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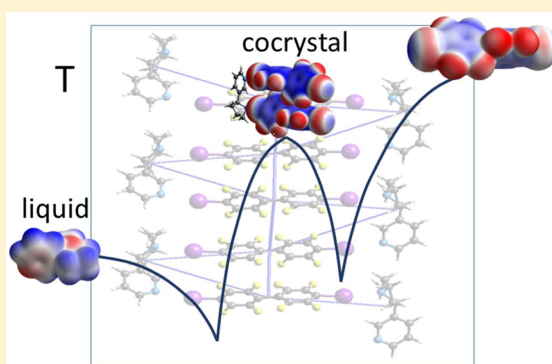
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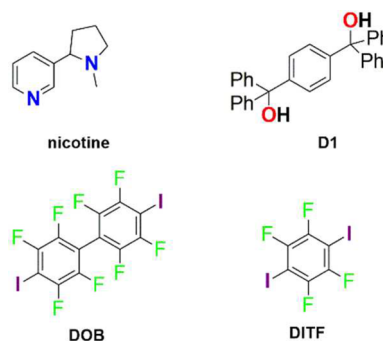
1 **Liquid Nicotine Tamed in Solid Forms by Cocrystallization**2 Davide Capucci,[†] Davide Balestri,[†] Paolo P. Mazzeo,^{†,§} Paolo Pelagatti,[†] Katia Rubini,[‡]
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5 Parma, Italy6 [‡]Dipartimento di Chimica 'G. Ciamician', Università di Bologna, Via Selmi, 2, I-40126 Bologna, Italy7 [§]Biopharmanet-tec, Parco delle Scienze, 27/A, I-43124 Parma, Italy8 **S** Supporting Information

9 **ABSTRACT:** We address the problem of stabilizing liquid nicotine in
10 solid forms at ambient conditions by cocrystallization. An intriguing
11 aspect of nicotine lies in the fact that its crystal structure has never been
12 reported in the literature, and this peculiarity may be ascribed to the
13 liquid–glass transition that occurs when nicotine is supercooled under
14 its melting point (−79 °C). Even though nicotine was considered a
15 rigid molecule, its glass forming nature could be due to a certain extent
16 of conformational variability, which has been assessed by a conformer
17 search of the Cambridge Crystallographic Data Centre software. The
18 design of cocrystals forms of nicotine is approached by analyzing its
19 molecular electrostatic potential. On the basis of these considerations,
20 three cofomers have been identified, and their crystal structure shows
21 that nicotine adapts to the packing features dictated by the cofomers.
22 The tool of packing energy frameworks has been used to discuss the stabilization of the cocrystals.

23 **INTRODUCTION**

24 Surprisingly, despite its fairly complex molecular structure,
25 nicotine is a liquid. We address the problem of taming liquid
26 nicotine in crystalline forms at ambient conditions. Crystal-
27 lization at a given temperature is the result of a struggle
28 between the destabilizing entropy contribution of the liquid
29 state and the stabilizing enthalpy optimization by crystal
30 ordering. Here we force the enthalpic stabilization by designing
31 cocrystals of nicotine. The reason for this work stems from the
32 fact that liquid formulations tend to be essentially less stable
33 than solid forms; therefore most active pharmaceutical
34 ingredients (APIs) and nutraceutical compounds are manufac-
35 tured and distributed as crystalline materials,¹ and their action
36 involves the delivery of the active molecule by a solubilization
37 process either in the body or on the environment. However,
38 some important molecules for human health are liquid at room
39 temperature, and we are currently exploring general strategies
40 to embed liquid ingredients in crystalline materials. Stabilization
41 of liquid APIs is of enormous interest for pharmaceutical
42 industries especially for storage, transportation, and handling.
43 Liquid nicotine is a toxic alkaloid found in the leaves of the
44 tobacco plants *Nicotiana tabacum* and *Nicotiana rustica* of the
45 family *Solanaceae*.² Nicotine is also a nootropic stimulant drug,
46 Because of its properties, nicotine has been of commercial
47 interest and employed for widely different uses such as
48 therapeutic use in treating nicotine dependence or as an
49 insecticide.³ Nicotine possesses two basic centers (Scheme 1);
50 therefore salt formation could be exploited as a well-known

Scheme 1. Nicotine and the Cofomers Used in This Work



51 method to build a crystalline material from a base; however,
52 salification alters the molecular electronic and hydrogen
53 bonding properties, as shown by computational simulation⁴
54 and affords a material sensitive to pH. On the other hand,
55 cocrystallization is considered a smart and dainty way to tune
56 solubility properties of solid phases leaving the molecule
57 chemically unchanged.⁵ Despite this extremely high interest
58 toward cocrystallization, no particular emphasis has been paid
59 so far toward using it as a general means to stabilize
60 compounds: among the few reports stressing how to stabilize

