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An experimental comparison of the K- and L-Auger electron spectra generated in the decays of ^{140}Nd and ^{111}In

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Abstract

The low-energy electron spectra generated in the decay of ^{140}Nd have been measured using a combined electrostatic spectrometer adjusted to the 4, 7, and 35 eV instrumental resolution. In order to estimate the therapeutic potential of low-energy electrons associated with the decay of ^{140}Nd, similar experiments have been performed with ^{111}In. Relative Auger electron intensity ratios per decay are: $^{111}In_{K-Auger}/^{140}Nd_{K-Auger} = 1.47(12)$, $^{111}In_{L-Auger}/^{140}Nd_{L-Auger} = 1.1(4)$, and $^{111}In_{L-Auger\ [2.8-7\,keV]}/^{140}Nd_{L-Auger\ [2.8-7\,keV]} = 0.24(11)$. The obtained K-Auger group intensity ratios have been compared with results of calculations. The good agreement found for the experimental and estimated values indicates that such information can be also derived using available nuclear and atomic data.

The relative intensity of L-Auger electrons emitted within the 2.8–7 keV interval is higher for ^{140}Nd by a factor of about 4 compared to ^{111}In. As the L-Auger emission is dominating relative to that of the K-Auger group, this implicates that any potential endotherapeutic strategy using ^{140}Nd-labelled targeting vectors requires a maximum accumulation of the endoradiotherapeutical close to the cell nucleus or the DNA of the tumour cell.

1. Introduction

The effective endoradiotherapy (ERT) of soft tissue tumours and small metastases with labelled complexes, particles, peptides, monoclonal antibodies or fragments requires the appropriate selection of a suitable radionuclide. Compared to high-energy β^- emitters such as ^{90}Y, for example, radiopharmaceuticals labelled with β^--emitting nuclides with lower β^- energy or with nuclides emitting α-particles or Auger electrons seem to be more adequate. These particles are generally characterised by a shorter range and a high linear energy transfer (LET) in tissue. In particular Auger electron emitters seem to be most effective to selectively treat small tumours or disseminated metastases by the double strand breaks they induce in the tumour cell DNA.

Among the Auger electron emitters, the radiolanthanide ^{140}Nd has some unique nuclear properties. The ^{140}Nd half-life of 3.37 d seems to be suitable for most of the usual treatments in ERT. It allows achieving a significant tumour to blood activity ratio and it is particularly useful for the application of molecules with relatively long biological kinetics such as peptides, monoclonal antibodies or fragments (Rösch and Forssell-Aronsson, 2004). The ^{140}Nd itself emits Auger electrons

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exclusively, not accompanied by high-energy γ-radiation. Positrons and 511 keV annihilation photons are, however, generated in the decay of its short-lived daughter ^{140}Pr ($T_{1/2}=3.39$ min). The calculated effective Auger electron yields (e.g. Bambynek et al., 1972; Krause, 1979) for the K-, L_1-, L_2- and L_3-shells are 0.083, 0.879, 0.865 and 0.882, respectively. These radiationless emissions are comparable with those of the most often considered Auger electron emitter ^{125}I, 0.128, 0.923, 0.915 and 0.926, respectively (Bambynek et al., 1972; Krause, 1979; Firestone and Shirley, 1996).

There are groups of Auger electrons emitted per decay creating a positively charged residual daughter atom. On averaging the Gaussian distribution, the corresponding charges range from +7 to +9 with maximum values as large as +20 to +30 (Metag et al., 1980) at least in the gaseous phase. This number of emitted Auger electrons parallels the therapeutic efficacy of ^{140}Nd. The estimated mean kinetic energy of the Auger electrons emitted in the ^{140}Nd/^{140}Pr decays amounts to about 3 keV (Larkins, 1977; Chen et al., 1979; Chen, 1985) compared to 2.6 keV for ^{125}I, with the dominating fraction of the L and M Auger electron emission with a mean energy of about 2 keV compared to 1.6 keV for ^{125}I. Consequently, the Auger electrons emitted in the ^{140}Nd decay chain thus are concentrated on a cellular dimension. The surrounding healthy tissue is effectively saved (Rösch and Forssell-Aronsson, 2004).

