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Mechanically Interlocked Profragrances for the Controlled Release of Scents

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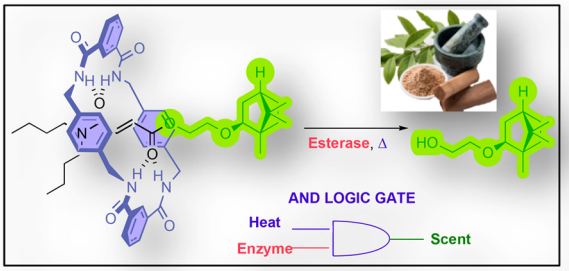
ABSTRACT: The synthesis of a series of interlocked profragrances and the study of the controlled release of the corresponding scents are reported. The structures of the profragrances are based on a [2]pseudorotaxane scaffold with a fumaramate thread derived from perfumery alcohols and a tetrabenzylamido ring. The delivery of the scents was accomplished by sequential thermal dethreading and further enzymatic hydrolysis. Alternatively, the dethreading can be achieved by increasing the polarity of the solvent or photochemical isomerization. The temperature of dethreading can be modulated by the steric demand of the ends of the thread, which allows the selection of different precursor structures depending on the desired rates of delivery. The inputs and outputs for the controlled release of the interlocked profragrances correspond to those of YES or AND logic gates.



INTRODUCTION

The pleasantness of the smell of many natural and synthetic scents is subtly integrated into our daily lives. Hence, natural and synthetic scents have found wide use in fine perfumery and body care and household products. These volatile compounds are characterized by their relatively low molecular weights, which allow for efficient evaporation.[1] However, the volatility of the scents constrains the longevity of the molecule's diffusion into air. The design of selective and efficient delivery systems to control the slow release of highly volatile odorants and to increase their stability has become a paramount endeavor in the fragrance industry.[2] Fragrances can be stabilized by entrapment in polymeric matrices or microcapsules.[3] Nevertheless, certain microcapsules present drawbacks such as low material stability or low perfume encapsulation capacity, especially for polar and hydrophilic perfumes with low molecular weights.[4−7] Profragrances, nonvolatile derivatives of scents, represent a valuable alternative because they can release the active compound through a suitable stimulus by selective cleavage of a covalent bond.[2,8,9]

The design of functional interlocked molecules programmed to perform specific tasks in response to an external stimulus has become a focus of today's nanoscience.[10,11] Stimulus-responsive rotaxanes are ideal candidates for achieving different functions such as switching properties, catalysis, or transport of cargo.[12,13] Biocompatible squaraine rotaxanes constitute effective imaging probes for medical applications.[14−17] Notably, Leigh et al. have developed an autonomous interlocked system capable of transporting an anticancer compound and launching its activity once placed inside the cancer cell.[18] More recently, Lewis and Vilar have designed a rotaxane-based delivery system that can act as a triggerable cage for G4 DNA binders.[19]

Despite a substantial amount of applications of interlocked molecules as stimulus-responsive systems, the uses of MIMs (mechanically interlocked molecules) in perfumery chemistry have been greatly neglected. Therefore, we envisioned that an interlocked structure might be suitable as a protective shield for selected perfumery alcohols and act as a novel and efficient delivery system to control the slow release. Thus, we designed scent delivery vectors based on the hydrogen-bonded [2]-rotaxanes *E*-**1** having a fumaramate thread and a benzylic amide macrocycle (Scheme 1).

Esterification of volatile alcohols **2a−f** (Chart 1) and further encapsulation into a polyamide ring would provide lower volatility and additional stability to the fragrance by mechanically interlocking encapsulation.[20−22] We envisaged two external inputs that would lead to the delivery of the scent: dethreading of the mechanically interlocked system and further enzymatic hydrolysis. The dethreading of rotaxanes *E*-**1** could be carried out by thermal and photochemical treatment, two

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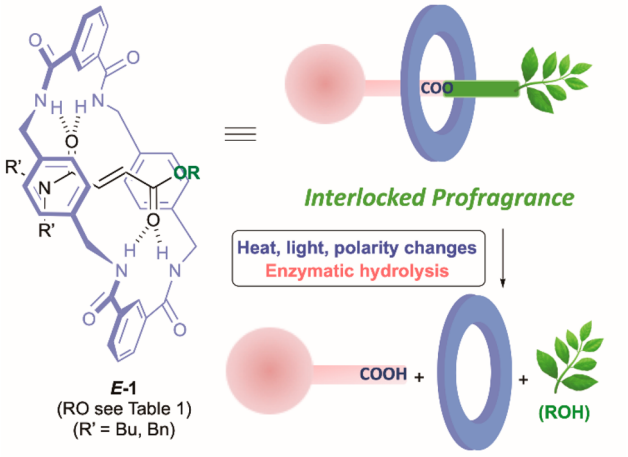
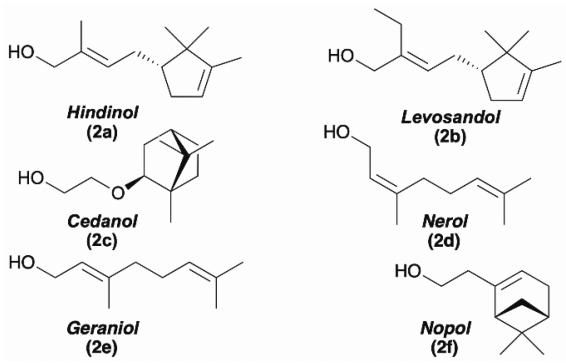
Scheme 1. Release of the Volatile Alcohol by Dethreading of *E*-1 and Further Hydrolysis of the Ester Functionality[a]



[a]ROH described in Chart 1.

Chart 1. Perfumery Alcohols Used in the Design of the Interlocked Profragrances *E*-1



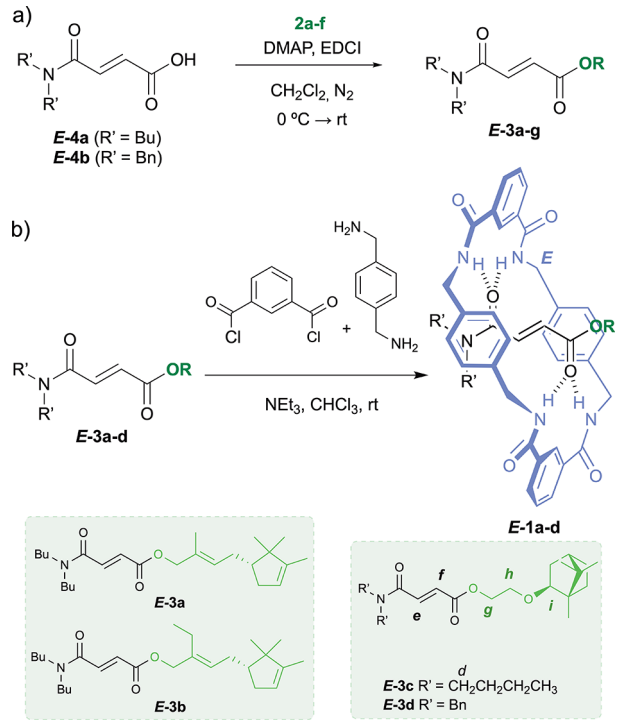
orthogonal methods of activation.[23] Likewise, changes in the polarity of the environment could also drive the deslipping of *E*-**1**.[24] Finally, enzymatic hydrolysis of the fumaramate ester would then release the volatile alcohol. Alternatively, hydrolytic treatment of rotaxanes *E*-**1** could remove its mechanical protection, furnishing the disassembly and direct delivery of the scent. Notably, the proximity of the macrocycle to the ester bond is expected to inhibit the enzyme activity when acting on the interlocked species, before its disassembly. Hence, entwined structures *E*-**1** would modulate the aroma volatilization responding to heat, light, polarity, or a chemical stimulus for the controlled delivery of the volatile alcohol-derived scents described in Chart 1.

Herein, we report the synthesis of the mechanically interlocked profragrances *E*-**1** (Scheme 1). The study of the controlled released of the corresponding volatile alcohol by sequential thermal or photochemical dethreading and further hydrolytic treatment shows that the delivery rate is dramatically affected by the structure of the scent, which acts as a kinetic barrier for the disassembly of the interlocked molecule. Additionally, we investigated if the input and output features of the mechanized profragrances *E*-**1** correspond to those of a logic gate.