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61 liquid APIs, we recently presented an investigation on the
62 stability and solubility of cocrystals containing propofol, a
63 widely used liquid anesthetic.⁶ Cocrystallization of volatile or
64 low melting compounds is an intriguing challenge, above all if
65 the molecule of interest is of pharmaceutical or environmental
66 relevance, or for the storage of gaseous compounds such as
67 acetylene.^{6–10} Aakeröy et. al have reported the stabilization of
68 volatile iodoperfluoroalkanes, that are generally recognized as
69 persistent potential pollutants, or even explosives, through
70 cocrystallization in recent works.^{11,12} On the other hand, only
71 one cocrystal of neutral nicotine¹³ has been reported in the
72 literature, but no real stress has ever been given to the
73 importance of stabilizing that compound through this method-
74 ology (a second example of highly disordered nicotine included
75 in a crystalline sponge has been recently reported¹⁴).

76 An intriguing aspect of nicotine lies in the fact that its crystal
77 structure as a pure compound has never been reported in the
78 literature, and this peculiarity may be ascribed to the liquid–
79 glass transition that occurs when nicotine is supercooled under
80 its melting point (−79 °C).¹⁵ Here we analyze the molecular
81 features which make nicotine reluctant to form a solid and
82 identify possible cofomers to achieve cocrystallization (Scheme
83 1).

84 ■ EXPERIMENTAL SECTION

85 **Synthesis.** (−)-Nicotine (99%), 1,4-diiodotetrafluorobenzene
86 (98%), and all the solvents for crystallization were purchased from
87 Sigma-Aldrich and used with no further purification in all
88 crystallization experiments. 4,4′-Diiodooctafluorobiphenyl (DOB)
89 has been synthesized starting from the commercial precursor 4,4′-
90 dibromooctafluorobiphenyl (98%) from Sigma-Aldrich Chemical Co.,
91 following a literature reported procedure slightly modified (Supporting
92 Information).^{16,17} 1,4-Bis(diphenylhydroxymethyl)benzene (D1) has
93 been synthesized from commercial precursor dimethyl terephthalate
94 (99%, Sigma-Aldrich), following a literature reported procedure
95 slightly modified¹⁸ (see Supporting Information).

96 **Cocrystallization.** Cocrystallizations of (−)-nicotine and related
97 cofomers (di-iodotetrafluoro benzene (DITF), DOB, and D1) were
98 carried out in ethyl acetate, tetrahydrofuran, and methanol. Solutions
99 containing (−)-nicotine and the proper cofomer with 1:1, 1:2, 2:1
100 molar ratios were left to slowly evaporate at room temperature until
101 tiny single crystals suitable for single-crystal X-ray diffraction (SC-
102 XRD) analysis formed. In all cases 1:1 cocrystals were obtained.

103 **Thermal Analysis.** Differential scanning calorimetry analysis on
104 nicotine–DITF and nicotine–DOB cocrystals powder samples were
105 performed with a PerkinElmer Diamond equipped with a model ULSP
106 90 ultracooler. Heating was carried out in open Al-pans at 5 °C/min in
107 the temperature range from −25 to 80 °C. The enthalpy of the
108 endothermic or exothermic event is determined by the integration of
109 the area under the differential scanning calorimetry (DSC) peak, which
110 is reported in J/g.

111 DSC trace of nicotine–D1 was collected with a PerkinElmer DSC
112 6000 in a sealed 50 μL Al-pan. The measurement was performed at
113 atmospheric pressure under a constant flow of nitrogen (20 mL
114 min^{−1}) in the temperature range from −30 to 110 °C. The enthalpy of
115 the endothermic or exothermic event is determined by the integration
116 of the area under the DSC peak, which is reported in J/g.

117 **SC-XRD Analysis on Cocrystals.** SC-XRD analysis was
118 performed on single crystal samples at room temperature (293 K)
119 on a SMART APEX2 diffractometer using Mo K α radiation (λ =
120 0.71073 Å) for nicotine–DITF; Lorentz polarization and absorption
121 correction were applied. Nicotine-DOB and nicotine-D1 were
122 collected at 100 K under nitrogen flux at Elettra Sincrotrone (Trieste,
123 Italy) at the XRD1 beamline with X-ray synchrotron radiation source
124 and a NdFe Multipole Wiggler (Hybrid linear) insertion device.
125 Beam energy was set at 4.27 keV with a power of 8.6 kW and a
126 beamsizes fwhm of 2.0 × 0.37 mm (0.7 × 0.2 mm fwhm beam size on

the sample) with photon flux 1012–1013 ph/sec. Pilatus 2 M detector
127 was used to collect the data; synchrotron data were processed by
128 using XDS software.¹⁹ Structures were solved by direct methods using
129 SHELXS²⁰ and refined by full-matrix least-squares on all F2 using
130 SHELXL implemented in Olex2.²¹ For nicotine–D1 and nicotine-
131 DITF anisotropic displacement parameters were refined except for
132 hydrogen atoms, while the crystal quality for nicotine–DOB allowed
133 refinement of anisotropic thermal ellipsoids only for iodine atoms.
134 Table 1 reports the results of crystal structures determination. CSD-

