Supporting Information

IMPROVED SYNTHESIS OF NALDEMEDINE TOSYLATE AND CRYSTAL STRUCTURES OF FOUR RELATED SOLID FORMS

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1. Geometrical parameters of hydrogen bonds

Table S1. Hydrogen bonds [Å and °] for **$15H^+TsO^-$**.

D—H···*A*	$d_{D—H}$	$d_{H\cdots A}$	$d_{D\cdots A}$	<(*D*H*A*)
N13—H13···O2A^{i}	0.878(14)	2.55(5)	3.180(6)	129(5)
N33—H33···O36	0.872(14)	2.18(4)	2.669(5)	115(4)
N33—H33···O1A^{ii}	0.872(14)	2.27(3)	2.982(5)	139(4)
O36—H36···O3A^{i}	0.828(14)	1.88(2)	2.686(5)	165(5)
O37—H37···O2A	0.831(14)	1.90(3)	2.684(4)	156(6)
O38—H38···O15	0.825(14)	1.74(3)	2.509(5)	153(6)

Symmetry transformations used to generate equivalent atoms:
(i) -x+3/2,-y+1,z-1/2 (ii) x+1/2,-y+3/2,-z+1

Table S2. Hydrogen bonds [Å and °] for **$15H^+TsO^-\cdot MeOH$**.

D—H···*A*	$d_{D—H}$	$d_{H\cdots A}$	$d_{D\cdots A}$	<(*D*H*A*)
N13—H13···O1S	0.887(13)	2.084(17)	2.931(3)	159(3)
N33—H33···O36	0.885(13)	2.16(3)	2.663(3)	116(2)
N33—H33···O1A^{i}	0.885(13)	2.28(2)	2.987(3)	136(2)
O36—H36···O3A^{ii}	0.835(13)	1.915(16)	2.726(3)	163(3)
O37—H37···O2A	0.845(13)	1.831(18)	2.639(3)	159(4)
O38—H38···O15	0.837(13)	1.71(2)	2.491(3)	155(4)
O1S—H1S···O37^{ii}	0.87(2)	1.89(3)	2.747(3)	168(4)

Symmetry transformations used to generate equivalent atoms:
(i) x+1/2,-y+3/2,-z+1 (ii) -x+3/2,-y+1,z-1/2

Table S3. Hydrogen bonds [Å and °] for **$16H^+TsO^-\cdot ACN$** (major disorder component).

D—H···*A*	$d_{D—H}$	$d_{H\cdots A}$	$d_{D\cdots A}$	<(*D*H*A*)
N13—H13···O3A^{i}	0.877(15)	2.34(7)	2.833(9)	116(6)
N33—H33A···O3A^{i}	0.88	2.22	3.030(11)	152.4
O37—H37···O1A	0.842(14)	2.09(2)	2.884(10)	158(4)

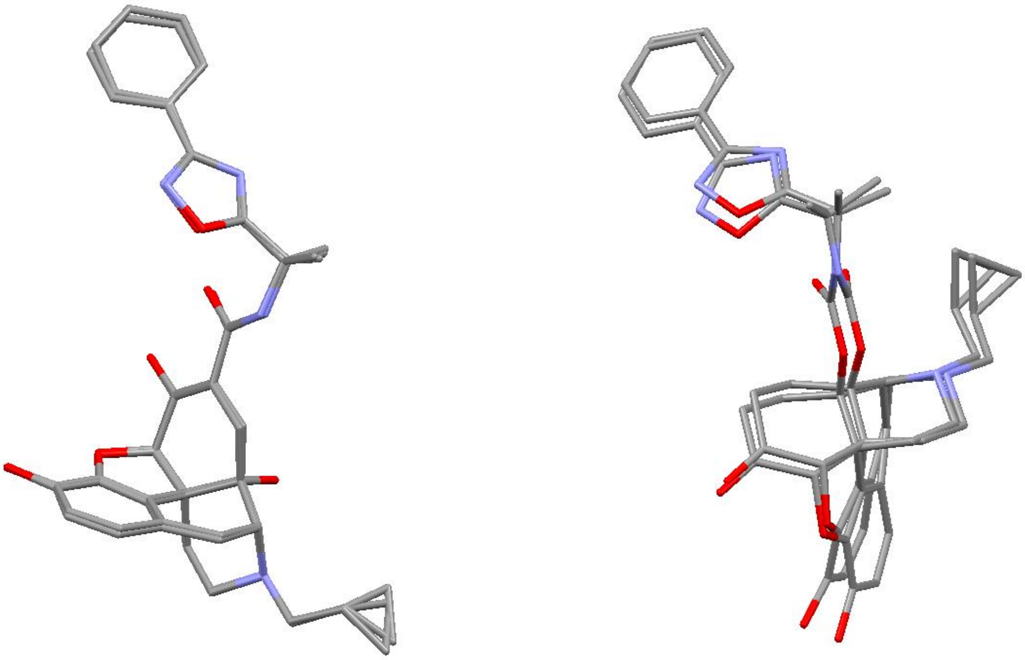
Symmetry transformations used to generate equivalent atoms:
(i) -x+1,y-1/2,-z+1

Table S4. Hydrogen bonds [Å and °] **$16H^+TsO^-\cdot ACE\cdot H_2O$**.