RESULTS AND DISCUSSION

Synthesis of the Profragrance-Based [2]Rotaxanes *E*-1a−d. Threads *E*-**3a−g** were prepared by esterification of odorants **2a−f** (Chart 1) with the corresponding (*E*)-4-(dibutyl or dibenzylamino)-4-oxobut-2-enoic acids *E*-**4a** and *E*-**4b** in yields ranging from 43% to 85% (Scheme 2a). As

Scheme 2. Synthesis of (a) Threads *E*-3a−g from Carboxylic Acids *E*-4a and *E*-4b and (b) [2]Rotaxanes *E*-1a−d by Using the Clipping Methodology



expected, threads *E*-**3a−g** are odorless solid compounds. Polyamide-based [2]rotaxanes *E*-**1a−d** were obtained by a five-component clipping reaction with *p*-xylylenediamine and isophthaloyl chloride in the presence of Et_3N (Scheme 2b). The obtained yields (8−14%) are reasonable by considering the moderate templating ability of amido esters.[25] In all cases, the identity was confirmed by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and high-resolution mass spectrometry, whereas 2D NMR was used to further prove that the mechanically interlocked scents were formed (Supporting Information). We did not succeed in preparing [2]rotaxanes derived from threads *E*-**3e−g**, probably because the terpenoid backbone is not bulky enough for stabilizing the mechanical bond, thus allowing the deslipping of the ring from the potential mechanically interlocked species. Thermogravimetric analysis showed that profragrances *E*-**1a−d** are stable and retain their structural integrity at the solid state up to 200 °C (Supporting Information).

Next, dethreading experiments were carried out to evaluate the effect of temperature, solvent polarity, or UV light on the stability and release time of the thread out of the macrocycle (Scheme 3 and Table 1). At first glance, the steric size of the stoppers seems to be the key element controlling the deslipping process. Nevertheless, additional factors, both enthalpic and entropic in nature, need to be considered.[23] Changes in the temperature or polarity of the environment also

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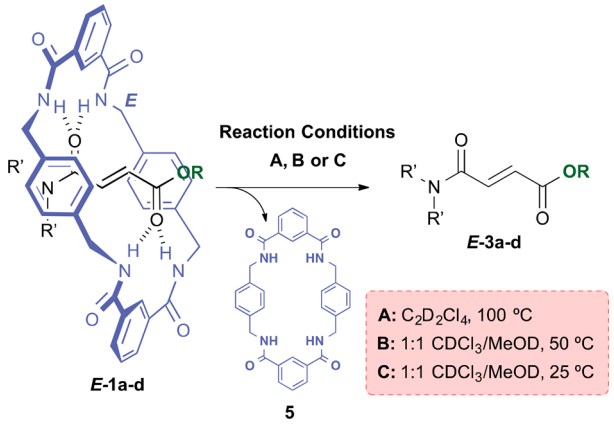
Scheme 3. Dethreading of [2]Rotaxanes *E*-1a–d under Three Different Reaction Conditions A–C[a]



[a]Identities of R and R′ listed in Table 1.

dramatically influence the stability and internal dynamics of the interlocked structures.[24,26,27] Dethreading processes of rotaxanes *E*-**1a–d** were studied under thermal conditions. Thus, we dissolved *E*-**1a–d** in $C_2D_2Cl_4$ and monitored the evolution of the deslipping at 100 °C by ^{1}H NMR spectroscopy (reaction conditions A in Scheme 3). Kinetic parameters for these transformations are included in Table 1 (entries 1–4).[28] The rates of dethreading for dibutylcarboxamides *E*-**1a–c** correlate to the bulkiness of the stopper coming from the scent moiety, that of *cedanol*-derived end (*E*-**1c**) being the most sterically demanding and, hence, featuring the longer half-life time (Table 1, entry 3).

Notably, the dethreading of dibenzylcarboxamide interlocked scent *E*-**1d**, with the bulkiest stoppers, did not take place under the tested reaction conditions. This observation apparently proves that the dethreading should take place by sliding the dibutylcarboxamide edge out of the macrocycle. The presence of polar solvent CD_3OD, with a keen avidity to hydrogen bonding, clearly interferes with the mechanical stability. Hence, the ring deslipping from pseudorotaxanes *E*-**1a** and *E*-**1b** could be expedited at 50 °C in a 1:1 $CDCl_3$/CD_3OD mixture to half-times of approximately 0.5 h (Table 1, entries 5 and 6). However, the dethreading of *E*-**1c** and that of *E*-**1d**, the latter with the most sterically demanding stoppers, were energetically unsurmountable under these conditions. Finally, the dethreading of *E*-**1a** and *E*-**1b** in a 1:1 $CDCl_3$/CD_3OD mixture at 25 °C is instantaneous with percentages of 10% and 9%, respectively (reaction conditions C in Scheme 3). Again, rotaxanes *E*-**1c** and *E*-**1d** do not experience dethreading in this medium.

Because ambient daylight is an omnipresent and green energy source, photorelease of scents constitutes a suitable mechanism for delivery control.[29,30] In particular, its orthogonality to other reaction conditions makes it a useful trigger for photoresponsive delivery systems. In fact, light irradiation is a highly harnessed stimulus for the control of molecular machinery.[31,32] For pseudorotaxanes *E*-**1a–c**, the *E*/*Z* isomerization of the fumaramate to a maleamate functionality would decrease the number of hydrogen bond interactions between the axle and macrocycle from four to two, thus facilitating the dethreading process (Scheme 4).

Rotaxane *E*-**1d** was excluded from this study because its more sterically demanding stoppers prevent the deslipping of the ring. Thus, we submitted rotaxanes *E*-**1a–c** to light irradiation (312 nm) in CH_2Cl_2 for a period of 90 min (Scheme 4). Rotaxanes *E*-**1a** and *E*-**1b**, derived from Hindinol (**2a**) and Levosandol (**2b**), respectively, disassembled *in situ*, leading to the corresponding maleamate threads *Z*-**3a** and *Z*-**3b**, respectively. However, we were capable of isolating rotaxane *Z*-**1c** with dibutylcarboxamido and Cedanol-derived ends. The thermal dethreading of *Z*-**1c** at 100 °C in $C_2D_2Cl_4$ was monitored by ^{1}H NMR (Supporting Information), affording a half-life of 7.7 h, which turned out to be approximately half of that for its *E*-**1c** isomer (Table 1, entry 10). The difference between the free energies of activation for the dethreading of *E*-**1c** and *Z*-**1c** amounts to 2.6 kJ mol^{-1}, a value that gives an approximate measurement of the difference in stability between both interlocked configurational isomers.[33,34] Finally, the shifts to lower frequencies of selected ^{1}H NMR resonances of the OR fragment in *Z*-**1c** with respect to those of *E*-**1c** support the movement of macrocycle **5** along the thread and the weaker interactions with the maleamate station (Figure 1, protons g–i; for lettering, see Scheme 2b). It is also worth noting that the macrocyclic methylene protons of *Z*-**1c** (Figure 1a, protons E) resonate as a broad singlet at 4.58

Table 1. Half-Life Times, Rate Constants, and Free Energies of Activation for the Dethreading of Rotaxanes *E*-1a–c and *Z*-1a–c under Different Conditions

entry	rotaxane	ROH	R′	solvent	*T* (°C)	$t_{1/2}$ (h)[a]	k (×10^5 s^{-1})[a]	$\Delta G^{\ddagger}$ (kJ mol^{-1})[b,c]
1	*E*-**1a**	Hindinol (**2a**)	Bu	$C_2D_2Cl_4$	100	2.0	9.7	120.7
2	*E*-**1b**	Levosandol (**2b**)	Bu	$C_2D_2Cl_4$	100	2.7	7.2	121.6
3	*E*-**1c**	Cedanol (**2c**)	Bu	$C_2D_2Cl_4$	100	17.5	1.1	127.5
4	*E*-**1d**	Cedanol (**2c**)	Bn	$C_2D_2Cl_4$	100	–[d]	–[d]	–[d]
5	*E*-**1a**	Hindinol (**2a**)	Bu	1:1 $CDCl_3$/MeOD	50	0.4	47.0	99.9
6	*E*-**1b**	Levosandol (**2b**)	Bu	1:1 $CDCl_3$/MeOD	50	0.6	30.8	101.0
7	*E*-**1c**	Cedanol (**2c**)	Bu	1:1 $CDCl_3$/MeOD	50	–[d]	–[d]	–[d]
8	*Z*-**1a**	Hindinol (**2a**)	Bu	CH_2Cl_2	25	–[e]	–[e]	–[e]
9	*Z*-**1b**	Levosandol (**2b**)	Bu	CH_2Cl_2	25	–[e]	–[e]	–[e]
10	*Z*-**1c**	Cedanol (**2c**)	Bu	$C_2D_2Cl_4$	100	7.7	2.5	124.9

[a]Dethreading monitored by ^{1}H NMR spectroscopy as a function of time and concentration of rotaxane and thread calculated from direct integration (Supporting Information). [b]Obtained from the Eyring equation. [c]Gibbs free energy of activation calculated at 100 or 50 °C (see *T*). [d]The rotaxane is stable at this temperature, and no dethreading was observed. [e]The dethreading takes places immediately after the photoisomerization; therefore, the corresponding *Z*-isomerized rotaxane could not be isolated, nor could the rate constant of dethreading be measured (see Scheme 4).