135 11

Table 1. Crystal Data and Structural Refinement

	nicotine–D1	nicotine–DITF	nicotine–DOB
empirical formula	C ₄₂ H ₄₀ N ₂ O ₂	C ₁₆ H ₁₄ F ₄ I ₂ N ₂	C ₂₂ H ₁₄ F ₈ I ₂ N ₂
formula weight	604.76	564.09	712.15
temperature/K	100.15	293	100
crystal system	triclinic	monoclinic	monoclinic
space group	P1	P2 ₁	P2 ₁
a/Å	8.226(2)	10.65(2)	8.779(2)
b/Å	8.962(2)	12.12(2)	28.979(6)
c/Å	11.968(2)	14.71(3)	18.082(4)
α /°	86.84(3)	90	90
β /°	87.90(3)	91.35(3)	90.68(3)
γ /°	68.29(3)	90	90
volume/Å ³	818.3(3)	1898(6)	4600(2)
Z	1	4	8
ρ_{calc} g/cm ³	1.227	1.974	2.057
μ /mm ^{−1}	0.073	3.350	2.712
F(000)	322.0	1064.0	2704.0
radiation/Å	synchrotron (λ = 0.700)	MoK α (λ = 0.71073)	synchrotron (λ = 0.700)
2 θ range for data collection/°	3.358–65.624	2.77–47.076	2.614–40.932
reflections collected	15436	12857	13463
independent reflections	9058 [R_{int} = 0.0301, R_{sigma} = 0.0487]	5436 [R_{int} = 0.0985, R_{sigma} = 0.1363]	8799 [R_{int} = 0.1682, R_{sigma} = 0.2830]
data/restraints/parameters	9058/3/419	5436/7/387	8799/244/443
goodness-of-fit on F^2	1.066	0.955	1.053
final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0408, wR_2 = 0.1035	R_1 = 0.0628, wR_2 = 0.1249	R_1 = 0.1374, wR_2 = 0.3413
final R indexes [all data]	R_1 = 0.0409, wR_2 = 0.1037	R_1 = 0.1473, wR_2 = 0.1588	R_1 = 0.2140, wR_2 = 0.3907
final ΔF max/min/e Å ^{−3}	0.37/−0.32	1.02/−0.67	2.87/−1.92
Flack parameter	0.0(2)	0.06(6)	0.00(13)

Enterprise was used for crystal packing and conformational analysis
136 within the CSD-Materials module.²² Estimation of the interaction
137 energy and energy frameworks were performed with CrystalExplor-
138 er17 using HF/3-21G basis set.^{23,24} Molecular electrostatic potential
139 (MEP) has been calculated with Tonto²⁵ using density functional
140 theory (B3LYP) using the 6-311G(d,p) basis set and displayed using
141 CrystalExplorer 17; MEP has been mapped on the electron density
142 surface cut at the 0.002 e/Å³ level. Crystallographic data for nicotine–
143 D1, nicotine–DITF, and nicotine–DOB have been deposited with the
144 Cambridge Crystallographic Data Centre as supplementary publication
145 CCDC 1557603–1557605.

146

147 ■ RESULTS

148 In order to achieve cocrystallization, molecules with different
149 functionalities are usually brought together relying on a wide
150 toolkit of intermolecular interactions spanning from weak
151 dispersive interactions to rather strong hydrogen or halogen

152 bonds. The predominant effect for molecular recognition is
 153 based on electrostatic complementarity.^{26,27} A guidance to
 154 understand the propensity of a molecule to establish favorable
 155 intermolecular contacts through its functional groups is given
 156 by the MEP, calculated from the electron charge distribution,
 157 visualized on the molecular surface.^{28,29} Figure 1 shows the

