Rich polymorphism in nicotinamide revealed by melt crystallization and crystal structure prediction

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Electronic Supplementary Information
## Content

1. Powder X-ray Diffraction (PXRD) .......................................................... 3

2. Raman Microscopy ................................................................................. 4

3. Fourier Transform Infrared (FTIR) Spectroscopy ............................... 5

4. Cross-nucleation among Forms γ, δ and ζ ........................................ 6

5. Formation of Form ι via Pseudoseeding ........................................... 7

6. Single-crystal Structure Determination .............................................. 7

7. Crystal Structure Prediction (CSP) ................................................... 11

8. Thermal Stability and Polymorphic Conversion .............................. 19

9. Supplementary Method .................................................................... 25
1. Powder X-ray Diffraction (PXRD)

Supplementary Figure 1. PXRD patterns of the NIC polymorphs
2. Raman Microscopy

Supplementary Figure 2. Raman spectra of NIC polymorphs. (a) 300-3500 cm$^{-1}$; (b) 300-1800 cm$^{-1}$; (c) 2900-3500 cm$^{-1}$
3. Fourier Transform Infrared (FTIR) Spectroscopy

Supplementary Figure 3. FTIR spectra of NIC polymorphs. (a) 500-3500 cm$^{-1}$; (b) 1000-1500 cm$^{-1}$; (c) 2800-3500 cm$^{-1}$
4. Cross-nucleation among Forms $\gamma$, $\delta$ and $\zeta$

Supplementary Figure 4. Cross-nucleation of Form $\delta$ on the growth fronts of Forms $\gamma$ and $\zeta$ at 70 °C. (a) Seeds of Form $\gamma$ were prepared first and then quenched at 70 °C to cross-nucleate Form $\delta$. (b) A NIC melt was quenched at room temperature to nucleate Form $\delta$ and then was transferred to 105 °C for cross-nucleating Form $\zeta$. This sample was quenched at 70 °C to trigger the cross-nucleation of Form $\delta$ on the surface of Form $\zeta$.

Supplementary Figure 5. Forms $\delta$ and $\zeta$ interactively cross-nucleate on each other at 95 °C. (a) Seeds of Form $\delta$ was transferred to 95 °C; (b) Form $\zeta$ cross-nucleated on the growth front of Form $\delta$ after 2 s; (c) Form $\delta$ nucleated on the surface of newly-grown Form $\zeta$ after 4 s; (d) Form $\zeta$ nucleated and grew on the surface of Form $\delta$ after 6 s.
5. Formation of Form \( \iota \) \textit{via} Pseudoseeding

Supplementary Figure 6. Formation of Form \( \iota \) and \( \iota \)-to-\( \alpha \) phase conversion at 90 °C. (a) Iso-nicotinamide (iso-NIC) Form I was seeded on the edge of the nicotinamide (NIC) melt. (b) NIC Form \( \iota \) nucleated on iso-NIC seeds; (c) NIC Form \( \iota \) rapidly converted to Form \( \alpha \)

6. Single-crystal Structure Determination

Supplementary Figure 7. Single crystals of NIC polymorphs grown from melt microdroplets
**Supplementary Table 1.** Cultivation conditions of NIC single crystals

| Polymorph | Partial melting temperature (°C) | Cultivation temperature (°C) | $T_{\text{Cultivation}}/T_{\text{Melting}}$ |
|-----------|----------------------------------|------------------------------|--------------------------------------------|
| α         | 129                              | 127                          | 0.995                                      |
| β         | 116.5                            | 110                          | 0.982                                      |
| γ         | 115                              | 110                          | 0.987                                      |
| δ         | 114                              | 108.5                        | 0.986                                      |
| ε         | 110.5                            | 108                          | 0.993                                      |
| ζ         | 109.5                            | 108                          | 0.996                                      |
| η         | 108                              | 106                          | 0.995                                      |
| θ         | 104.5                            | 102                          | 0.992                                      |
| ι         | 103                              | 95                           | 0.979                                      |

![Form α](image1.png)

![Form β](image2.png)

![Form γ](image3.png)

![Form δ](image4.png)
Supplementary Figure 8. Calculated and experimental PXRD patterns of NIC polymorphs. (a) Form α; (b) Form β; (c) Form γ; (d) Form δ; (e) Form ε; (f) Form ζ; (g) Form η; (h) Form θ; (i) Form ι.
**Supplementary Figure 9.** Crystal packing diagrams of NIC polymorphs. All structures are shown along the $b$-axis, except for Forms $\delta$ and $\theta$, where the structures are shown along the $a$-axis. Different colors are used to indicate conformationally distinct molecules.

