Enigmatic astatine

D. Scott Wilbur points out the difficulty in studying the transient element astatine, and the need to understand its basic chemical nature to help in the development of targeted radiotherapy agents.

Since the discovery of astatine over 70 years ago[1], many of its characteristics have remained elusive. Unlike the other halogens, abundant and ubiquitous in nature, astatine is one of the rarest of all elements. This arises from the fact that it has no stable isotopes; the longest lived of its 32 known radioisotopes, ^{210}At, has a half-life of only 8.1 hours. The rarity and radioactive nature of element 85 lends to its mystery, as it cannot be observed or weighed in a conventional sense. Even its colour is unknown; based on increasingly dark colours for halogens from fluorine to iodine, however, black seems a logical guess.

The rarity of this radioactive element is reflected in its name, derived from the Greek word αστατος (astatos) meaning 'unstable'[2]. What little astatine is present in nature comes from the decay of heavy radioactive elements found in the Earth's crust. The total amount of natural astatine at any given time has been estimated to be between a few hundred milligrams[3] and 30 g. In any case, naturally occurring astatine isotopes are too unstable, and would be too difficult to obtain, for characterization. Fortunately, the two longest-lived isotopes — ^{210}At and ^{211}At (half-life = 7.21 h) — can both be produced by α-beam irradiation of bismuth-209 targets (pictured, on aluminium support).

© DON HAMLIN

Nevertheless, these longer-lived isotopes can only be produced in small quantities[4], which, combined with their short half-lives and high costs, have considerably limited astatine research. Of the artificial isotopes, ^{211}At has been the primary focus of chemical studies owing to its potential in medicine. The other 'long'-lived isotope, ^{210}At, is not suitable because it decays into polonium-210 — the notorious radiation poison used to kill the Russian Federal Security Service officer Alexander Litvinenko in 2006, after he took political asylum in the United Kingdom.

Although some chemical data has been compiled for astatine isotopes, many physical properties have only been extrapolated. Similar to other halogens, astatine undergoes nucleophilic and electrophilic reactions. The reproducibility of some reactions however has proved highly variable. This may arise in part from the low amounts of astatine present, resulting in very high reaction dilutions. Quantities of ^{211}At used in chemical and radiolabelling reactions range from 37 kBq to 4 GBq. These only represent from ~4.8×10^{-13} to ~5.2×10^{-8} g of ^{211}At — and this upper limit is rarely encountered, because of the costs involved and the potential for radiation damage to the molecule being labelled. For most reactions, the quantity of ^{211}At present ranges from 10^{-13}–10^{-9} g, and can be smaller than that of trace organic species and metals in solvents. Impurities may thus interfere with the reactions studied, and might even catalyse reaction pathways other than that expected.

The interest in ^{211}At in medicine mentioned above arises from its potential use in systemically targeted therapy of cancers — it is one of only a few α-emitting radioisotopes considered appropriate for medical use[5], as most others can cause severe damage to internal organs. Its short path length (60–90 μm) and high-energy α-particles (6.0–7.5 MeV) are very effective in killing cells bound by a carrier-targeting agent[6]. However, a major impediment to practical applications is the low stability of astatine bonds with aromatic carbon bonds *in vivo*[7]. The development of labelling reagents containing more stable aromatic astatine–boron bonds has improved that situation, and studies evaluating bonding with other elements may further advance it.

To determine *in vivo* stability, the same cancer-targeting molecule can be labelled with ^{211}At and (stably) with radioiodine (^{125}I, ^{123}I or ^{131}I), and the two co-injected. The concentrations of ^{211}At in various tissues (higher lung, spleen, stomach and thyroid) indicate whether it is being released from the carrier molecule. However, even in studies in which low stomach and thyroid (neck) concentrations suggest that ^{211}At and ^{125}I are both stable to *in vivo* dehalogenation, very dissimilar concentrations may be observed for the two elements in other organs such as kidney and liver. This is likely to be due to variations in metabolism of the radioiodinated and astatinated molecules, or may arise from preferential clearance of the radioiodinated metabolites.

In the quest to produce targeted therapeutics for treatment of cancer and other diseases, many of the basic chemical studies with ^{211}At have unfortunately been set aside. Although some of its physical properties will continue to elude direct characterization, it is apparent that we need to gain a better understanding of its basic chemical and radiochemical properties to unravel the enigma of astatine. ❐

D. SCOTT WILBUR is at the Department of Radiation Oncology, University of Washington, Box 355016, 616 NE Northlake Place, Seattle, Washington 98105, USA.
e-mail: dswilbur@uw.edu

References

1. Corson, D. R. *et al. Phys. Rev.* **58,** 672–678 (1940).
2. Corson, D. R. *et al. Nature* **159,** 24 (1947).
3. Kugler, H. K. & Keller, C. (eds) *Astatine* 10–14 (Gmelin, Handbook of Inorganic Chemistry series, 1985).
4. Zalutsky M. R. & Pruszynski, M. *Curr. Radiopharm.* **4,** 177–185 (2011).
5. Wilbur, *D. S. Curr. Radiopharm.* **4,** 214–247 (2011).
6. Hall, R. J. & Giaccia A. J. *Radiobiology for the Radiologist* 6th edn, 106–116 (Lipincott Williams & Wilkins, 2006).
7. Wilbur, *D. S. Curr. Radiopharm.* **1,** 144–176 (2008).