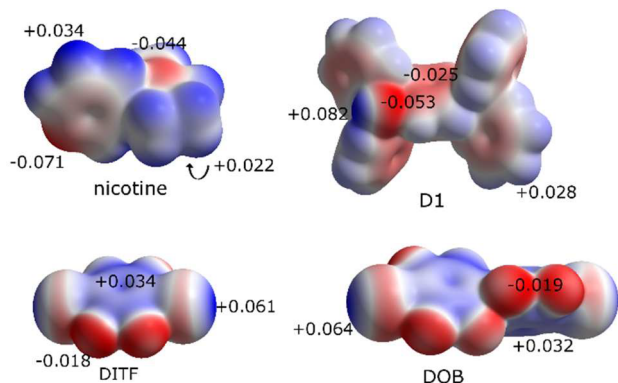


Figure 1. Molecular electrostatic potential (MEP) plotted on the electron density surface (drawn at the 0.002 au level) for nicotine, D1, DITF, and DOB. Significant local maximum and minimum values are reported (a.u.). The arrow indicates the charge on the pyrrolidine hidden surface.

158 electrostatic potential mapped on the molecular surface for
 159 nicotine, evidencing two remarkable negative spots correspond-
 160 ing to the nitrogen atoms, and a positive region at the
 161 pyrrolidine ring surface (hidden in Figure 1, view of the
 162 pyrrolidine ring is in the Supporting Information) and at the
 163 pyridine edge. The choice of coformers for nicotine was
 164 focused to small organic molecules able to interact with the
 165 negative spots of the nicotine MEP through suitable functional
 166 groups (Figure 1 and Scheme 1). Promising synthons have
 167 been selected considering both hydrogen bond and halogen
 168 bond interactions. Although early spectroscopic and computa-
 169 tional works indicated the pyridinic nitrogen has much better
 170 hydrogen bond accepting capability,³⁰ it has been recently
 171 shown that both nitrogens can accept hydrogen bonds from
 172 water, with the pyridinic one being more efficient.⁴ The same
 173 trend is here observed by comparing the MEP values
 174 corresponding to the two nitrogens (Figure 1). Previous
 175 works reported in the literature showed that 4,4'-bis-
 176 (diphenylhydroxymethyl)biphenyl is a wheel and axle molecule
 177 which efficiently enclathrated guest molecules among which
 178 nicotine.¹³ Therefore we synthesized D1 as a potential good
 179 coformer for nicotine cocrystals. Diiodoperfluorurate aromatic
 180 derivatives have been described as efficient halogen bond
 181 donors (electron acceptors), which could equally well combine
 182 with the electron donor propensity of the nicotine nitrogens.³¹
 183 DITF and DOB have been chosen as halogen bonding
 184 coformers.

185 **Crystal Structures.** ORTEP drawings of all the structures
 186 are reported in the Supporting Information. Table 2 reports the
 187 significant supramolecular interactions.

188 Nicotine–D1 crystallizes in the chiral space group *P1* in a 1:1
 189 stoichiometric ratio. The molecular conformation of nicotine is
 190 determined by the torsion angle τ [C38–C34–C33–N1] =
 191 140°, ruling the reciprocal orientation of the two nitrogen
 192 atoms (Figure 2). As expected from the design of the cocrystal,
 193 the crystal packing is dominated by the hydrogen bonds

Table 2. Hydrogen Bond and Halogen Bond Geometries

compound	pyridine N	pyrrolidine N
nicotine–D1	O...N = 2.790(2) Å	O...N ($x, y + 1, z + 1$) = 2.928(2) Å
	O–H...N = 151.35(7)°	O–H...N = 152.84(7)°
nicotine–DITF	N...I ($x - 1, y + 1, z + 1$) = 2.869(4) Å	N...I = 3.02(3) Å
	N...I ($x - 2, y, z$) = 2.921(4) Å	N...I = 3.03(3) Å
	N...I = 2.808(5) Å	N...I = 2.91(5) Å
nicotine–DOB	I...N ($2 - x, 1/2 + y, 1 - z$) = 2.852(5) Å	I...N ($1 - x, 1/2 + y, 1 - z$) = 2.97(6) Å
	N...I = 2.901(3) Å	N...I = 3.00(8) Å
	I...N ($-x, 1/2 + y, 2 - z$) = 2.934(5) Å	I...N ($1 - x, 1/2 + y, 2 - z$) = 2.91(5) Å

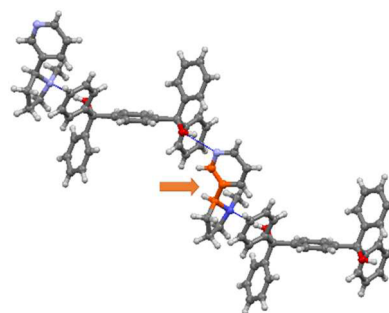


Figure 2. Crystal structure of nicotine–D1, showing the hydrogen bond pattern. Torsion angle τ (see text) is highlighted in orange.