D—H···*A*	$d_{D—H}$	$d_{H\cdots A}$	$d_{D\cdots A}$	<(*D*H*A*)
O1W—H1WA···O2A^{i}	0.839(14)	1.948(17)	2.765(3)	164(4)
O1W—H1WB···O38	0.839(14)	2.045(17)	2.867(3)	166(4)
N33—H33···O3A	0.874(14)	1.938(18)	2.782(3)	162(3)
N13—H13···O37^{ii}	0.884(14)	2.215(15)	3.095(3)	175(3)
O37—H37···O1W	0.838(14)	1.829(17)	2.653(3)	168(4)

Symmetry transformations used to generate equivalent atoms:
(i) -x+1,y-1/2,-z+1 (ii) 2 -x+1,y+1/2,-z+1

2. Comparison of molecular geometries

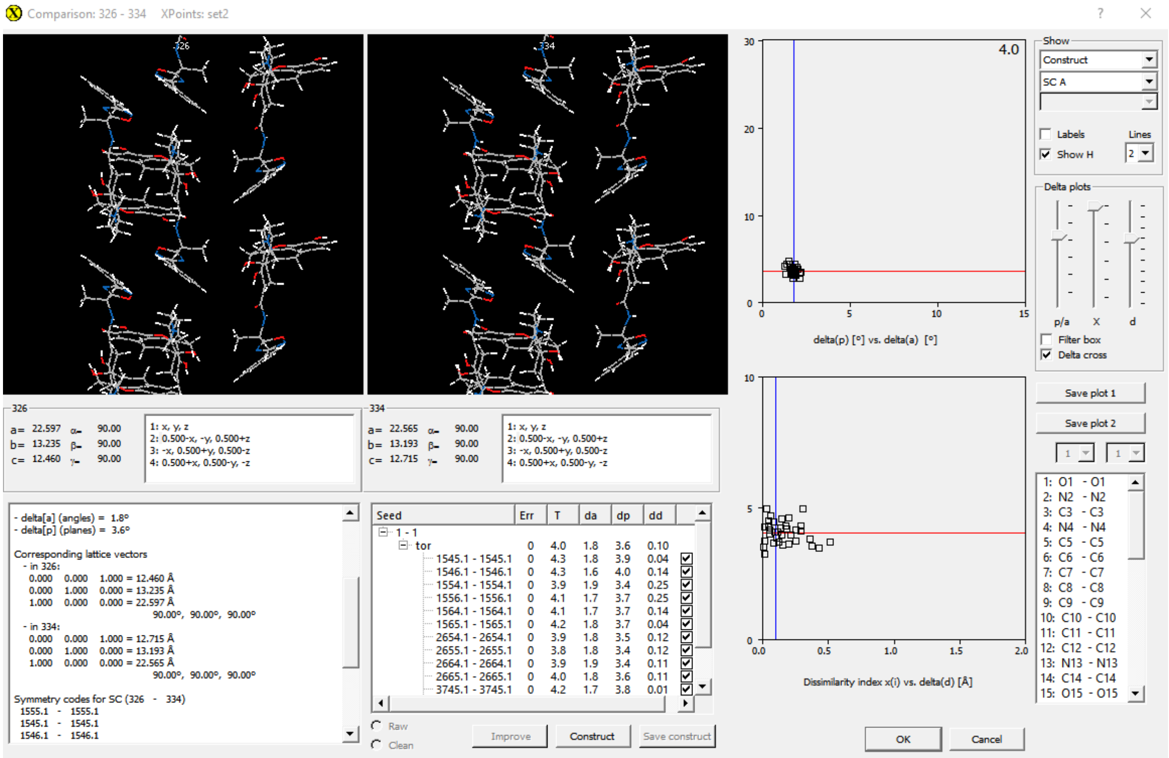


$rmsd_1$ = 0.1508 Å
a)

$rmsd_1$ = 0.4749 Å
b)

Fig. S1. Molecular overlays for cations, obtained by least-squares fitting all non-H atoms: **a)** $15H^+$ in **$15H^+TsO^-$** and **$15H^+TsO^-\cdot MeOH$**; **b)** $16H^+$ in **$16H^+TsO^-\cdot ACN$** and **$16H^+TsO^-\cdot ACE\cdot H_2O$**. The is a significant variation between the structures of the second set.