**Supplementary Table 2.** Torsion angle $\theta$ (C5-C4-C6-N2') in 37 NIC conformations

| Polymorph | $\theta$ (C5-C4-C6-N2') |
|-----------|-------------------------|
|           | Mol. 1 | Mol. 2 | Mol. 3 | Mol. 4 |
| $\alpha$  | -23.1  | -      | -      | -      |
| $\beta$   | 12.6   | -8.7   | -23.1  | -15.6  |
| $\gamma$  | 0.6    | -175.1 | 15.5   | 178.2  |
| $\delta$  | 0.1    | 160.9  | -      | -      |
| $\epsilon$| -151.5 | -      | -      | -      |
| $\zeta$   | 1.0    | -175.3 | -      | -      |
| $\eta$    | 25.4   | -3.2   | -      | -      |
| $\theta$  | -6.0   | 0.9    | 7.3    | -176.7 |
|           | -171.0 | 2.8    | -5.3   | 173.1  |
|           | -5.1   | -169.1 | -14.4  | 176.3  |
|           | 4.0    | 4.5    | 0.9    | 8.2    |
|           | -3.6   | -4.3   | 167.7  | -2.6   |
| $\iota$  | -28.8  | -      | -      | -      |
7. Crystal Structure Prediction (CSP)

Supplementary Table 3. Details of predicted low-energy structures of NIC

| Rank | Relative Lattice Energy (kJ/mol) | Cell Dimensions | Density (g/cm$^3$) | Z' | Space Group | Conformer Type* | Corresponding Polymorph |
|------|---------------------------------|-----------------|-------------------|----|-------------|-----------------|------------------------|
|      |                                 | a (Å)           | b (Å)             | c (Å) | α | ρ | γ |                |                      |                         |
| 1    | 0                               | 3.925           | 15.217            | 9.475  | 90.000 | 97.211 | 90.000 | 1.445 | 1 P21/c (14) | I | α |                 |
| 2    | 0.53                            | 4.489           | 28.482            | 8.941  | 90.000 | 87.367 | 90.000 | 1.421 | 2 P21/c (14) | I, I | - |                 |
| 3    | 1.1                             | 12.969          | 5.109             | 17.111 | 90.000 | 92.998 | 90.000 | 1.433 | 2 P21/c (14) | I, I | - |                 |
| 4    | 1.34                            | 3.881           | 10.299            | 19.458 | 90.000 | 47.769 | 90.000 | 1.409 | 1 P21/c (14) | II | - |                 |
| 5    | 1.45                            | 9.962           | 5.100             | 14.042 | 90.000 | 127.225 | 90.000 | 1.428 | 1 P21/c (14) | I | - |                 |
| 6    | 1.47                            | 13.183          | 12.193            | 3.762  | 93.036 | 94.538 | 71.330 | 1.421 | 2 P-1 (2) | I, I | η |                 |
| 7    | 1.49                            | 7.399           | 20.949            | 7.342  | 90.000 | 90.249 | 90.000 | 1.426 | 2 P21/c (14) | I, II | δ |                 |