194 involving the –OH groups of the D1 coformer as donors and
 195 both the nicotine nitrogen atoms as acceptors (Table 2),
 196 generating chains promoted by the anti orientation of the two
 197 nitrogen atoms (Figure 2).

198 Because of the wheel-and-axle shape of the coformer, the
 199 chains are assembled so that the D1 ligands are arranged in
 200 arrays of parallel molecules slightly offset to promote
 201 interdigitation of phenyl groups (Figure 3), as observed for
 202 families of similar organic and organometallic compounds.^{32–34}

203 The role of the interactions between the coformer molecules
 204 in partially driving the packing is shown by the calculation of
 205 intermolecular potential energy performed by CrystalExplor-
 206 er17 (Figure 3) and visualized by the energy framework
 207 method³⁵ (Figure 4). While the strongest interaction is
 208 between the hydrogen bonded molecules, the second major

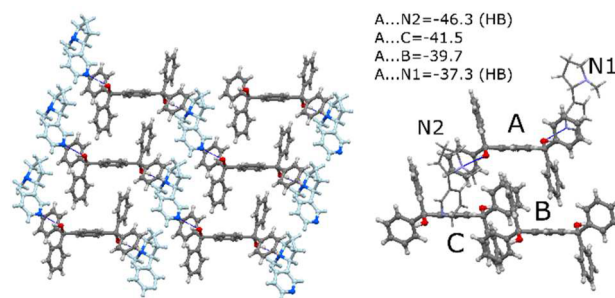


Figure 3. Left: arrays of hydrogen bonded chains in the crystal packing of nicotine–D1. Right: main interactions between neighboring molecules (kJ/mol), comprising hydrogen bonds (HB) and edge-to-face CH... π interactions between D1 molecules.

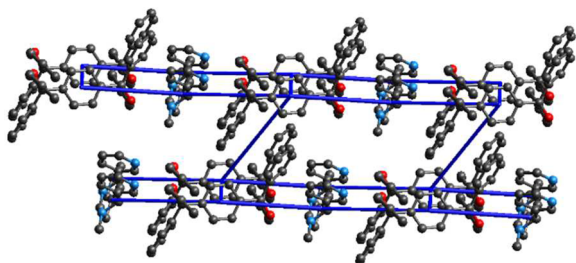


Figure 4. Energy framework for nicotine-D1, showing the four main interactions present in the packing.

209 source of packing stabilization is the offset stacking between D1
210 molecules. The MEP of D1, shown in Figure 1, justifies the
211 offset stacking as a way to optimize edge-to-face interactions
212 which bring into proximity the oppositely charged parts of the
213 molecule.

214 Inspection of the packing energy framework (Figure 4)
215 shows that the packing of the conformer D1 represent a
216 scaffold to which nicotine adapts to optimize hydrogen bond
217 interactions. The energy framework method consists in
218 representing the interactions between nearest neighboring
219 molecules as tubes connecting molecular centroids. Tubes
220 diameter is proportional to the energy strength, so that the
221 main interactions responsible of the crystal stabilization are
222 visible at a glance.

223 Nicotine-DITF crystallizes in the $P2_1$ chiral space group,
224 with a 1:1 stoichiometric ratio, and $Z' = 2$ (Figure 5). Both
225 independent nicotine molecules present the anti conformation
226 of the two rings, defined by torsion angles τ of 140° and 143° ,
227 respectively.

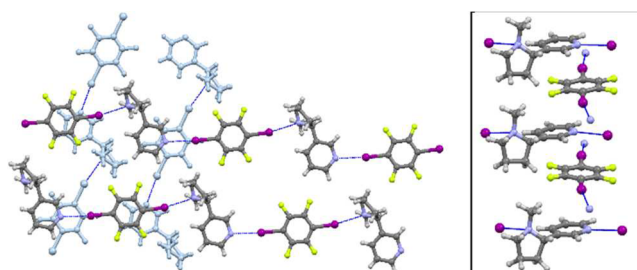


Figure 5. Crystal packing of nicotine-DITF, dominated by halogen bonded chains. Chains are tilted by 60° , as shown in shading. Inset: detail of close packing between tilted chains.

228 As expected from cocrystal design strategy, the packing
229 topology is dominated by the halogen bonds between the
230 iodinated cofomer and the nicotine nitrogen atoms, featuring a
231 chain motif topologically similar to the one observed with the
232 D1 cofomer (Table 2). However, in this case the halogen
233 bonded chains are arranged in skew orientation, with an angle
234 of 60° between the vectors describing adjacent chains, which
235 are crystallographically independent. From the examination of
236 the molecular electrostatic potential mapped on the molecular
237 surface it is evident that the best fit between nicotine and DITF
238 is reached with a parallel stacking of the pyridine on the
239 tetrafluoro benzene ring, exploiting the complementary electro-
240 static potential of the two surfaces (Figure 1). Interaction of the
241 negative fluorinated edge of DITF with the pyrrolidine positive
242 surface is also stabilizing (Supporting Information). The
243 halogen bonded chains are therefore tilted in order to optimize

the fit between the pyrrolidine ring and DITF. Inspection of the
energy framework (Figure 6) confirms that the main interaction
dominating the packing is the stacking between nicotine and
DITF, while the halogen bond adapts to this scaffold.