3. Comparison of crystal packing arrangements



Show
Construct
SC A
☐ Labels
☑ Show H
Lines 2
☐ Filter box
☑ Delta cross

326

a= 22.597 α= 90.00
b= 13.235 β= 90.00
c= 12.460 γ= 90.00

1: x, y, z
2: 0.500-x, -y, 0.500+z
3: -x, 0.500+y, 0.500-z
4: 0.500+x, 0.500-y, -z

334

a= 22.565 α= 90.00
b= 13.193 β= 90.00
c= 12.715 γ= 90.00

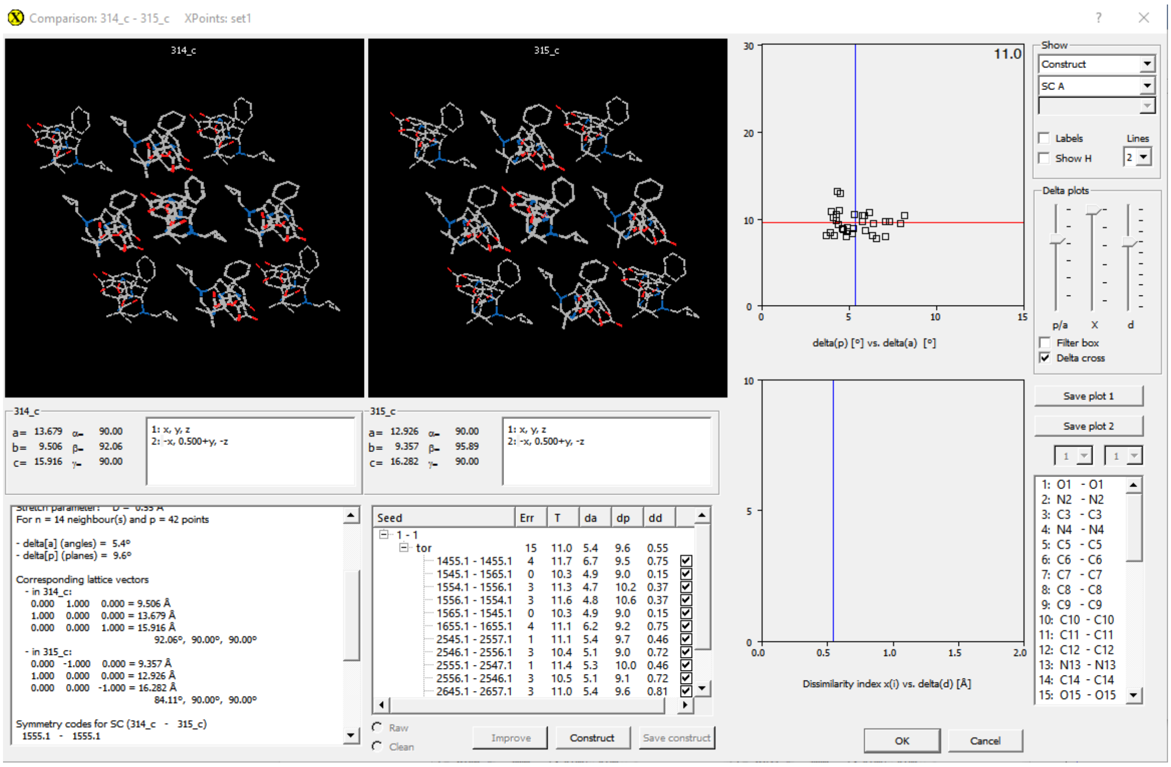
1: x, y, z
2: 0.500-x, -y, 0.500+z
3: -x, 0.500+y, 0.500-z
4: 0.500+x, 0.500-y, -z

```
- delta[a] (angles) =  1.8°
- delta[p] (planes) =  3.6°

Corresponding lattice vectors
  - in 326:
    0.000   0.000   1.000 = 12.460 Å
    0.000   1.000   0.000 = 13.235 Å
    1.000   0.000   0.000 = 22.597 Å
                        90.00°,  90.00°,  90.00°
  - in 334:
    0.000   0.000   1.000 = 12.715 Å
    0.000   1.000   0.000 = 13.193 Å
    1.000   0.000   0.000 = 22.565 Å
                        90.00°,  90.00°,  90.00°

Symmetry codes for SC (326   -   334)
  1555.1   -   1555.1
  1545.1   -   1545.1
  1546.1   -   1546.1
```