| 8    | 1.73                            | 5.174           | 14.346            | 3.814  | 90.000 | 86.075 | 90.000 | 1.436 | 1 P21 (4) | II | ε |                 |
| 9    | 2.22                            | 5.058           | 5.735             | 20.134 | 90.000 | 77.909 | 90.000 | 1.42 | 1 P21/c (14) | II | - |                 |
| 10   | 2.37                            | 8.117           | 5.044             | 13.955 | 90.000 | 96.975 | 90.000 | 1.43 | 1 P21/c (14) | I | - |                 |
| 11   | 2.39                            | 9.996           | 6.066             | 9.884  | 90.000 | 101.461 | 90.000 | 1.381 | 1 P21/c (14) | I | ι |                 |
| 12   | 2.57                            | 3.686           | 12.941            | 12.654 | 104.621 | 89.252 | 95.395 | 1.395 | 2 P-1 (2) | I, I | - |                 |
| 13   | 2.70                            | 5.652           | 20.033            | 5.067  | 84.828 | 88.279 | 89.495 | 1.42 | 2 P-1 (2) | I, II | - |                 |
| 14   | 2.72                            | 7.518           | 7.235             | 24.531 | 90.000 | 120.218 | 90.000 | 1.407 | 2 P21/c (14) | II, II | - |                 |
|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |   |
| 15 | 2.83 | 14.980 | 3.884 | 10.311 | 90.000 | 108.918 | 90.000 | 1.429 | 1 | P21/c (14) | I | - |
| 16 | 2.97 | 13.737 | 3.916 | 10.566 | 90.000 | 92.663 | 90.000 | 1.429 | 1 | P21/c (14) | I | - |
| 17 | 3.08 | 5.101 | 5.669 | 20.042 | 90.000 | 94.097 | 90.000 | 1.403 | 1 | P21/c (14) | I | - |
| 18 | 3.11 | 3.776 | 28.797 | 6.696 | 90.000 | 129.034 | 90.000 | 1.434 | 1 | P21/c (14) | II | - |
| 19 | 3.14 | 8.040 | 5.060 | 30.382 | 90.000 | 112.595 | 90.000 | 1.422 | 2 | P21/c (14) | I, I | - |
| 20 | 3.14 | 15.066 | 5.018 | 17.468 | 90.000 | 58.847 | 90.000 | 1.436 | 2 | P21/c (14) | I, I | - |
| 21 | 3.27 | 28.189 | 3.890 | 10.422 | 90.000 | 89.044 | 90.000 | 1.42 | 2 | P21/c (14) | I, II | - |
| 22 | 3.31 | 18.082 | 7.139 | 8.968 | 90.000 | 91.632 | 90.000 | 1.402 | 2 | P21/c (14) | I, I | - |
| 23 | 3.37 | 9.882 | 5.099 | 22.885 | 90.000 | 97.068 | 90.000 | 1.418 | 2 | P21/c (14) | I, I | - |
| 24 | 3.42 | 5.034 | 5.488 | 20.343 | 90.000 | 90.000 | 90.000 | 1.443 | 1 | P212121 (19) | II | - |
| 25 | 3.44 | 6.284 | 14.218 | 8.333 | 90.000 | 128.530 | 90.000 | 1.393 | 1 | P21/c (14) | I | - |
| 26 | 3.45 | 7.700 | 7.436 | 11.011 | 90.000 | 67.642 | 90.000 | 1.391 | 1 | P21/c (14) | I | - |