As a trivalent lanthanide, ^{140}Nd should provide an excellent chemical potential for use either as ^{140}Nd ligand complexes alone or as conjugates being coupled to various compounds via bifunctional chelators. This might be of particular interest to label octreotide derivatives, or other peptides, binding with high affinity and specificity to tumours, expressing the corresponding receptors on the cell membrane similar to the ^{111}In-, ^{68}Ga- or ^{90,86}Y-analogues.

^{140}Nd decays to the short-lived intermediate isotope ^{140}Pr ($T_{1/2}=3.39$ min), which further decays via electron capture and positron emission (51% β^+, $E_{max}=2.3$ MeV) to stable ^{140}Ce, cf. Fig. 1. While the contribution from the decay of the daughter nuclide to the total dosimetry needs to be studied in detail, it is obvious that the decay of ^{140}Pr offers the possibility of using positron emission tomography (PET) to determine quantitatively the uptake kinetics and radiation doses of the ^{140}Nd-labelled endoradiotherapeuticals. First PET images of a ^{140}Nd of a ^{140}Nd/^{140}Pr phantom have been acquired (Rösch et al., 1999a). ERT and PET are thus being bridged inherently and might allow quantitative validations as described for ^{90}Y (ERT) and ^{86}Y (PET) (cf. Herzog et al., 1993; Rösch et al., 1996; Rösch et al., 1999b; Förster et al., 2001).

The decay of ^{140}Pr will contribute to the overall radiation dosimetry of the ^{140}Nd/^{140}Pr system. The positrons emitted by ^{140}Pr and the subsequent 511 keV annihilation photons will affect tissue in the range of several mm for the positrons and several cm for the photons. However, the therapeutic potential on the cellular level, i.e. close to the physiological localization of the ^{140}Nd-labelled targeting molecules, depends on the structure of the emitted Auger electron spectrum. Those spectra, unfortunately, are known mainly from theoretical estimations. It was the aim of this work to determine experimentally the energy of Auger electrons generated in the decay of the ^{140}Nd chain. These energies shall be compared to those of ^{111}In, as used recently in the endoradiotherapeutic treatment of neuroendocrine tumours using [^{111}In]-DTPA-(D)Phe-octreotide (McCarthy et al., 1998; Tiensuu et al., 1999) because of its emission of Auger electrons as well (McLean et al., 1989). The results of a detailed investigation of the KLL and (KLM + KLX) Auger groups of ^{111}Cd generated in the decay of ^{111}In have recently been published (Kovalík et al., 1999).

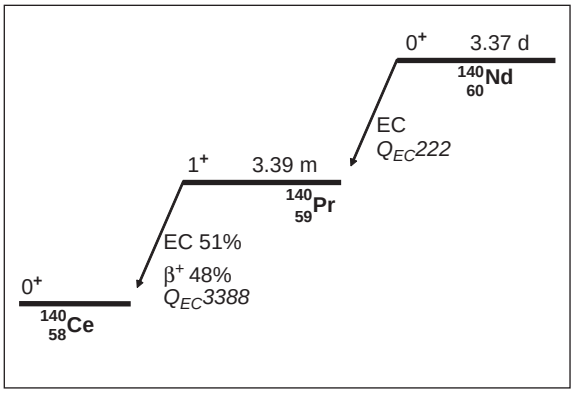

Fig. 1. Schematic decay of ^{140}Nd (Firestone and Shirley, 1996).

2. Experiments and methods

2.1. Source preparation

^{140}Nd was produced by the spallation of tantalum irradiated with 660 MeV protons at the phasatron of the JINR, Dubna. A standard chemical procedure (Chung et al., 1984) was employed to separate the isotope from the irradiated target. ^{111}In was produced in the reaction ^{109}Ag(α,2n)^{111}In by irradiation of a natural silver target with 30 MeV α-particles at the accelerator U-200 of the JINR, Dubna. Cation-exchange chromatography (Filosofov et al., 2001) was employed to separate the no-carrier-added (n.c.a.) isotope ^{111}In. Sources of ^{140}Nd and ^{111}In for electron spectrum measurements were prepared by modified Langmuir–Blogett (LB) method (Kovalík et al., 1999). This method was developed for preparation of minimum size thin radioactive sources for low-energy electron spectroscopy. A chemi-sorption

