⁺ complex (now a 17-electron species) was obtained by observation of a single C=O stretch, whereas M(CO)₉⁺ exhibited a band characteristic of a CO ligand in a weakly bound second ligand shell.

The study of Wu *et al.* challenges previous notions of limitations in the 18-electron rule and provides complexes exhibiting very interesting bonding motifs in the process. Whether the distinctive properties of such compounds can be exploited remains to be seen, but the study foreshadows additional complexes that might be generated and test the limits of the 18-electron rule. ■

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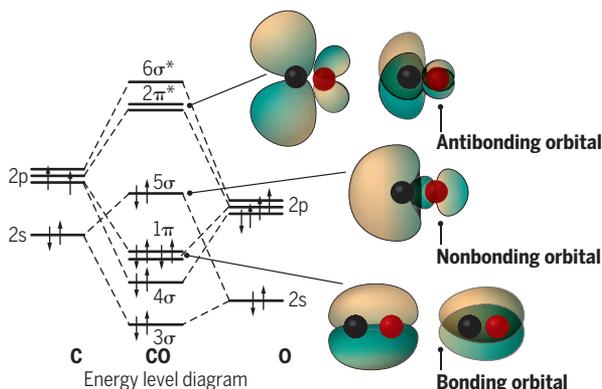
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Building an unexpected bond

Alkaline earth carbonyls reported by Wu *et al.* can be understood from simple bonding concepts.

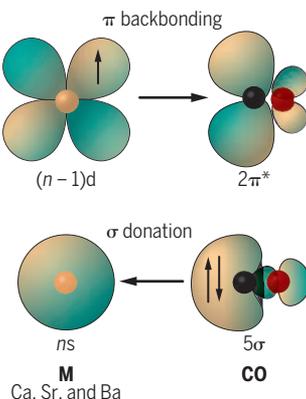
Bonding in carbon monoxide

The molecular orbital diagram for the formation of carbon monoxide from carbon and oxygen atoms is shown. Several of the molecular orbitals are shown to the right.



Creating alkaline earth carbonyls

The bonding interactions between an alkaline earth metal (M) and carbon monoxide are shown. Vertical arrows indicate electrons in both parts.



carbonyls can be used to assess the relative strength of binding interactions in coordination complexes. The highest occupied molecular orbital (HOMO) in CO corresponds to a lone pair of electrons on the C atom (see the figure, left), so CO binds to metals at the C atom, except in extraordinary circumstances. Furthermore, this orbital can donate two electrons to the metal center. In the CO triple bond (one σ and two π bonds), four of the six electrons come from the more electronegative O atom. The dipole moment of CO is relatively small (0.122 debye), and counterintuitively, the C atom has the negative charge. However, as the C=O bond stretches, the electrons follow the more electronegative O atom, and the dipole moment of CO increases dramatically. Thus, CO molecules “light up” in infrared (IR) spectroscopy because they have a large change in their dipole moment upon stretching.

This property of the CO ligand can then be used to assess how it binds to metals. The

ond or even a third bond between the metal and the carbon (see the figure, right). This type of electron-exchange bonding is often referred to as the Dewar-Chatt-Duncanson model (4, 5), although these authors actually addressed similar σ and π interactions between metals and olefins. The strength of these “backbonding” interactions can be assessed by measuring the C=O stretching frequency. As electrons are donated into the antibonding LUMOs, the C=O bond becomes weaker and its vibrational frequency is lowered. For example, in Ni(CO)₄, the stretch shifts down to ~2060 cm⁻¹ from the free CO at 2143 cm⁻¹. The shift increases for isoelectronic anionic analogs that backbond more effectively, as in Co(CO)₄⁻ at ~1890 cm⁻¹ and Fe(CO)₄²⁻ at ~1790 cm⁻¹ (6).

Wu *et al.* generated complexes of Ca, Sr, and Ba with CO in a cold (4 K) neon matrix that allowed weakly bound species to form (7). They interrogated the matrix using IR irradiation, finding single intense

18 electrons and counting

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