| 27 | 3.48 | 14.518 | 5.166 | 3.879 | 97.019 | 84.483 | 91.142 | 1.411 | 1 | P-1 (2) | I | - |
| 28 | 3.48 | 11.247 | 5.125 | 9.983 | 86.839 | 97.710 | 89.975 | 1.425 | 2 | P-1 (2) | I, II | - |
| 29 | 3.49 | 13.954 | 5.136 | 16.037 | 90.000 | 83.318 | 90.000 | 1.421 | 2 | P21/c (14) | I, II | - |
| 30 | 3.5 | 5.086 | 5.676 | 19.904 | 90.000 | 90.000 | 90.000 | 1.412 | 1 | P212121 (19) | I | - |
| 31 | 3.51 | 20.294 | 5.080 | 5.487 | 90.000 | 89.914 | 90.000 | 1.434 | 2 | P21 (4) | I, II | - |
| 32 | 3.54 | 5.390 | 5.070 | 20.737 | 90.000 | 91.638 | 90.000 | 1.432 | 1 | P21/c (14) | II | - |
| 33 | 3.55 | 5.098 | 14.493 | 18.125 | 90.000 | 121.317 | 90.000 | 1.418 | 2 | P21/c (14) | II, II | - |
| 34 | 3.57 | 8.704 | 5.100 | 12.869 | 87.806 | 86.431 | 87.132 | 1.425 | 2 | P-1 (2) | I, I | - |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 35 | 3.59 | 11.544 | 5.047 | 19.792 | 90.000 | 82.202 | 90.000 | 1.42 | 2 | P21/c (14) | I, I |   |   |
| 36 | 3.76 | 3.809 | 5.155 | 29.070 | 89.643 | 90.164 | 95.525 | 1.428 | 2 | P-1 (2) | I, II |   |   |
| 37 | 3.8 | 14.983 | 3.833 | 9.914 | 90.000 | 90.000 | 90.000 | 1.425 | 1 | Pca21 (29) | II |   |   |
| 38 | 3.83 | 31.732 | 5.214 | 16.636 | 90.000 | 123.874 | 90.000 | 1.42 | 2 | C2/c (15) | I, II |   |   |
| 39 | 3.84 | 15.235 | 3.956 | 20.923 | 90.000 | 64.748 | 90.000 | 1.422 | 2 | P21/c (14) | I, I |   |   |
| 40 | 3.89 | 9.909 | 5.130 | 22.565 | 90.000 | 97.083 | 90.000 | 1.425 | 2 | P21/c (14) | I, II |   |   |
| 41 | 3.89 | 17.008 | 5.144 | 13.824 | 90.000 | 107.953 | 90.000 | 1.41 | 2 | P21/c (14) | I, II |   |   |
| 42 | 4 | 14.078 | 3.910 | 20.803 | 90.000 | 85.113 | 90.000 | 1.422 | 2 | P21/c (14) | I, I |   |   |
| 43 | 4.02 | 15.219 | 5.063 | 16.179 | 90.000 | 66.267 | 90.000 | 1.422 | 2 | P21/c (14) | I, I |   |   |
| 44 | 4.06 | 17.704 | 6.741 | 9.834 | 90.000 | 91.279 | 90.000 | 1.383 | 2 | P21/c (14) | I, II |   |   |
| 45 | 4.08 | 8.899 | 6.803 | 9.745 | 90.000 | 91.420 | 90.000 | 1.375 | 1 | P21/c (14) | II |   |   |
| 46 | 4.1 | 5.124 | 11.270 | 11.206 | 66.704 | 83.063 | 91.151 | 1.379 | 2 | P-1 (2) | I, I |   |   |
| 47 | 4.1 | 28.406 | 3.860 | 10.404 | 90.000 | 93.134 | 90.000 | 1.424 | 2 | P21/c (14) | I, II |   |   |
| 48 | 4.12 | 8.783 | 12.957 | 5.167 | 98.157 | 101.024 | 87.672 | 1.42 | 2 | P-1 (2) | I, II |   |   |
| 49 | 4.13 | 28.751 | 3.804 | 5.216 | 84.551 | 92.895 | 91.187 | 1.43 | 2 | P-1 (2) | II, II |   |   |
| 50 | 4.14 | 5.196 | 28.733 | 3.826 | 93.328 | 85.156 | 88.425 | 1.428 | 2 | P-1 (2) | I, II |   |   |