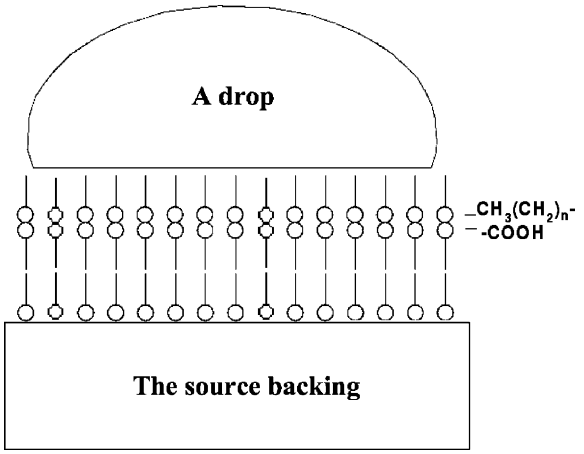

Fig. 2. Chemi-sorption of radionuclide ions from a drop of an aqueous solution onto an organic surface providing constituents forming oriented monomolecular layers attached to a metallic backing.

of ^{140}Nd or ^{111}In cations from a single drop of aqueous solution at pH = 5 onto a LB monomolecular layer, previously transferred to a metallic backing, was performed within few hours at a temperature of 60 °C (see Fig. 2). Absolute activities of the prepared ^{140}Nd and ^{111}In sources were determined using the 511 keV annihilation peaks of the β^+ branch of the ^{140}Pr decay and the 171.20 and 245.35 keV gamma rays of ^{111}In, respectively.

2.2. Spectrum measurements

Auger electron spectra of ^{111}Cd and ^{140}Pr/^{140}Ce generated in EC-decays of ^{111}In and ^{140}Nd, respectively, were measured using a combined electrostatic spectrometer (Briançon et al., 1984). The spectrometer consists of a retardation sphere followed by a double-pass cylindrical mirror energy analyser. The region of L-Auger electrons of ^{111}Cd was scanned with the instrumental resolution of 4 eV and that of ^{140}Pr + ^{140}Ce with the instrumental resolution of 7 eV. The energy regions of the K-Auger groups of ^{111}Cd and ^{140}Pr + ^{140}Ce were recorded with the 35 eV instrumental resolution.

Scanning of the spectra was performed by point-by-point sweeping over the required energy interval. The absolute energy scale of the spectrometer was calibrated by means of suitable low-energy conversion electron lines of the 8.41008(21) keV, 63.12081(4) keV, and 20.74378(10) keV nuclear transitions in ^{169}Tm resulting from the EC decay of ^{169}Yb and the 14.41302(32) keV nuclear transition in ^{57}Fe (from the EC-decay of ^{57}Co); cf. (Lederer and Shirley, 1978a). Information on the transmission curve of the electron spectrometer in the very low-energy region from 1 to 20 keV for the instrumental resolution of 35 eV was derived from the ^{241}Pu β^- spectrum measurements and extrapolated to higher energies from intensities of conversion electron lines of ^{169}Tm obtained with the instrumental resolution of 4 and 7 eV (Gorozhankin et al., 1996). Additional measurements without any source in the spectrometer were performed for estimation of the background level.

2.3. Electron spectrum evaluation

After a background subtraction the measured spectra were corrected for the half-lives of ^{140}Nd ($T_{1/2} = 3.37$ d) and ^{111}In ($T_{1/2} = 2.83$ d) and for a change of the spectrometer transmission (Gorozhankin et al., 1996). Examples of the measured spectra after corrections are shown in Figs. 3 and 4. Energies and intensities of spectrum components were determined using a method and a computer code described in detail in Kovalik et al. (1992).

3. Results and discussion

3.1. The K- and L-Auger electron groups of ^{140}Pr

From the measured spectra of Auger electrons emitted in the ^{140}Nd decay, a ratio of 45(5):2.4(2):1.0(1) was determined for the (LMM + LMX + LXY):KLL:(KLM + KLX) group intensity ratio of ^{140}Pr. Mean energies of the (LMM + LMX + LXY), KLL and (KLM + KLX) groups of ^{140}Pr were obtained to be 4.0(4), 28.6(4) and 33.9(3) keV, respectively.

As the theory on the K- and L-Auger transitions is quite successful in its predictions, a reliable estimation of the structure of K- and L-Auger electron spectra in a wide range of atomic numbers can be obtained, using theoretical transition energies, e.g. (Larkins, 1977), and intensities, e.g. (Chen et al., 1979, 1980; Chen, 1985).