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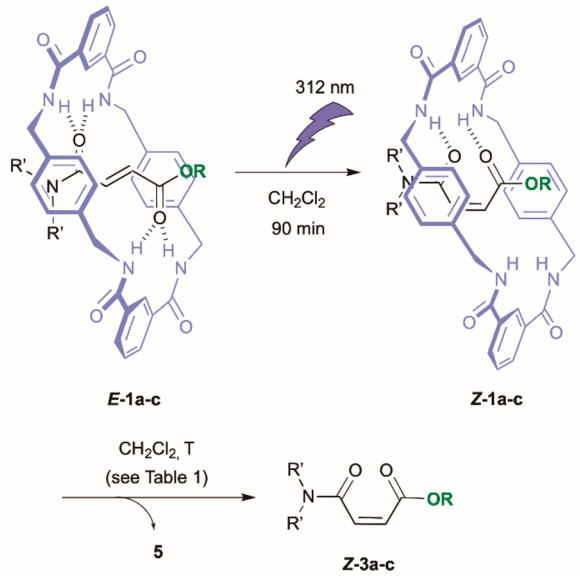
Scheme 4. Photoisomerization of [2]Rotaxanes *E*-1a−c under UV Light and Further Dethreading of the Resulting [2]Rotaxanes *Z*-1a−c[a]



[a]Identities of R and R′ listed in Table 1.

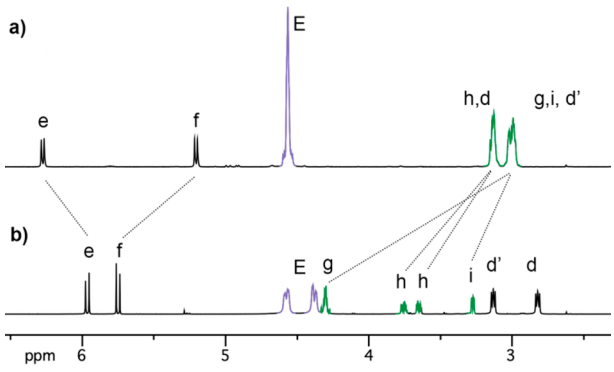


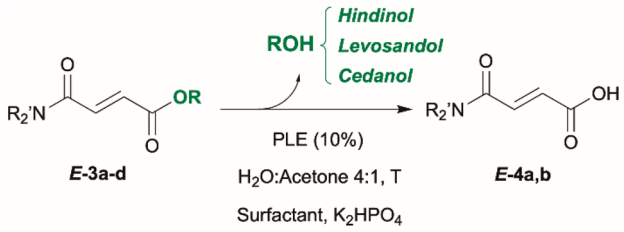
Figure 1. Selected region of the ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) spectra of (a) *Z*-**1c** and (b) *E*-**1c**. Lettering in Scheme 2b.

ppm while the corresponding signals of *E*-**1c** (Figure 1b) are non-equivalent (4.58 and 4.38 ppm) as a result of the different magnetic environments ascribed to its axial and equatorial positions of the macrocycle adopting a symmetrical chairlike conformation. This difference is associated with the rotational motion of the ring of single-binding site amide-based [2]rotaxanes,[34] which happens at a higher speed in interlocked profragrance *Z*-**1c** than in its isomer, *E*-**1c**.

Lipases represent an important class of enzymes that are found in human skin, allowing the bond cleavage of an ester functionality under neutral and mild conditions.[2] In a first proof of concept, we tested the release of scent from non-interlocked profragrances *E*-**3a−d** through enzymatic hydrolysis by using *Candida rugosa* and *Candida antarctica* lipases (not shown). Because no conversion was observed in any case, the hydrolysis of *E*-**3a−d** was conducted by employing pig liver esterase (PLE) in a 4:1 water/acetone mixture, solvents compatible with perfumery applications[35] (Scheme 5 and Table 2).

Additionally, potassium dihydrogen phosphate and Arquad were added as the buffer and surfactant, respectively.

Scheme 5. Hydrolysis of Profragrances *E*-3a−d in the Presence of PLE[a]



[a]Temperature and reaction times listed in Table 2.

Surfactants are included in most perfumery aqueous formulations to solubilize hydrophobic compounds.[36−38] At selected reaction times, an aliquot was taken from the reaction mixture and $CHCl_3$ was added. The organic phase was washed with aqueous HCl and brine, and the solvent removed under reduced pressure. Conversion of *E*-**3a−d** into *E*-**4a** and *E*-**4b** was determined by ^{1}H NMR spectroscopy from the crude product by integration of the olefinic protons (Table 2). Control experiments for the lack of an enzyme, a surfactant, or a base demonstrated that the presence of both the enzyme and the base is mandatory for the reaction to take place (Supporting Information).

The hydrolysis of *E*-**3a−d** worked smoothly with conversions of 20−33% at 25 °C after 24 h (Table 2, entries 1, 4, 7, and 10, respectively). As the temperature increased to 40 °C, conversions increased to 46−72% (Table 2, entries 2, 5, 8, and 11, respectively). Apparently, complete conversions were obtained at 60 °C and shorter times (Table 2, entries 3, 6, 9, and 12, respectively). Curiously, the hydrolysis of threads *Z*-**3a−c** under the same conditions was much slower than that of their *E* isomers at 20, 40, or 60 °C (Table 2). On the contrary, the delivery of the scents was also slower from rotaxanes *E*-**1a−d** (Scheme 6 and Table 2). Thus, the enzymatic hydrolysis of *E*-**1a** and *E*-**1b** derived from Hindinol and Levosandol needed 48 h to achieve <50% conversion (Table 2, entries 1 and 4, respectively). At this time, ^{1}H NMR spectra showed resonances that could be assigned to fumaramic acid *E*-**4a** and free axle *E*-**3** as the only reaction products.

The lack of rotaxane *E*-**1** in the reaction mixture indicates that the ester hydrolysis takes place after the dethreading event. This fact brings to light the mechanical protecting role of the macrocycle in profragrances *E*-**1a−d**. This hypothesis agrees well with the fact that the bulkiness of the stopping terpenoid decisively influences the rate of formation of hydrolytic product *E*-**4** and, by extension, the delivery of the scent. According to this assumption, the hydrolysis of the ester functionality in rotaxanes *E*-**1c** and *E*-**1d**, derived from the more sterically demanding Cedanol, is slower than that of *E*-**1a** and *E*-**1b**. Thus, the delivery of Cedanol from *E*-**1c** needs 32 days (768 h) at 25 °C to achieve 54% conversion (Table 2, entry 7). No hydrolysis was observed for rotaxane *E*-**1d** with a dibenzylcarboxamide stopper after 7 days at this temperature or 40 °C (Table 2, entries 10 and 11). The hydrolysis could be boosted by increasing the temperature to 60 °C. At this temperature, conversions of 70% and 95% were observed for rotaxanes *E*-**1c** and *E*-**1d**, respectively, although with reaction times ranging from 8 h to 7 days (168 h) (Table 2, entries 9 and 12, respectively). Direct hydrolysis without previous dethreading cannot be discarded for *E*-**1d**.