Seed	Err	T	da	dp	dd	
1 - 1						
tor	0	4.0	1.8	3.6	0.10	
1545.1 - 1545.1	0	4.3	1.8	3.9	0.04	☑
1546.1 - 1546.1	0	4.3	1.6	4.0	0.14	☑
1554.1 - 1554.1	0	3.9	1.9	3.4	0.25	☑
1556.1 - 1556.1	0	4.1	1.7	3.7	0.25	☑
1564.1 - 1564.1	0	4.1	1.7	3.7	0.14	☑
1565.1 - 1565.1	0	4.2	1.8	3.7	0.04	☑
2654.1 - 2654.1	0	3.9	1.8	3.5	0.12	☑
2655.1 - 2655.1	0	3.8	1.8	3.4	0.12	☑
2664.1 - 2664.1	0	3.9	1.9	3.4	0.11	☑
2665.1 - 2665.1	0	4.0	1.8	3.6	0.11	☑
3745.1 - 3745.1	0	4.2	1.7	3.8	0.01	☑

1: O1 - O1
2: N2 - N2
3: C3 - C3
4: N4 - N4
5: C5 - C5
6: C6 - C6
7: C7 - C7
8: C8 - C8
9: C9 - C9
10: C10 - C10
11: C11 - C11
12: C12 - C12
13: N13 - N13
14: C14 - C14
15: O15 - O15

Fig. S2. Screenshot showing the results of an *XPac* packing comparison of 15H$^+$ units in **15H$^+$TsO$^-$** (labelled as "326") and **15H$^+$TsO$^-$·MeO** ("334"), which indicate 3D isostructurality (dissimilarity index x = 4.0). Matching unit cell parameters are displayed in the bottom left box. Details of the analysis are described in the experimental section of the manuscript.



314_c

a= 13.679 α= 90.00
b= 9.506 β= 92.06
c= 15.916 γ= 90.00

1: x, y, z
2: -x, 0.500+y, -z

315_c

a= 12.926 α= 90.00
b= 9.357 β= 95.89
c= 16.282 γ= 90.00

1: x, y, z
2: -x, 0.500+y, -z

```
Stretch parameter:    D = 0.55 Å
For n = 14 neighbour(s) and p = 42 points

- delta[a] (angles) =  5.4°
- delta[p] (planes) =  9.6°

Corresponding lattice vectors
  - in 314_c:
    0.000    1.000    0.000 = 9.506 Å
    1.000    0.000    0.000 = 13.679 Å
    0.000    0.000    1.000 = 15.916 Å
                                    92.06°,  90.00°,  90.00°
  - in 315_c:
    0.000   -1.000    0.000 = 9.357 Å
    1.000    0.000    0.000 = 12.926 Å
    0.000    0.000   -1.000 = 16.282 Å
                                    84.11°,  90.00°,  90.00°

Symmetry codes for SC (314_c  -   315_c)
  1555.1  -   1555.1
```

Seed	Err	T	da	dp	dd	
1 - 1						
tor	15	11.0	5.4	9.6	0.55	
1455.1 - 1455.1	4	11.7	6.7	9.5	0.75	☑
1545.1 - 1565.1	0	10.3	4.9	9.0	0.15	☑
1554.1 - 1556.1	3	11.3	4.7	10.2	0.37	☑
1556.1 - 1554.1	3	11.6	4.8	10.6	0.37	☑
1565.1 - 1545.1	0	10.3	4.9	9.0	0.15	☑
1655.1 - 1655.1	4	11.1	6.2	9.2	0.75	☑
2545.1 - 2557.1	1	11.1	5.4	9.7	0.46	☑
2546.1 - 2556.1	3	10.4	5.1	9.0	0.72	☑
2555.1 - 2547.1	1	11.4	5.3	10.0	0.46	☑
2556.1 - 2546.1	3	10.5	5.1	9.1	0.72	☑
2645.1 - 2657.1	3	11.0	5.4	9.6	0.81	☑

1: O1 - O1
2: N2 - N2
3: C3 - C3
4: N4 - N4
5: C5 - C5
6: C6 - C6
7: C7 - C7
8: C8 - C8
9: C9 - C9
10: C10 - C10
11: C11 - C11
12: C12 - C12
13: N13 - N13
14: C14 - C14
15: O15 - O15

Fig. S3. Screenshot showing the results of an *XPac* packing comparison of 16H$^+$ units in **16H$^+$TsO^{--}·ACN** (labelled as "315") and **15H$^+$TsO$^-$·MeO·H$_2$O** ("314"), which indicate a homeostructural relationship (dissimilarity index *x* = 11.0). Matching unit cell parameters are displayed in the bottom left box. Note that the monoclinic angle β = 92.06° in **15H$^+$TsO$^-$·MeO·H$_2$O 16H$^+$TsO^{--}·ACN** is not equivalent to the report monoclinic angle β' = 95.89° in the conventional setting of **15H$^+$TsO$^-$·MeO·H$_2$O**. Rather, it is equivalent to the complementary angle of (180° – β') = 84.11°. Therefore, the true difference in stacking angles of naldemedinium units between the two structures is 7.95° (and more than twice as large as a comparison of unit cell parameters would suggest in absence of a detailed packing analysis). Details of the analysis are described in the experimental section of the manuscript.