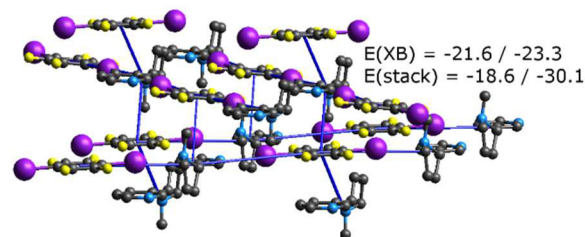


Figure 6. Energy framework representation for nicotine-DITF. Ranges of the energy of the halogen bonds ($E(XB)$) and stacking ($E(\text{stack})$) interactions relative to the pairs of independent molecules are reported in kJ/mol.

Nicotine-DOB crystallizes in the $P2_1$ chiral space group, with a 1:1 stoichiometry and $Z' = 4$ (Figure 7).

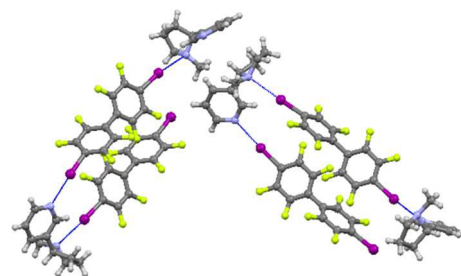


Figure 7. Four independent molecules in nicotine-DOB cocrystal. All the four nicotine molecules adopt the syn conformation to form halogen bonds, which are highlighted.

The four independent nicotine molecules present the same syn orientation of the nitrogen atoms on the two rings, defined by torsion angles τ respectively of -54° , -56° , -58° , and -59° around the single bond joining the rings. The crystal packing, as expected, is based on halogen bonds (Table 2) involving nicotine molecules which bridge arrays of stacked DOB molecules, in a ladder motif (Figure 8). In the crystal packing

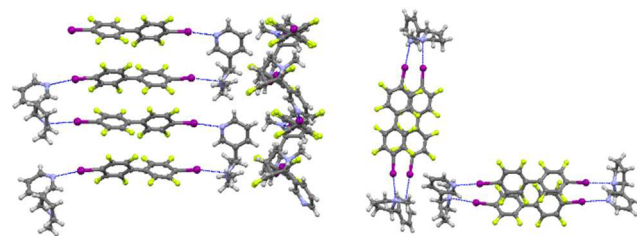


Figure 8. Left: two orthogonal ladder motifs are generated by halogen bonds with nicotine in the syn conformation. Right: edge-on view of the two independent ladders, tilted by 90° .

there are two independent arrays, tilted by about 90° . From the analysis of the molecular electrostatic potential (Figure 1) it is evident that, besides the halogen bonds, the stacking of DOB molecules is the stable motif driving the packing arrangement, because it allows the approach of the negative ridge of the

262 aromatic rings to the positively charged ring surface (Figure SI-
263 7, Supporting Information).

264 The energy framework analysis (Figure 9) confirms that the
265 predominant stabilization in the crystal packing is due to
266 dispersive interactions between stacked DOB cofomers.

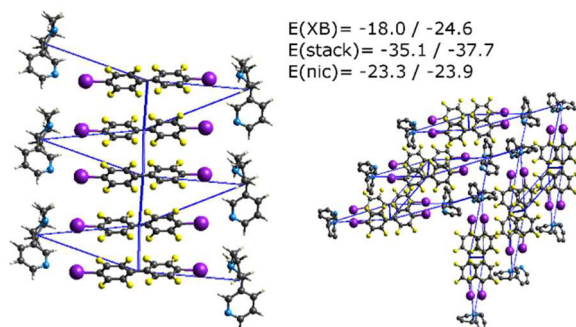


Figure 9. Energy framework representation for nicotine-DOB. Left: ladder motif; right: orthogonal arrangement of ladder motifs. Ranges of the energy of the interactions relative to the pairs of independent molecules are reported in kJ/mol. $E(\text{XB})$ refers to halogen bonds, $E(\text{stack})$ and $E(\text{nic})$ to DOB \cdots DOB and nicotine \cdots nicotine interactions, respectively.

