Preparation of spin-labeled ibuprofen and its interaction with 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine bilayer

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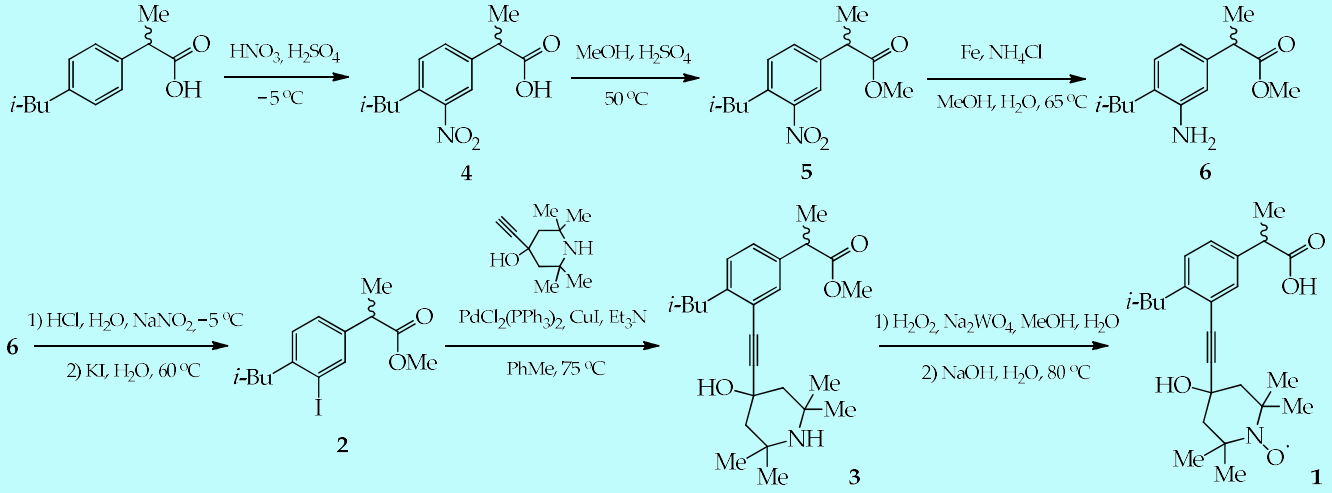
Ibuprofen, along with aspirin and paracetamol, is the most significant non-steroidal anti-inflammatory drug, and is widely used for analgesic and antipyretic purposes. Different methods are used to study ibuprofen-mediated changes in model lipid membranes. Electron paramagnetic resonance (EPR) spectroscopy could be applied to study its interaction with biological membranes and proteins if its spin-labeled analogs were synthesized.

Here, a simple sequence of ibuprofen transformations: nitration, esterification, reduction, Sandmeyer reaction, Sonogashira cross-coupling, oxidation and saponification was developed to attain this goal (Scheme 1). The synthesis resulted in spin-labeled ibuprofen (ibuprofen-SL) in which the spin label TEMPOL is attached to the benzene ring.



Scheme 1 Synthesis of ibuprofen-SL **1**.

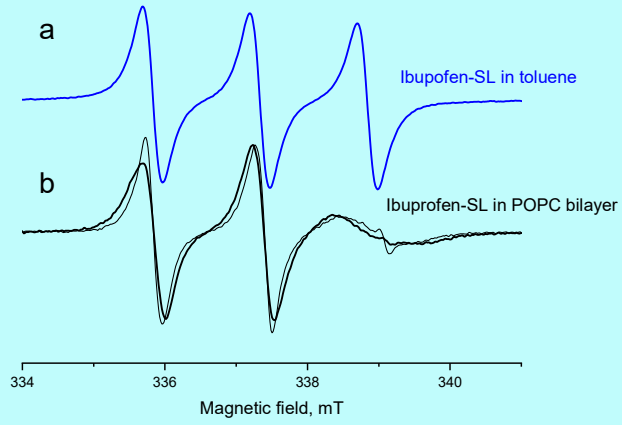


Figure 1. Room-temperature EPR spectra of ibuprofen-SL: for its 1 mM solution in toluene (**a**), and in presence of POPC bilayers (**b**). In the latter case, the samples were prepared either by mixing ibuprofen-SL and POPC prior to the bilayer's preparation (thick line), or by adding the solution of ibuprofen-SL in DMSO to the pure POPC bilayers (thin line).

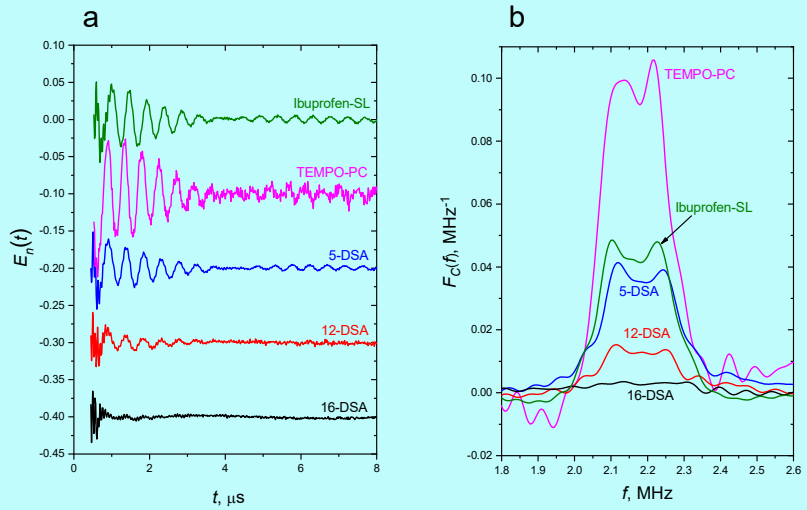


Figure 2. (**a**) ESEEM time traces for ibuprofen-SL in D_2O-hydrated POPC bilayer. For comparison, the analogous data for TEMPO-PC (adapted from under permission) and 5(12,16)-DSA are given. The data are vertically shifted for convenience. (**b**) Fourier transforms of the time domain data.

EPR data show that spin-labeled ibuprofen interacts with lipid membranes. The immersion depth into the membrane was found with pulsed EPR (^{2}H ESEEM spectroscopy) in D_2O-hydrated bilayers, the results indicate that spin label is buried into the membrane interior, which is in agreement with literature MD data on the immersion of the ibuprofen molecule.

Reference:
Baranov, D.S.; Smorygina, A.S.; Dzuba, S.A. Synthesis of Spin-Labeled Ibuprofen and Its Interaction with Lipid Membranes. *Molecules* **2022**, *27*, 4127. https:// doi.org/10.3390/molecules27134127

RSF Russian Science Foundation

The research was performed under the financial support of the Russian Science Foundation (grant no. 21-13-00025)