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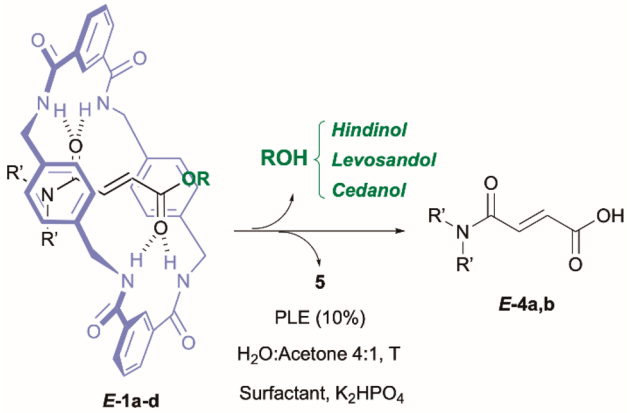
Table 2. Hydrolytic Release of Scents from Threads *E*-3a−d and *Z*-3a−c and Rotaxanes *E*-1a−d in the Presence of PLE,[a] Arquad,[b] and K_2HPO_4[c] at 25, 40, and 60 °C and Reaction Times and Conversions

entry	ROH	R′	*T* (°C)	*E*-3 *t* (h)	*E*-3 (% conversion)[d,e]	*Z*-3 *t* (h)	*Z*-3 (% conversion)[d,e]	*E*-1 *t* (h)	*E*-1 (% conversion)[e]
1	Hindinol (**2a**)	Bu	25	24	33	24	5	48	50[d,f]
2	Hindinol (**2a**)	Bu	40	24	51	24	13	–	–
3	Hindinol (**2a**)	Bu	60	16	>95	24	42	–	–
4	Levosandol (**2b**)	Bu	25	24	20	24	5	48	23[d,f]
5	Levosandol (**2b**)	Bu	40	24	46	24	8	–	–
6	Levosandol (**2b**)	Bu	60	16	87	24	33	–	–
7	Cedanol (**2c**)	Bu	25	24	22	24	5	768	54[g]
8	Cedanol (**2c**)	Bu	40	24	56	24	16	48	45[g]
9	Cedanol (**2c**)	Bu	60	16	>95	24	50	8	95[d,f]
10	Cedanol (**2c**)	Bn	25	24	31[h]	–	–	168	0[i]
11	Cedanol (**2c**)	Bn	40	24	72[h]	–	–	168	0[i]
12	Cedanol (**2c**)	Bn	60	24	>95	–	–	168	70[h,i]

[a]Ten percent with respect to the substrate. [b]Ten percent in water. [c]At 50 mM. [d]Determined by ^{1}H NMR from the crude product by integration of the olefinic protons (error of 5%). [e]An aliquot was taken from the reaction mixture, and $CHCl_3$ (5 mL) was added. The organic phase was washed with 1 M HCl and brine, and the solvent removed under reduced pressure. [f]Fumaramic acid *E*-**4** and free axle *E*-**3** were the only reaction products. No rotaxane was observed. [g]Fumaramic acid *E*-**4**, free axle *E*-**3**, and free macrocycle **5** were the only reaction products. The conversion was determined from the integration of the olefinic signals of axle and fumaramic acid *E*-**4**. [h]Determined by ^{1}H NMR from the crude product by integration of the benzylic protons. [i]Resonances corresponding to axle *E*-**3d** were not observed.

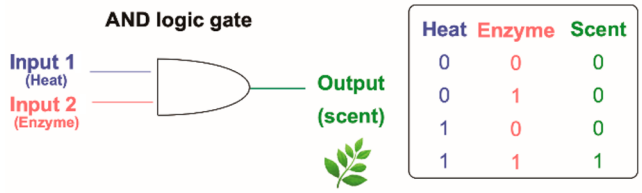
Scheme 6. Hydrolysis of Profragrances *E*-1a−d in the Presence of PLE[a]



[a]Temperature and reaction times listed in Table 2.

Controlled delivery of fragrance molecules is the fulcrum of digital scent technology, which may add another dimension to electronics. Molecular logic gates are molecules that perform logical operations based on chemical or physical inputs and produce a defined output.[39−41] Since the first molecular gate was synthesized by de Silva and co-workers,[42] a variety of molecular systems capable of realizing Boolean logic gates have been designed, some of them employing stimulus-responsive rotaxanes.[43−46] A set of ion-driven molecular logic gates have been already implemented in detergent micelles by arranging the association between available lumophores and receptors.[47] A YES single-input gate is one of the simplest logic devices, passing the input bits to the output without changes. From this point of view, rotaxanes *E*-**1a** and *E*-**1b** working with PLE at room temperature could be considered as YES gates, the input being the enzymatic hydrolysis and the output being the release of Hindinol, Levosandol, or Cedanol. When the number of inputs increases from 1 to 2, more complex logic gates emerge. For instance, an AND gate gives an output of 1 only if both inputs are held at 1 each. Considering both heat and the enzyme as inputs, rotaxanes *E*-**1c** and *E*-**1d** could be considered as an AND gate working at 60 °C, because the release of Cedanol (output) takes place only when both stimuli are present. The truth table featured by rotaxanes *E*-**1c** and *E*-**1d** is represented in Scheme 7.

Scheme 7. Physical Electronic Symbols of the Two-Input AND Logic Gate and Truth Table Featuring Interlocked Profragrances *E*-1c and *E*-1d



CONCLUSIONS

The controlled delivery of sandalwood scents Hindinol, Levosandol, and Cedanol can be achieved by means of interlocked profragrances based on a [2]pseudorotaxane structure with a tetrabenzylamido macrocycle and a fumaramate thread derived from the perfumery alcohols. The macrocycle provides extra stability to the scent, an important factor to be considered during storage. The release of the scents can be conducted by sequential dethreading and further enzymatic hydrolysis by employing PLE. The temperature of dethreading is dependent on the steric demand of the ends of the thread (dibutyl or dibenzylcarboxamido), a fact that would allow the selection of different precursor structures depending on the desired rates of delivery. Alternatively, the dethreading can also be achieved by increasing the polarity of the solvent or by photochemical isomerization. The inputs and output for the controlled release of the scents featured by the synthesized interlocked profragrances correspond to those of YES or AND logic gates.

The significance of a new field always depends on how it is useful for real life applications. On the basis of the results of this proof of concept, this novel category of a smart scent

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dispenser paves the way for the development of interlocked profragrances as suitable delivery systems of volatile scents.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification. HPLC grade solvents were nitrogen-saturated, dried, and deoxygenated using an Innovative Technology Inc. Pure-Solv 400 Solvent Purification System. Column chromatography was carried out using silica gel (60 Å, 70−200 μm, SDS) as the stationary phase, and TLC was performed on precoated silica gel on aluminum cards (0.25 mm thick, with a fluorescent indicator at 254 nm) and observed under UV light. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Bruker Avance 300, 400, and 600 MHz instruments. ^{1}H NMR chemical shifts are reported relative to Me_4Si and were referenced via residual proton resonances of the corresponding deuterated solvent, whereas ^{13}C{^{1}H} NMR spectra are reported relative to Me_4Si using the carbon signals of the deuterated solvent. Signals in the ^{1}H and ^{13}C{^{1}H} NMR spectra of the synthesized compounds were assigned with the aid of DEPT-135 and two-dimensional NMR experiments (COSY, HMQC, and HMBC). Abbreviations of coupling patterns are as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Coupling constants (J) are expressed in hertz. High-resolution mass spectra (HRMS) were recorded on a HPLC/MS TOF 6220 mass spectrometer. TGA analyses were conducted in a SDT 2960 TA Instruments instrument by heating at a rate of 10 °C/min up to 600 °C under a nitrogen gas atmosphere (120 mL/min). Takasago Int. Chemicals Europe in Murcia provided the scents depicted in Chart 1: Hindinol $[\alpha]_D^{25}$ +1.6° (c 0.0013, $CHCl_3$), Levosandol $[\alpha]_D^{25}$ −0.5° (c 0.0012, $CHCl_3$), Cedanol $[\alpha]_D^{25}$ +1.2° (c 0.0010, $CHCl_3$), and Nopol $[\alpha]_D^{25}$ −43.3° (c 0.0016, $CHCl_3$).[48] The synthesis of carboxylic acids *E*-**4a** and *E*-**4b** was conducted following previously reported procedures.[49]

General Procedure for the Synthesis of Threads *E*-3a−g. To a solution of the corresponding fragrance (1.0 equiv) in anhydrous CH_2Cl_2 (40 mL) under a N_2 atmosphere were added carboxylic acid *E*-**4a** or *E*-**4b** (1.2 equiv) and DMAP (0.2 equiv) at 0 °C. After the mixture had been stirred for 10 min, EDCI (1.1 equiv) was added. The reaction mixture was stirred at room temperature overnight. After this time, the reaction mixture was subsequently washed with water (2 × 50 mL), 1 M HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel, to give the corresponding thread.