| 51 | 4.21 | 29.483 | 3.803 | 10.226 | 90.000 | 99.407 | 90.000 | 1.434 | 2 | P21/c (14) | II, II |   |   |
| 52 | 4.2 | 29.760 | 3.805 | 10.432 | 90.000 | 99.739 | 90.000 | 1.399 | 2 | P21/c (14) | II, II |   |   |
| 53 | 4.21 | 5.170 | 29.159 | 3.805 | 90.000 | 96.167 | 90.000 | 1.423 | 2 | P21 (4) | I, II |   |   |
| 54 | 4.22 | 29.201 | 3.781 | 5.179 | 94.902 | 87.861 | 91.252 | 1.425 | 2 | P-1 (2) | II, II |   |   |
|    |   |   |   |   |   |   |   |   |   |   |   |   |
|----|---|---|---|---|---|---|---|---|---|---|---|---|
| 55 | 4.22 | 7.035 | 5.087 | 16.183 | 90.000 | 97.923 | 90.000 | 1.414 | 1 | P21/c (14) | I | - |
| 56 | 4.24 | 8.466 | 13.091 | 5.178 | 88.478 | 86.437 | 86.553 | 1.419 | 2 | P-1 (2) | II, II | - |
| 57 | 4.26 | 14.583 | 3.869 | 10.443 | 90.000 | 75.728 | 90.000 | 1.421 | 1 | P21/c (14) | II | - |
| 58 | 4.27 | 27.938 | 3.922 | 10.530 | 90.000 | 96.260 | 90.000 | 1.415 | 2 | P21/c (14) | I, II | - |
| 59 | 4.28 | 35.570 | 3.762 | 20.968 | 90.000 | 125.528 | 90.000 | 1.421 | 2 | C2/c (15) | II, II | - |
| 60 | 4.31 | 8.367 | 5.182 | 13.437 | 92.682 | 96.109 | 90.000 | 1.409 | 2 | P-1 (2) | I, II | - |
| 61 | 4.32 | 12.951 | 5.088 | 8.669 | 90.000 | 86.264 | 90.000 | 1.423 | 2 | P21 (4) | I, I | - |
| 62 | 4.33 | 7.948 | 8.151 | 10.099 | 80.733 | 106.920 | 75.803 | 1.381 | 2 | P-1 (2) | I, II | - |
| 63 | 4.34 | 8.418 | 6.900 | 9.953 | 90.000 | 92.028 | 90.000 | 1.404 | 1 | P21/c (14) | I | - |
| 64 | 4.35 | 15.374 | 5.121 | 15.891 | 90.000 | 113.228 | 90.000 | 1.411 | 2 | P21/c (14) | I, I | - |
| 65 | 4.39 | 29.043 | 3.824 | 10.336 | 90.000 | 81.062 | 90.000 | 1.431 | 2 | P21/c (14) | I, II | - |
| 66 | 4.41 | 14.750 | 3.898 | 20.770 | 90.000 | 73.221 | 90.000 | 1.419 | 2 | P21/c (14) | I, I | - |
| 67 | 4.42 | 20.816 | 5.815 | 10.003 | 90.000 | 103.182 | 90.000 | 1.376 | 2 | P21/c (14) | I, II | - |
| 68 | 4.44 | 8.975 | 7.036 | 9.209 | 90.000 | 92.232 | 90.000 | 1.396 | 1 | P21/c (14) | I | - |
| 69 | 4.45 | 6.911 | 16.205 | 5.115 | 89.478 | 87.535 | 96.469 | 1.427 | 2 | P-1 (2) | I, II | - |
| 70 | 4.45 | 5.010 | 14.345 | 8.125 | 90.000 | 91.026 | 90.000 | 1.389 | 1 | P21/c (14) | I | - |
| 71 | 4.46 | 5.043 | 14.544 | 7.900 | 90.000 | 91.377 | 90.000 | 1.4 | 1 | P21/c (14) | II | - |
| 72 | 4.48 | 5.239 | 28.649 | 3.811 | 88.174 | 84.994 | 84.958 | 1.43 | 2 | P-1 (2) | I, II | - |
| 73 | 4.48 | 3.838 | 5.286 | 14.364 | 82.405 | 89.350 | 82.293 | 1.417 | 1 | P-1 (2) | I | - |
| 74 | 4.48 | 29.065 | 3.830 | 10.299 | 90.000 | 82.461 | 90.000 | 1.427 | 2 | P21/c (14) | I, II | - |