The experimental values are lower than the corresponding theoretical estimations (Larkins, 1977; Chen et al., 1979, 1980; Chen, 1985). This indicates that the experimental K- and L-Auger electron spectra were shifted to lower energies due to inelastic scattering of the investigated Auger electrons in the radioactive sources used. The distortion increases with decreasing primary energy of the electrons. Nevertheless, at the present inelastic scattering of electrons with energies from units of keV can be reliably calculated by means of Monte-Carlo simulations (cf. e.g., Špalek and Dragoun, 1993; Baro et al., 1995); supposed precise information on both the composition and the structure of the source are available.

3.2. A comparison of the K-Auger electron groups

The intensity ratio per decay of the K-Auger groups generated in the ^{111}In decay (K-Auger electron spectrum

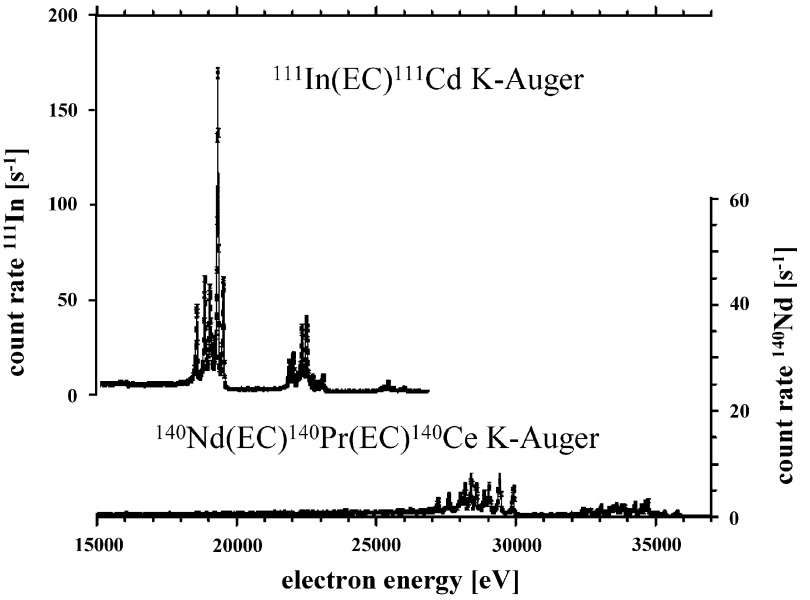

Fig. 3. K-Auger spectra of ^{111}Cd and ^{140}Pr + ^{140}Ce measured at the instrumental resolution of 35 eV and the 10 eV step size. The spectra were corrected for half-lives and the spectrometer transmission changing and are normalised to the same absolute source activity and the same effective spectrometer transmission.

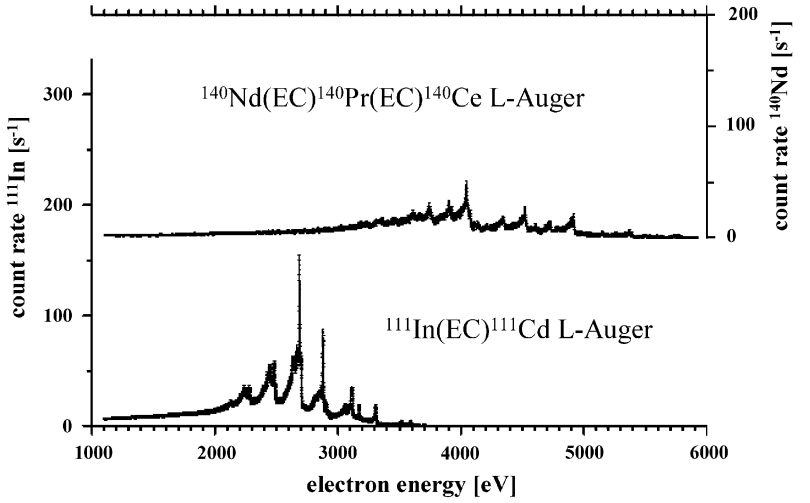

Fig. 4. L-Auger spectra of ^{111}Cd measured at the instrumental resolution of 4 eV and the 1 eV step size and those of ^{140}Pr + ^{140}Ce measured at the instrumental resolution of 7 eV and the 1 eV step size. The spectra were corrected for half-lives and spectrometer transmission changing, and are normalised to the same absolute source activity and same effective spectrometer transmission.