Thread *E*-3a. Thread *E*-**3a** was prepared following the described procedure from Hindinol (427 mg, 2.2 mmol) and carboxylic acid *E*-**4a** (549 mg, 2.42 mmol). The resulting residue was purified by silica gel chromatography eluting with hexanes/AcOEt (100:0 to 80:20). The solvent was removed under reduced pressure to give the title product as a yellow oil (599 mg, 68%): $[\alpha]_D^{25}$ −6.6° (c 0.0129, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.36 (d, J = 15.2 Hz, 1H), 6.83 (d, J = 15.2 Hz, 1H), 5.53 (tq, J = 7.2, 1.2 Hz, 1H), 5.21−5.20 (m, 1H), 4.58 (s, 2H), 3.40−3.37 (m, 2H), 3.33−3.31 (m, 2H), 2.28−2.21 (m, 1H), 2.20−2.15 (m, 1H), 2.04−1.98 (m, 1H), 1.84−1.76 (m, 2H), 1.68 (s, 3H), 1.60−1.59 (m, 3H), 1.57−1.51 (m, 4H), 1.35−1.29 (m, 4H), 0.98 (s, 3H), 0.95−0.91 (m, 6H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 165.9 (C), 164.2 (C), 148.6 (C), 134.3 (CH), 131.0 (CH), 130.1 (CH), 129.6 (C), 121.7 (CH), 71.0 (CH_2), 50.2 (CH), 48.1 (CH_2), 46.8 (C), 46.5 (CH_2), 35.6 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 25.9 (CH_3), 20.3 (CH_2), 20.0 (CH_2), 19.8 (CH_3), 14.1 (CH_3), 13.9 (CH_3), 13.8 (CH_3), 12.7 (CH_3); HRMS (ESI) calcd for $C_{25}H_{42}NO_3$ $[M + H]^+$ 404.3165, found 404.3149.

Thread *E*-3b. Thread *E*-**3b** was prepared following the described procedure from Levosandol (420 mg, 2 mmol) and carboxylic acid *E*-**4a** (549 mg, 2.4 mmol). The resulting residue was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (100:0 to 80:20). The solvent was removed under reduced pressure to give the title product as a yellow oil (661 mg, 79%): $[\alpha]_D^{25}$ −4.9° (c 0.0131, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.36 (d, J = 15.2 Hz, 1H), 6.83 (d, J = 15.2 Hz, 1H), 5.50 (t, J = 7.2 Hz, 1H), 5.22−5.21 (m, 1H), 4.65−4.60 (m, 2H), 3.40−3.37 (m, 2H), 3.33−3.31 (m, 2H), 2.28−2.22 (m, 1H), 2.21−2.17 (m, 1H), 2.13 (q, J = 7.6 Hz, 2H), 2.04−1.99 (m, 1H), 1.85−1.75 (m, 2H), 1.59−1.60 (m, 3H), 1.59−1.52 (m, 4H), 1.35−1.29 (m, 4H), 1.01 (t, J = 7.6 Hz, 3H), 0.99 (s, 3H), 0.95−0.91 (m, 6H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 165.9 (C), 164.2 (C), 148.6 (C), 135.4 (C), 134.3 (CH), 131.1 (CH), 130.2 (CH), 121.7 (CH), 69.2 (CH_2), 50.4 (CH), 48.2 (CH_2), 46.9 (C), 46.6 (CH_2), 35.6 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 28.1 (CH_2), 25.9 (CH_3), 21.5 (CH_2), 20.3 (CH_2), 20.1 (CH_2), 19.8 (CH_3), 13.9 (CH_3), 13.8 (CH_3), 13.0 (CH_3), 12.7 (CH_3); HRMS (ESI) calcd for $C_{26}H_{44}NO_3$ $[M + H]^+$ 418.3321, found 418.3302.

Thread *E*-3c. Thread *E*-**3c** was prepared following the described procedure from Cedanol (463 mg, 2.3 mmol) and carboxylic acid *E*-**4a** (549 mg, 2.42 mmol). The resulting residue was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (100:0 to 80:20). The solvent was removed under reduced pressure to give the title product as a yellow oil (755 mg, 81%): $[\alpha]_D^{25}$ +2.4° (c 0.0155, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.35 (d, J = 15.3 Hz, 1H), 6.81 (d, J = 15.2 Hz, 1H), 4.31−4.25 (m, 2H), 3.64 (ddd, J = 10.8, 6.3, 4.3 Hz, 1H), 3.53 (ddd, J = 11.0, 5.5, 4.0 Hz, 1H), 3.40−3.37 (m, 2H), 3.33−3.31 (m, 2H), 3.21 (dd, J = 7.6, 3.5 Hz, 1H), 1.75−1.71 (m, 1H), 1.68−1.62 (m, 2H), 1.59−1.51 (m, 5H), 1.50−1.46 (m, 1H), 1.35−1.29 (m, 4H), 0.98−0.92 (m, 11H), 0.86 (s, 3H), 0.78 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 165.9 (C), 164.2 (C), 134.3 (CH), 130.9 (CH), 87.6 (CH), 66.9 (CH_2), 64.5 (CH_2), 49.3 (C), 48.1 (CH_2), 46.6 (CH_2), 46.5 (C), 45.1 (CH), 38.6 (CH_2), 34.5 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 27.4 (CH_2), 20.34 (CH_2), 20.30 (CH_3), 20.2 (CH_3), 20.0 (CH_2), 13.9 (CH_3), 13.8 (CH_3), 11.9 (CH_3); HRMS (ESI) calcd for $C_{24}H_{42}NO_4$ $[M + H]^+$ 408.3114, found 408.3103.

Thread *E*-3d. Thread *E*-**3d** was prepared following the described procedure from Cedanol (303 mg, 1.53 mmol) and carboxylic acid *E*-**4b** (500 mg, 1.69 mmol). The resulting residue was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (100:0 to 80:20). The solvent was removed under reduced pressure to give the title product as a yellow oil (311 mg, 43%): $[\alpha]_D^{25}$ −3.1° (c 0.0113, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 7.45 (d, J = 15.3 Hz, 1H), 7.39−7.28 (m, 6H), 7.25−7.23 (m, 2H), 7.17−7.14 (m, 2H), 6.97 (d, J = 15.3 Hz, 1H), 4.64 (s, 2H), 4.52 (s, 2H), 4.25−4.28 (m, 2H), 3.62 (ddd, J = 11.0, 5.8, 4.3 Hz, 1H), 3.51 (ddd, J = 11.0, 5.2, 4.2 Hz, 1H), 3.19 (dd, J = 7.6, 3.4 Hz, 1H), 1.72−1.61 (m, 3H), 1.58−1.52 (m, 1H), 1.51−1.43 (m, 1H), 0.99−0.91 (m, 2H), 0.90 (s, 3H), 0.83 (s, 3H), 0.77 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 165.6 (C), 165.4 (C), 136.7 (C), 135.9 (C), 133.9 (CH), 132.3 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 87.6 (CH), 66.9 (CH_2), 64.6 (CH_2), 50.2 (CH_2), 49.3 (C), 48.5 (CH_2), 46.5 (C), 45.1 (CH), 38.6 (CH_2), 34.4 (CH_2), 27.4 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 11.8 (CH_3); HRMS (ESI) calcd for $C_{30}H_{38}NO_4$ $[M + H]^+$ 476.2801, found 476.2788.