S14
| ID | a   | b   | c   | χ1  | χ2  | D1  | D2  | P  | Space Group |  \( h \) \( k \) \( l \) | Comment |
|----|-----|-----|-----|-----|-----|-----|-----|---|-------------|---------|---------|
| 75 | 4.49 | 28.521 | 5.231 | 3.905 | 98.848 | 88.113 | 85.176 | 1.416 | P-1 (2) | I, II | - |
| 76 | 4.5 | 29.028 | 3.820 | 10.425 | 90.000 | 79.863 | 90.000 | 1.425 | P21/c (14) | II, II | - |
| 77 | 4.51 | 8.557 | 5.100 | 26.307 | 90.000 | 84.959 | 90.000 | 1.419 | P21/c (14) | I, I | - |
| 78 | 4.51 | 15.180 | 5.161 | 16.975 | 90.000 | 120.133 | 90.000 | 1.41 | P21/c (14) | II, II | - |
| 79 | 4.51 | 13.973 | 5.099 | 20.079 | 90.000 | 53.116 | 90.000 | 1.418 | P21/c (14) | I, II | - |
| 80 | 4.52 | 8.552 | 5.203 | 31.202 | 90.000 | 55.229 | 90.000 | 1.423 | P21/c (14) | II, II | - |
| 81 | 4.53 | 27.679 | 3.949 | 10.534 | 90.000 | 95.199 | 90.000 | 1.415 | P21/c (14) | I, II | - |
| 82 | 4.56 | 6.828 | 5.162 | 16.206 | 90.000 | 95.107 | 90.000 | 1.426 | P21/c (14) | II | - |
| 83 | 4.56 | 8.202 | 5.122 | 27.533 | 90.000 | 96.027 | 90.000 | 1.41 | P21/c (14) | I, II | - |
| 84 | 4.56 | 13.884 | 5.096 | 8.141 | 90.000 | 96.597 | 90.000 | 1.417 | P21 (4) | I, II | - |
| 85 | 4.57 | 30.774 | 3.819 | 10.100 | 90.000 | 107.202 | 90.000 | 1.431 | C2/c (15) | II | - |
| 86 | 4.6 | 28.326 | 5.294 | 3.857 | 98.840 | 88.032 | 88.666 | 1.421 | P-1 (2) | I, II | - |
| 87 | 4.61 | 11.421 | 5.076 | 20.099 | 90.000 | 83.614 | 90.000 | 1.401 | P21/c (14) | I, I | - |
| 88 | 4.62 | 8.527 | 5.217 | 13.373 | 81.145 | 90.638 | 78.471 | 1.41 | P-1 (2) | II, II | - |
| 89 | 4.62 | 20.204 | 5.133 | 22.102 | 90.000 | 98.464 | 90.000 | 1.431 | C2/c (15) | I, II | - |
| 90 | 4.64 | 15.278 | 5.141 | 15.990 | 90.000 | 66.419 | 90.000 | 1.41 | P21/c (14) | I, II | - |
| 91 | 4.66 | 10.471 | 5.157 | 11.522 | 90.000 | 66.525 | 90.000 | 1.421 | P21 (4) | I, II | - |
| 92 | 4.69 | 10.547 | 8.056 | 8.030 | 107.755 | 99.302 | 108.692 | 1.376 | P-1 (2) | I, II | ζ |
| 93 | 4.72 | 29.119 | 3.797 | 10.387 | 90.000 | 80.979 | 90.000 | 1.43 | P21/c (14) | I, II | - |
| 94 | 4.74 | 3.763 | 5.212 | 14.554 | 94.434 | 92.416 | 96.178 | 1.435 | P-1 (2) | II | - |