of ^{111}Cd) and the decay of ^{140}Nd (K-Auger electron spectrum of ^{140}Pr/^{140}Ce) was derived from the measured spectra to be $^{111}In_{K\text{-}Auger}/^{140}Nd_{K\text{-}Auger} = 1.47(12)$. In this determination, the negligibly low intensities of the (KMM + KXY)-Auger electron groups, relative to that of the (KLL + KLX) groups, were not taken into account. The main contributions to the experimental errors, which represent more than 90% of the overall experimental errors, arise from lack of enough precise information on (1) the scattering of studied electrons in the spectrometer, (2) the energy dependence of the spectrometer transmission, (3) possible time instabilities of the detector efficiency (a channel electron multiplier), (4) the absolute activities of the measured sources, (5) the shapes of the low-energy tails of the measured Auger electron spectrum lines caused (as mentioned above) by

inelastic scattering of the Auger electrons in the measured sources, which are different for different electron energies.

The intensity ratio of the two Auger electron groups was estimated to be 1.52. In this determination, several published data were used such as electron capture probabilities (Dzhelepov et al., 1972) for different atomic shells for the EC-decay of ^{111}In, ^{140}Nd and ^{140}Pr, K-shell fluorescence yields for $Z=48$, 58 and 59 (Lederer and Shirley, 1978a), internal conversion coefficients (Hager and Saltzer, 1968) and probabilities for different decay channels of ^{140}Pr (Lederer and Shirley, 1978b). This agreement of the measured and estimated values of the K-Auger electron group intensity ratios validates the procedure applied for experimental spectra evaluation. It also indicates that available nuclear and atomic data are reliable and precise enough to derive that relative information.

3.3. A comparison of the L-Auger electron groups

A comparison of the L-Auger electron groups generated in the decays of ^{111}In and ^{140}Nd is more complicated because of the very long low-energy "tails" of the L-Auger electron spectrum, caused by inelastic scattering of the Auger electrons in the radioactive source. It is known that these "tails" approach "zero" energy. In the investigated region of units of keV energy, shapes of the L-Auger electron spectrum depend much more on the electron energy than in the case of the K-Auger electrons group. It is thus difficult to calculate precisely the electron line shape for a real radioactive source generally, and in particular, in the lowest energy region.

The value of $^{111}\mathrm{In}_{\text{L-Auger}}/^{140}\mathrm{Nd}_{\text{L-Auger}}=1.1(4)$ determined for the intensity ratio of the L-Auger electrons emitted in the ^{111}In decay (L Auger electron spectrum of ^{111}Cd) and the decay of ^{140}Nd (L-Auger electron spectrum of ^{140}Pr/^{140}Ce) is thus affected by a significant systematic uncertainty. Finally, we determined an intensity ratio of the L-Auger electrons in the very low-energy region (<7 keV), relevant to the energy region of the L-Auger electrons emitted in the decay of ^{140}Nd. For this region, a value of $^{111}\mathrm{In}_{\text{L-Auger [2.8–7 keV]}}/^{140}\mathrm{Nd}_{\text{L-Auger [2.8–7 keV]}}=0.24(11)$ was determined. This indicates an about four-fold higher intensity of low-energy Auger electrons for ^{140}Nd compared to ^{111}In in the energy region of the ^{140}Nd L-Auger electron emission.

4. Conclusion

The intensities of Auger electrons emitted via the decay of ^{140}Nd have been measured experimentally and were compared to the ^{111}In Auger electron groups. For relatively high-energy K-Auger electrons in the range of about 18–40 keV, the intensities are higher by a factor of about 1.5 for ^{111}In as compared to the ^{140}Nd decay chain. This experimental result agrees well with an estimated ratio, derived from atomic and nuclear data. In the lower energy range of 1–7 keV, L-Auger electron intensities are almost similar for ^{111}In and ^{140}Nd. However, for the range of 2.8–7 keV, which covers the energy region of the L-Auger group of the ^{140}Nd decay chain, ^{140}Nd Auger electron intensities are dominating by a factor of about 4 compared to those emitted by ^{111}In.

As the ratio of ^{140}Nd L-Auger group intensities to K-Auger electron group intensities amounts to about 18:1, the endotherapeutic potential of ^{140}Nd labelled tumour targeting vectors is directly related to intensities and energies of those L-Auger electron emissions. In this case, both ^{140}Nd and ^{111}In are shown to be comparable. However, as the range of these low-energy electrons in tissue is small, this clearly indicates that the efficacy of potential application will require the accumulation of the labelled compounds close to the tumour cell nucleus or DNA.

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