Thread *E*-3e. Thread *E*-**3e** was prepared following the general procedure from Nerol (308 mg, 2 mmol) and carboxylic acid *E*-**4a** (500 mg, 2.2 mmol). The crude product was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (99:1 to 96:4). The solvent was removed under reduced pressure to give the title product as a yellow oil (499 mg, 69%): $[\alpha]_D^{25}$ −1.6° (c 0.0117, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 7.35 (d, J = 15.2 Hz, 1H), 6.80 (d, J = 15.2 Hz, 1H), 5.38 (tm, J = 7.2 Hz, 1H), 5.10−5.06 (m, 1H), 4.67 (dd, J = 7.3, 0.8 Hz, 2H), 3.39−3.30 (m, 4H), 2.15−2.07 (m, 4H), 1.76 (m, 3H), 1.67 (m, 3H), 1.59 (s, 3H), 1.57−1.49 (m, 4H), 1.36−1.27 (m, 4H), 0.95−0.90 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 166.0 (C), 164.2 (C), 143.1 (C), 134.2 (CH), 132.3 (C), 131.1 (CH), 123.5 (CH), 118.8 (CH), 61.8 (CH_2), 48.1 (CH_2), 46.5 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 26.7

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(CH_2), 25.8 (CH_3), 23.6 (CH_3), 20.3 (CH_2), 20.0 (CH_2), 17.7 (CH_3), 13.9 (CH_3), 13.8 (CH_3); HRMS (ESI) calcd for $C_{22}H_{38}NO_3$ $[M + H]^+$ 364.2852, found 364.2842.

Thread *E*-3f. Thread *E*-**3f** was prepared following the previously described procedure from Geraniol (308 mg, 2 mmol) and carboxylic acid *E*-**4a** (500 mg, 2.2 mmol). The resulting residue was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (100:0 to 90:10). The solvent was removed under reduced pressure to give the title product as a yellow oil (601 mg, 83%): $[\alpha]_D^{25}$ +0.5° (*c* 0.0149, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 7.36 (d, *J* = 15.2 Hz, 1H), 6.81 (d, *J* = 15.2 Hz, 1H), 5.37 (tm, *J* = 7.1 Hz, 1H), 5.10−5.06 (m, 1H), 4.71 (d, *J* = 7.1 Hz, 2H), 3.41−3.31 (m, 4H), 2.13−2.03 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.59−1.51 (m, 4H), 1.38−1.28 (m, 4H), 0.97−0.91 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 166.1 (C), 164.3 (C), 142.9 (C), 134.3 (CH), 132.0 (C), 131.1 (CH), 123.8 (CH), 118.0 (CH), 62.1 (CH_2), 48.1 (CH_2), 46.5 (CH_2), 39.6 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 26.4 (CH_2), 25.8 (CH_3), 20.4 (CH_2), 20.1 (CH_2), 17.8 (CH_3), 16.6 (CH_3), 13.9 (CH_3), 13.8 (CH_3); HRMS (ESI) calcd for $C_{22}H_{38}NO_3$ $[M + H]^+$ 364.2852, found 364.2843.

Thread *E*-3g. Thread *E*-**3g** was prepared following the described procedure from Nopol (333 mg, 2 mmol) and carboxylic acid *E*-**4a** (500 mg, 2.2 mmol). The resulting residue was purified by column chromatography (silica gel) eluting with hexanes/AcOEt (5:1 to 3:1). The solvent was removed under reduced pressure to give the title product as a yellow oil (639 mg, 85%): $[\alpha]_D^{25}$ −20.3° (*c* 0.0155, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 7.33 (d, *J* = 15.2 Hz, 1H), 6.79 (d, *J* = 15.2 Hz, 1H), 5.30−5.29 (m, 1H), 4.24−4.13 (m, 2H), 3.40−3.29 (m, 4H), 2.38−2.30 (m, 3H), 2.27−2.15 (m, 2H), 2.07−2.03 (m, 2H), 1.59−1.50 (m, 4H), 1.36−1.29 (m, 4H), 1.26 (s, 3H), 1.13 (d, *J* = 8.6 Hz, 1H), 0.95−0.90 (m, 6H), 0.80 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 165.9 (C), 164.2 (C), 144.0 (C), 134.1 (CH), 131.1 (CH), 119.1 (CH), 63.3 (CH_2), 48.1 (CH_2), 46.6 (CH_2), 45.6 (CH), 40.7 (CH), 38.1 (C), 35.9 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 26.3 (CH_3), 21.2 (CH_3), 20.3 (CH_2), 20.0 (CH_2), 13.9 (CH_3), 13.8 (CH_3); HRMS (ESI) calcd for $C_{23}H_{38}NO_3$ $[M + H]^+$ 376.2852, found 376.2838.

General Procedure for the Preparation of [2]Rotaxanes *E*-1a−d. A solution of the thread (1 equiv) and Et_3N (12 equiv) in $CHCl_3$ (400 mL) was stirred vigorously, while two solutions of (i) *p*-xylylene diamine (8 equiv) and Et_3N (12 equiv) in $CHCl_3$ (20 mL) and (ii) isophthaloyl chloride (8 equiv) in $CHCl_3$ (20 mL) were simultaneously added over a period of 4 h using a motor-driven syringe pump. After being stirred at room temperature for 4 h, the resulting suspension was filtered through a Celite pad and subsequently washed with water (400 mL), an aqueous solution of 1 M HCl (2 × 300 mL), a saturated solution of $NaHCO_3$ (2 × 300 mL), and brine (200 mL). The organic phase was dried over $MgSO_4$, and the solvent removed under reduced pressure. The resulting solid was purified by column chromatography (silica gel) to yield unconsumed thread and [2]rotaxane.

Rotaxane *E*-1a. Rotaxane *E*-**1a** was obtained from thread *E*-**3a** (460 mg, 1.14 mmol) by using the general procedure described above. The crude product was purified by column chromatography on silica gel eluting with 7:3 $CHCl_3$/AcOEt to give the title product as a white solid (149 mg, 14%): mp 99−101 °C; $[\alpha]_D^{25}$ −1.5° (*c* 0.0103, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 8.53 (s, 2H), 8.29 (dd, *J* = 7.8, 1.6 Hz, 4H), 7.66 (t, *J* = 7.8 Hz, 2H), 7.40 (s, 4H), 7.04 (s, 8H), 5.97 (d, *J* = 14.9 Hz, 1H), 5.71 (d, *J* = 14.9 Hz, 1H), 5.66 (tm, *J* = 7.2 Hz, 1H), 5.20−5.19 (m, 1H), 4.68−4.52 (m, 6H), 4.35 (s, 4H), 3.11−3.09 (m, 2H), 2.84−2.81 (m, 2H), 2.26−2.21 (m, 2H), 2.09−2.05 (m, 1H), 1.85−1.77 (m, 5H), 1.59−1.58 (m, 3H), 1.40−1.35 (m, 2H), 1.12−1.06 (m, 4H), 0.98 (s, 3H), 0.80−0.78 (m, 6H), 0.57−0.54 (m, 3H), 0.52−0.47 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 168.7 (C), 165.8 (C), 163.5 (C), 148.6 (C), 137.6 (C), 133.4 (C), 132.9 (CH), 132.1 (CH), 129.8 (CH), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.5 (C), 122.8 (CH), 121.5 (CH), 73.0 (CH_2), 50.1 (CH), 48.9 (CH_2), 47.9 (CH_2), 46.8 (C), 43.8 (CH_2), 35.6 (CH_2), 32.3 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 25.9 (CH_3), 20.1 (CH_2), 19.8 (CH_3), 19.7 (CH_2), 14.6 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 12.8 (CH_3); HRMS (ESI) calcd for $C_{57}H_{70}N_5O_7$ $[M + H]^+$ 936.5275, found 936.5279.