267 **Thermal Analysis.** Differential scanning calorimetry
268 (Figure 10) on nicotine-DITF (mp 109 °C) shows a neat

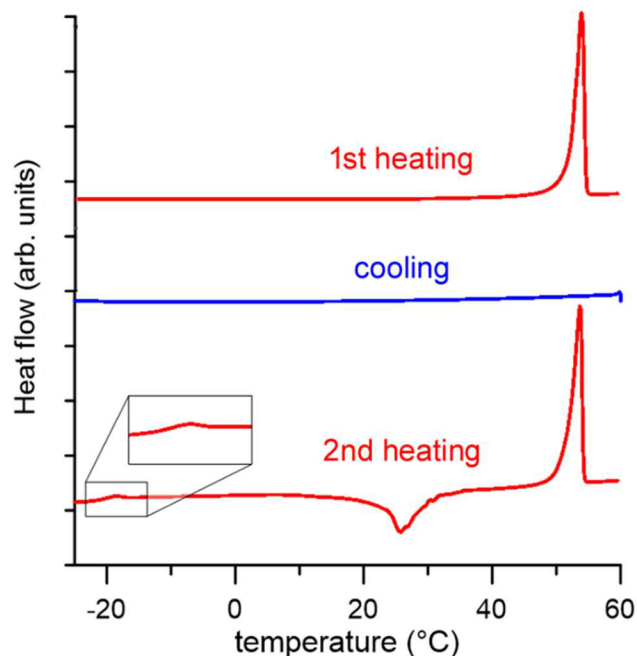


Figure 10. DSC experiment on nicotine-DITF cocrystal (endo up). Glass transition on the second heating ramp is magnified in the inset.

269 melting peak during the first heating run with a maximum at 54
270 °C ($\Delta H = 27.6$ kJ/mol) (see also Supporting Information).
271 During the cooling scan no phenomena are observed, while in
272 the second heating run a glass transition appears between -22
273 °C and -18 °C. A broad exothermic peak, with a minimum at
274 26 °C ($\Delta H = -18.7$ kJ/mol) represents the recrystallization of
275 the cocrystal. The melting of the cocrystal is confirmed by the
276 presence of a third peak in the DSC, endothermic, with a
277 maximum at 54 °C ($\Delta H = 26.4$ kJ/mol) and perfectly

comparable, both for temperature and for enthalpy, to the
melting peak of the first heating. This proves that the system is
thermally reversible and degradation or loss of any components
does not occur. The glass transition shows that the cocrystal is
not ready to crystallize during the cooling phase, giving a glass.
It is important to note that nicotine is characterized by glass
transition which occurs below -79 °C; therefore, it is a
definitely difficult molecule to crystallize, probably for the
presence of multiple orientations of the two rings which
generate free volume in the solid phase.

DSC analysis was performed on nicotine-DOB (mp 146
°C) (Supporting Information) following the typical first
heating-cooling-second heating experiment. During the first
heating an endothermic peak with a maximum at 68 °C ($\Delta H =$
24.3 kJ/mol) is visible and ascribable to melting of the
cocrystal. The cooling run is characterized by a progressive
decrease in heat flow from 80 °C down to -20 °C, but no
relevant peaks are present. During the second heating, a glass
transition occurs between -10 °C and -5 °C, similarly to what
has been observed for nicotine-DITF, but no recrystallization
phenomena are observed.

DSC measurement on nicotine-D1 (mp 169 °C) points out
a neat endothermic peak at 92 °C, related to the cocrystal
melting ($\Delta H = 37.9$ kJ/mol). During the cooling scan, no
recrystallization phenomenon is detected. Similarly to nic-
otine-DOB and nicotine-DITF, a glass transition occurred
also for nicotine-D1 during the second heating ramp, in the
range between -27 to -15 °C. Like for nicotine-DOB, no
recrystallization events are observed during the second heating
scan. The melting point of all these cocrystals are intermediate
between those of the pure components. Looking at the trend of
the differences between the melting point of the cocrystals with
respect to those of the cofomers, it is seen that DITF has the
smallest difference (55 °C), while DOB and D1 perform
similarly (78 and 77 °C respectively).

