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Fliposomes: pH-controlled Release from Liposomes Containing New *trans*-2-Morpholinocyclohexanol-based Amphiphiles that Perform a Conformational Flip and Trigger an Instant Cargo Release upon Acidification

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Abstract - A new type of pH-sensitive liposome (fliposomes) was designed based on the amphiphiles that are able to perform a pH-triggered conformational flip (flipids). This flip disrupts the liposome membrane and causes rapid release of the liposome cargo, specifically in the areas of increased acidity. The flipids (**1-3**) are equipped with a *trans*-2-morpholinocyclohexanol conformational switch. pH-Sensitive fliposomes containing one of these flipids, POPC and PEG-ceramide (molar ratio 50/45/5) were constructed and characterized. These compositions were stable at 4°C and pH 7.4 for several months. Fliposomes loaded with ANTS/DPX demonstrated an unusually quick content release (in a few seconds) at pH below 5.5, which was more efficient in the case of flipid **1** with the shorter linear C₁₂-tails. The pH-titration curve for the fliposome leakage paralleled the curve for the acid-induced conformational flip of **1-3** studied by ¹H NMR. A plausible mechanism of the pH-sensitivity starts with an acid-triggered conformational flip of **1**, **2** or **3**, which changes the molecular size and shape, shortens the lipid tails, and perturbs the liposome membrane resulting in the content leakage.