Rotaxane *E*-1b. Rotaxane *E*-**1b** was obtained from thread *E*-**3b** (661 mg, 1.57 mmol) by using the general procedure described above. The solid crude was purified by column chromatography on silica gel by eluting with 7:3 $CHCl_3$/AcOEt to give the title product as a white solid (185 mg, 12%): mp 71−73 °C; $[\alpha]_D^{25}$ −9.7° (*c* 0.0099, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 8.53 (s, 2H), 8.30 (dd, *J* = 7.8, 1.6 Hz, 4H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 4.6 Hz, 4H), 7.04 (s, 8H), 5.98 (d, *J* = 15.0 Hz, 1H), 5.72 (d, *J* = 15.0 Hz, 1H), 5.62 (t, *J* = 7.2 Hz, 1H), 5.21−5.19 (m, 1H), 4.69 (s, 2H), 4.65−4.55 (m, 4H), 4.38 (d, *J* = 11.8 Hz, 4H), 3.15−3.13 (m, 2H), 2.85−2.83 (m, 2H), 2.28−2.20 (m, 4H), 2.09−2.05 (m, 1H), 1.86−1.76 (m, 2H), 1.60 (dt, *J* = 2.5, 1.3 Hz, 3H), 1.44−1.39 (m, 2H), 1.15−1.10 (m, 4H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.99 (s, 3H), 0.83−0.80 (m, 6H), 0.59−0.51 (m, 5H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 168.7 (C), 165.8 (C), 163.7 (C), 148.6 (C), 137.8 (C), 134.5 (C), 133.6 (C), 132.8 (CH), 132.2 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH), 122.8 (CH), 121.5 (CH), 70.7 (CH_2), 50.3 (CH), 49.0 (CH_2), 47.9 (CH_2), 46.9 (C), 43.8 (CH_2), 35.7 (CH_2), 32.3 (CH_2), 29.9 (CH_2), 28.3 (CH_2), 25.9 (CH_3), 21.5 (CH_2), 20.2 (CH_2), 19.8 (CH_3), 19.7 (CH_2), 13.7 (CH_3), 13.6 (CH_3), 13.0 (CH_3), 12.7 (CH_3); HRMS (ESI) calcd for $C_{58}H_{72}N_5O_7$ $[M + H]^+$ 950.5432, found 950.5428.

Rotaxane *E*-1c. Rotaxane *E*-**1c** was obtained from thread *E*-**3c** (599 mg, 1.48 mmol) by using the general procedure described above. The solid crude was purified by column chromatography on silica gel eluting with $CHCl_3$/acetone (9:1 to 7:3) to give the title product as a white solid (150 mg, 11%): mp 184−186 °C; $[\alpha]_D^{25}$ −3.1° (*c* 0.0132, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 8.51 (s, 2H), 8.30 (dd, *J* = 7.8, 1.5 Hz, 4H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.35 (s, 4H), 7.05 (s, 8H), 5.96 (d, *J* = 15.0 Hz, 1H), 5.75 (d, *J* = 15.0 Hz, 1H), 4.58 (dd, *J* = 13.7, 4.7 Hz, 4H), 4.38 (dd, *J* = 14.0, 4.0 Hz, 4H), 4.33−4.27 (m, 2H), 3.76 (ddd, *J* = 11.3, 5.9, 3.6 Hz, 1H), 3.65 (ddd, *J* = 11.3, 5.7, 3.6 Hz, 1H), 3.28 (dd, *J* = 7.7, 3.5 Hz, 1H), 3.14−3.12 (m, 2H), 2.84−2.81 (m, 2H), 1.78−1.74 (m, 1H), 1.66−1.60 (m, 3H), 1.50−1.46 (m, 1H), 1.43−1.38 (m, 2H), 1.15−1.08 (m, 4H), 0.97−0.94 (m, 5H), 0.89 (s, 3H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.76 (s, 3H), 0.57−0.50 (m, 5H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 169.0 (C), 165.7 (C), 163.7 (C), 137.8 (C), 133.6 (C), 132.1 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 129.0 (CH), 122.7 (CH), 88.2 (CH), 66.7 (CH_2), 66.4 (CH_2), 49.5 (C), 48.9 (CH_2), 47.9 (CH_2), 46.6 (C), 45.0 (CH), 43.8 (CH_2), 38.5 (CH_2), 34.5 (CH_2), 32.2 (CH_2), 29.9 (CH_2), 27.3 (CH_2), 20.20 (CH_3), 20.16 (CH_3), 20.1 (CH_2), 19.7 (CH_2), 13.7 (CH_3), 13.6 (CH_3), 12.0 (CH_3); HRMS (ESI) calcd for $C_{56}H_{70}N_5O_8$ $[M + H]^+$ 940.5224, found 940.5220.

Rotaxane *E*-1d. Rotaxane *E*-**1d** was obtained from thread *E*-**3d** (311 mg, 0.65 mmol) by using the general procedure described above. The solid crude was purified by column chromatography on silica gel by eluting with 7:3 $CHCl_3$/AcOEt to give the title product as a white solid (50 mg, 8%): mp 288−290 °C; $[\alpha]_D^{25}$ −3.6° (*c* 0.0010, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 8.26−8.24 (m, 6H), 7.61 (t, *J* = 7.9 Hz, 2H), 7.39−7.31 (m, 3H), 7.22−7.20 (m, 2H), 7.15−7.08 (m, 5H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.93 (s, 8H), 6.65 (d, *J* = 6.9 Hz, 2H), 5.92 (d, *J* = 15.0 Hz, 1H), 5.82 (d, *J* = 15.1 Hz, 1H), 4.40−4.38 (m, 10H), 4.25−4.22 (m, 4H), 3.72 (ddd, *J* = 11.2, 5.6, 3.8 Hz, 1H), 3.62 (ddd, *J* = 11.3, 5.4, 3.9 Hz, 1H), 3.25 (dd, *J* = 7.6, 3.5 Hz, 1H), 1.73 (dq, *J* = 12.8, 3.6 Hz, 1H), 1.63−1.56 (m, 3H), 1.48−1.43 (m, 1H), 0.98−0.93 (m, 2H), 0.90 (s, 3H), 0.85 (s, 3H), 0.73 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 168.4 (C), 165.8 (C), 165.0 (C), 137.8 (C), 135.5 (C), 134.1 (C), 133.6 (C), 132.2 (CH), 130.5 (CH), 130.0 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 125.5 (CH), 122.5 (CH), 88.3 (CH), 66.8 (CH_2), 66.4 (CH_2), 51.5 (CH_2), 51.4 (CH_2), 49.5 (C), 46.6 (C), 45.0 (CH), 43.8 (CH_2), 38.6 (CH_2), 34.5 (CH_2), 27.3 (CH_2), 20.2 (2 × CH_3), 12.0 (CH_3); HRMS (ESI) calcd for $C_{62}H_{66}N_5O_8$ $[M + H]^+$ 1008.4911, found 1008.4896.

Isolation of Threads *Z*-3a−c and [2]Rotaxane *Z*-1c by Irradiation under UV Light. The corresponding threads *E*-**3a−c** (0.1 mmol) or [2]rotaxane *E*-**1** (0.025 mmol) was placed in a quartz

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tube, dissolved in dichloromethane (40 mL) under a nitrogen gas atmosphere, and irradiated under UV light (312 nm) for 90 min.

Thread *Z*-3a. *Z*-**3a** was obtained from thread *E*-**3a** (40 mg, 0.098 mmol) by using the previously described method. After irradiation at 312 nm for 90 min, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluting with 4:1 hexanes/AcOEt. The title product was isolated as a yellow oil (9.9 mg, 25%): $[\alpha]_D^{25}$ +1.8° (*c* 0.0099, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 6.54 (d, *J* = 11.9 Hz, 1H), 5.99 (d, *J* = 12.0 Hz, 1H), 5.50 (t, *J* = 7.2 Hz, 1H), 5.21 (d, *J* = 1.5 Hz, 1H), 4.52 (s, 2H), 3.39−3.35 (m, 2H), 3.23−3.19 (m, 2H), 2.28−2.14 (m, 2H), 2.03−1.95 (m, 1H), 1.85−1.74 (m, 2H), 1.66 (s, 3H), 1.63−1.53 (m, 5H), 1.53−1.45 (m, 2H), 1.39−1.27 (m, 4H), 0.98 (s, 3H), 0.96−0.88 (m, 6H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 166.6 (C), 164.7 (C), 148.6 (C), 138.4 (CH), 130.2 (CH), 129.8 (C), 122.8 (CH), 121.8 (CH), 71.0 (CH_2), 50.3 (CH), 48.2 (CH_2), 46.9 (C), 44.6 (CH_2), 35.6 (CH_2), 30.7 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.0 (CH_3), 20.4 (CH_2), 20.1 (CH_2), 19.8 (CH_3), 14.2 (CH_3), 14.0 (CH_3), 13.9 (CH_3), 12.7 (CH_3); HRMS (ESI) calcd for $C_{25}H_{42}NO_3$ $[M + H]^+$ 404.3165, found 404.3145.