DISCUSSION

From the thermal analyses it is evident that nicotine is awkward
in achieving close-packing, given its tendency to form glass
phases. This can be related to conformational frustration.
Noticeably, nicotine was considered a rigid molecule, where the
most stable conformation has the pyridine and pyrrolidine rings
oriented roughly perpendicular to one another with the methyl
and pyridyl substituents in the trans configuration with a
torsional barrier of approximately 110 kJ/mol.³⁰ By contrast, a
recent extensive computational exploration of nicotine gas-
phase conformations has shown that the molecule presents
eight lowest energy isomers in a range of 30 kJ/mol, and they
were found to interconvert via low (<25 kJ/mol) rotational
barriers around the pyridine-pyrrolidine bond.³⁶ The main
variability described for these conformers refers to the
puckering of the pyrrolidine ring, the reciprocal orientation of
the methyl substituents and of the pyridine with respect to the
pyrrolidine ring, and the rotation around the pyridine-
pyrrolidine bond, indicated with τ in the previous discussion.
In fact we observed two different major conformations in our
structures, corresponding to the two lowest energy conformers
found by the computational investigation, differing mainly for
the reciprocal orientation of the two rings around the central
bond, by approximately 2.5 kJ/mol³⁶ (for a comparison with
the computations see Supporting Information). This means
that the packing effects allow to sample different minima in the
conformational landscape of nicotine. The different conformational

variability of nicotine is reflected by the distribution of the torsion angle τ across the three crystal structures reported here (Figure 11), containing altogether seven conformers, combined

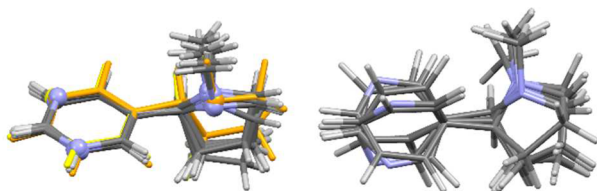


Figure 11. Left: comparison of the conformations observed in the crystal structures of nicotine cocrystals (KERSAB highlighted in yellow, nitrogen atoms evidenced to mark syn/anti geometries). Right: model conformational variability for nicotine based on analogue crystal structures from CSD conformer analysis.

with the two observed in the other cocrystal reported so far (CSD refcode KERSAB¹³), while the molecular structure of nicotine reported in ref 14 is too disordered to determine a reliable conformation.

In the two major conformations found here, one has torsion angle τ ranging from -54° to 59° (syn) and one has torsion angle τ ranging from 140° to 143° (anti). A screening of realistic conformations observed in the crystal structures of molecules similar to nicotine has been performed with the conformer generator module of the CSD system³⁷ and shows a remarkable variety of possible observable orientations of the two rings around the bond joining them (Figure 11, right). If on one hand this hampers a neat crystallization of the pure compound, it also makes nicotine adaptable to different packing environments, thus generating several possible packing motifs, depending on the reciprocal orientation of the two nitrogen atoms. Namely, one-dimensional chains are attained when nicotine occurs in anti conformation, while ladder motifs occur when nicotine displays a syn conformation. In the cocrystals reported here, the coformer...coformer interactions (wheel-and-axle arrangement in nicotine–D1, offset aromatic stacking in nicotine–DITF, DOB stacking in nicotine–DOB) govern the structural motifs found in the packing, while nicotine is ready to adapt its conformation in order to optimize the strong hydrogen bond, or halogen bond interactions formed through its nitrogen atoms. The strength of these interactions is shown by the fact that all the cocrystals reported here show melting temperature at least 130°C higher than the melting temperature of -79°C reported for pure nicotine.³⁸ Noticeably, form thermal data emerge that the hydrogen bonded coformer D1 could play a stronger stabilizing role, reflected in the higher melting enthalpy of the nicotine–D1 cocrystal.

CONCLUSIONS

"It's an odd case, Sir. Never come across a case of nicotine poisoning before in all my experience. No more has our Doctor Davis."

"I always thought it was a kind of disease you got from over-smoking."

"To tell the truth, so did I, Sir. But the doctor says that the pure alkaloid is an odorless liquid, and that a few drops of it are enough to kill a man almost instantaneously."

—*Three Act Tragedy*, Agatha Christie
Apart from its deadly aura related to the plague of tabagism³⁹ and to its high toxicity,⁴⁰ nicotine is an elusive molecule when

we consider its ability to close pack in a crystalline form. Despite its molecular weight and complexity, nicotine is in fact a liquid with extremely low melting point, reluctant to crystallize. This can be related to its conformational frustration, and we have introduced the idea that this fact can be exploited to obtain cocrystals whose supramolecular arrangement is dictated by the coformer packing characteristics, and nicotine adapts to these. In this way we have obtained three new high melting forms of nicotine-containing compounds, which open the route to new methods of formulation of this ingredient in a solid form.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b00887.

Synthesis of D1 and DOB. ORTEP drawings of the crystal structures of nicotine–D1, nicotine–DITF, and nicotine–DOB. DSC plots for nicotine–DOB, nicotine–D1, and nicotine–DITF. Comparison of conformations in this work and from literature. MEP of nicotine and the cofomers in the cocrystals (PDF)

Accession Codes

CCDC 1557603–1557605 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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