Thread *Z*-3b. *Z*-**3b** was obtained from thread *E*-**3b** (40 mg, 0.095 mmol) by using the previously described method. After irradiation at 312 nm for 90 min, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluting with 4:1 hexane/AcOEt. The title product was isolated as a yellow oil (9.1 mg, 23%): $[\alpha]_D^{25}$ −2.2° (*c* 0.0091, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 6.54 (d, *J* = 12.1 Hz, 1H), 5.98 (d, *J* = 12.0 Hz, 1H), 5.47 (t, *J* = 7.2 Hz, 1H), 5.21 (dt, *J* = 3.2, 1.5 Hz, 1H), 4.56 (s, 2H), 3.39−3.35 (m, 2H), 3.23−3.19 (m, 2H), 2.29−2.23 (m, 1H), 2.22−2.14 (m, 1H), 2.11 (q, *J* = 7.6 Hz, 2H), 2.00 (ddd, *J* = 14.2, 10.3, 7.4 Hz, 1H), 1.85−1.76 (m, 2H), 1.63−1.56 (m, 5H), 1.53−1.45 (m, 2H), 1.41−1.24 (m, 4H), 1.01−0.88 (m, 12H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 166.6 (C), 164.7 (C), 148.6 (C), 138.4 (CH), 135.6 (C), 130.2 (CH), 122.8 (CH), 121.8 (CH), 68.8 (CH_2), 50.5 (CH), 48.2 (CH_2), 46.9 (C), 44.5 (CH_2), 35.6 (CH_2), 30.7 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 25.9 (CH_3), 21.3 (CH_2), 20.4 (CH_2), 20.0 (CH_2), 19.8 (CH_3), 14.0 (CH_3), 13.8 (CH_3), 12.9 (CH_3), 12.7 (CH_3); HRMS (ESI) calcd for $C_{26}H_{43}NNaO_3$ [M + Na] 440.3141, found 440.3135.

Thread *Z*-3c. *Z*-**3c** was obtained from thread *E*-**3c** (40 mg, 0.099 mmol) by using the previously described method. After irradiation at 312 nm for 90 min, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluting with 4:1 hexane/AcOEt. The title product was isolated as a yellow oil (10.0 mg, 25%): $[\alpha]_D^{25}$ −2.7° (*c* 0.0100, $CHCl_3$); ^{1}H NMR (401 MHz, $CDCl_3$, 298 K) δ 6.53 (d, *J* = 12.0 Hz, 1H), 5.98 (d, *J* = 11.9 Hz, 1H), 4.24−4.21 (m, 2H), 3.61 (ddd, *J* = 10.7, 5.8, 4.8 Hz, 1H), 3.50 (dt, *J* = 11.0, 4.9 Hz, 1H), 3.39−3.35 (m, 2H), 3.23−3.18 (m, 3H), 1.76−1.69 (m, 1H), 1.67−1.45 (m, 8H), 1.41−1.32 (m, 2H), 1.31−1.22 (m, 2H), 0.98−0.89 (m, 11H), 0.86 (s, 3H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ 166.6 (C), 164.7 (C), 138.6 (CH), 122.7 (CH), 87.6 (CH), 66.9 (CH_2), 64.1 (CH_2), 49.4 (C), 48.2 (CH_2), 46.5 (C), 45.2 (CH), 44.6 (CH_2), 38.6 (CH_2), 34.5 (CH_2), 30.8 (CH_2), 29.4 (CH_2), 27.4 (CH_2), 20.4 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 20.1 (CH_2), 14.0 (CH_3), 13.8 (CH_3), 11.9 (CH_3); HRMS (ESI) calcd for $C_{24}H_{41}NNaO_4$ [M + Na] 430.2933, found 430.2934.

Rotaxane *Z*-1c. *Z*-**1c** was obtained from [2]rotaxane *E*-**1c** (40 mg, 0.043 mmol) by using the previously described method. After irradiation at 312 nm for 90 min, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluting with 4:1 $CHCl_3$/acetone. The title product was isolated as a white solid (19.6 mg, 49%): mp >300 °C; $[\alpha]_D^{25}$ −3.3° (*c* 0.0113, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 8.22 (dd, *J* = 7.8, 1.6 Hz, 4H), 7.89 (s, 2H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.20−7.17 (m, 10H), 7.13 (t, *J* = 5.3 Hz, 2H), 6.28 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 4.62−4.53 (m, 8H), 3.15−3.12 (m, 4H), 3.03−2.98 (m, 5H), 1.59−1.54 (m, 1H), 1.52−1.45 (m, 3H), 1.41−1.35 (m, 5H), 1.31−1.27 (m, 2H), 1.08−1.02 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.89−0.81 (m, 2H), 0.74 (s, 3H), 0.71−0.66 (m, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ 166.41 (C), 166.39 (C), 165.2 (C), 164.2 (C), 138.8 (CH), 137.7 (C), 137.5 (C), 134.44 (C), 134.38 (C), 132.04 (CH), 132.01 (CH), 129.5 (CH), 129.06 (CH), 129.05 (CH), 122.9 (CH), 122.7 (CH), 89.1 (CH), 67.5 (CH_2), 64.1 (CH_2), 49.6 (C), 48.8 (CH_2), 46.4 (C), 45.3 (CH_2), 44.7 (CH), 44.4 (CH_2), 44.3 (CH_2), 38.4 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 26.9 (CH_2), 20.3 (CH_2), 20.2 (CH_2), 20.12 (CH_3), 20.10 (CH_3), 13.9 (CH_3), 13.5 (CH_3), 12.3 (CH_3); HRMS (ESI) calcd for $C_{56}H_{70}N_5O_8$ $[M + H]^+$ 940.5224, found 940.5236.

Enzyme-Catalyzed Hydrolysis of Threads *E*-3, *Z*-3, and [2]Rotaxane *E*-1. A solution of the corresponding threads *E*-**3a−d** and *Z*-**3a−c** or [2]rotaxanes *E*-**1a−d** (10 mg) in acetone (0.5 mL) was added to a vial containing a solution of porcine liver esterase (1 mg, 10% by weight with respect to the substrate), Arquad (200 mg, 10% by weight in water), and an aqueous solution of K_2HPO_4 (50 mM, 2 mL). Aliquots were extracted from the reaction mixture, dissolved in $CHCl_3$ (5 mL), and subsequently washed with 1 M HCl (2 × 2 mL) and brine (2 × 2 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was analyzed by TLC and ^{1}H NMR spectroscopy. The conversion of corresponding threads *E*-**3a−d** and *Z*-**3a−c** or [2]rotaxanes *E*-**1a−d** into the corresponding carboxylic acids *E*-**4b** and *E*-**4b** was determined by integration of the olefinic/benzylic protons from both the starting ester and the resulting carboxylic acid in the ^{1}H NMR spectra of their respective crude products. We observed the shielding of the olefinic protons in the spectra of carboxylic acids *E*-**4** when compared to the values of the pure compounds. These shifts were attributed to the unavoidable presence of the surfactant. The amount of scents in the crude product could not be accurately measured due to their high volatility. Control experiments without an enzyme, a surfactant, or a base are described in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01725.

Kinetic measurements for the determination of the deslipping rate constants by thermal dethreading in $C_2D_2Cl_4$ or a 1:1 $CDCl_3$/MeOD mixture, thermogravimetric analysis of [2]rotaxanes *E*-**1a−d**, control experiments for the enzyme-catalyzed hydrolysis of threads *E*-**3b** and *E*-**3c**, ^{1}H and ^{13}C{^{1}H} NMR spectra of all newly synthesized compounds, and ^{1}H−^{1}H COSY, HSQC, and ^{1}H−^{1}H NOESY spectra of *E*-**3a−c**, *E*-**1a−c**, and *Z*-**1c** (PDF)

FAIR data, including the primary NMR FID files, for compound *E*-**1a** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**1b** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**1c** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**1d** (ZIP)

FAIR data, including the primary NMR FID files, for compound *Z*-**1c** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3a** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3b** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3c** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3d** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3e** (ZIP)

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FAIR data, including the primary NMR FID files, for compound *E*-**3f** (ZIP)

FAIR data, including the primary NMR FID files, for compound *E*-**3g** (ZIP)

FAIR data, including the primary NMR FID files, for compound *Z*-**3a** (ZIP)

FAIR data, including the primary NMR FID files, for compound *Z*-**3b** (ZIP)

FAIR data, including the primary NMR FID files, for compound *Z*-**3c** (ZIP)

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Notes

The authors declare no competing financial interest.

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