S15
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 95 | 4.77 | 34.668 | 5.130 | 13.482 | 90.000 | 108.386 | 90.000 | 1.426 | 2 | C2/c (15) | I, II |   |   |
| 96 | 4.77 | 9.169 | 5.117 | 30.234 | 90.000 | 126.232 | 90.000 | 1.418 | 2 | P21/c (14) | II, II |   |   |
| 97 | 4.77 | 22.964 | 10.050 | 5.083 | 90.000 | 90.000 | 90.000 | 1.383 | 2 | P212121 (19) | I, I |   |   |
| 98 | 4.77 | 11.322 | 5.082 | 20.043 | 90.000 | 81.203 | 90.000 | 1.424 | 2 | P21/c (14) | I, II |   |   |
| 99 | 4.77 | 29.023 | 5.176 | 3.817 | 96.414 | 91.562 | 91.304 | 1.425 | 2 | P-1 (2) | I, II |   |   |
| 100 | 4.79 | 13.872 | 5.200 | 20.304 | 90.000 | 52.013 | 90.000 | 1.406 | 2 | P21/c (14) | I, II |   |   |
| 101 | 4.79 | 14.490 | 4.083 | 10.439 | 90.000 | 109.979 | 90.000 | 1.398 | 1 | P21/c (14) | I |   |   |
| 102 | 4.79 | 15.612 | 3.788 | 20.978 | 90.000 | 114.430 | 90.000 | 1.436 | 2 | P21/c (14) | II, II |   |   |
| 103 | 4.8 | 8.604 | 5.091 | 30.197 | 90.000 | 120.114 | 90.000 | 1.418 | 2 | P21/c (14) | I, I |   |   |
| 104 | 4.84 | 9.951 | 6.800 | 20.121 | 90.000 | 59.575 | 90.000 | 1.382 | 2 | P21/c (14) | I, I |   |   |
| 105 | 4.84 | 27.331 | 4.202 | 10.317 | 90.000 | 79.431 | 90.000 | 1.393 | 2 | P21/c (14) | I, I |   |   |
| 106 | 4.85 | 13.772 | 6.454 | 6.796 | 98.306 | 91.531 | 83.758 | 1.365 | 2 | P-1 (2) | II, II |   |   |
| 107 | 4.85 | 12.920 | 5.099 | 17.353 | 90.000 | 93.711 | 90.000 | 1.422 | 2 | P21/c (14) | I, I |   |   |
| 108 | 4.86 | 3.887 | 29.301 | 5.129 | 90.000 | 96.967 | 90.000 | 1.399 | 1 | P21/c (14) | I |   |   |
| 109 | 4.86 | 7.487 | 5.149 | 38.496 | 90.000 | 129.130 | 90.000 | 1.409 | 2 | P21/c (14) | II, II |   |   |
| 110 | 4.89 | 14.698 | 3.846 | 10.064 | 90.000 | 93.193 | 90.000 | 1.428 | 1 | P21/c (14) | II |   |   |
| 111 | 4.89 | 8.556 | 13.362 | 5.234 | 89.892 | 76.551 | 93.129 | 1.396 | 2 | P-1 (2) | I, II |   |   |
| 112 | 4.9 | 27.869 | 3.885 | 10.581 | 90.000 | 94.882 | 90.000 | 1.421 | 2 | P21/c (14) | I, I |   |   |
| 113 | 4.91 | 16.446 | 3.894 | 21.090 | 90.000 | 122.398 | 90.000 | 1.423 | 2 | P21/c (14) | I, I |   |   |
| 114 | 4.91 | 5.277 | 14.414 | 3.896 | 86.837 | 80.386 | 99.677 | 1.413 | 1 | P-1 (2) | II |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 115 | 4.91 | 7.311 | 10.764 | 7.983 | 69.878 | 83.423 | 96.205 | 1.402 | 2 | P-1 (2) | I, II |
| 116 | 4.92 | 28.114 | 3.860 | 10.573 | 90.000 | 96.133 | 90.000 | 1.422 | 2 | P21/c (14) | I, II |
| 117 | 4.93 | 10.381 | 5.145 | 21.314 | 90.000 | 93.127 | 90.000 | 1.427 | 2 | P21/c (14) | II, II |
| 118 | 4.94 | 8.453 | 13.419 | 5.207 | 79.269 | 96.926 | 94.814 | 1.411 | 2 | P-1 (2) | I, II |
| 119 | 4.94 | 13.644 | 5.121 | 20.221 | 90.000 | 53.524 | 90.000 | 1.428 | 2 | P21/c (14) | I, II |
| 120 | 4.94 | 3.797 | 29.395 | 5.173 | 94.289 | 96.574 | 91.178 | 1.419 | 2 | P-1 (2) | I, II |
| 121 | 4.96 | 5.086 | 6.906 | 16.661 | 90.000 | 97.346 | 90.000 | 1.398 | 1 | P21/c (14) | I |
| 122 | 4.97 | 13.686 | 5.123 | 16.347 | 90.000 | 95.854 | 90.000 | 1.423 | 2 | P21/c (14) | I, II |
| 123 | 4.97 | 26.726 | 5.145 | 16.459 | 90.000 | 94.095 | 90.000 | 1.437 | 2 | C2/c (15) | I, II |
| 124 | 4.98 | 18.546 | 6.838 | 9.314 | 90.000 | 90.790 | 90.000 | 1.374 | 2 | P21/c (14) | I, II |

* The conformers were divided into two types according to the value of the torsion angle θ (C5-C4-C6-N2') : type I refers to the conformers with -45° < θ < 45°, and type II refers to the conformers with 135° < θ ≤ 180° or -180° ≤ θ < -135°.
Supplementary Table 4. Comparison of the predicted structures with the experimentally observed structures of NIC

| Structure | RMSD15 (Å) | Relative Lattice Energy (kJ/mol) | Rank | Z’ |
|-----------|------------|----------------------------------|------|----|
| Form α    | 0.228      | 0                                | 1    | 1  |
| Form β    | 0.077      | 3.09                             | NI*  | 4  |
| Form γ    | 0.045      | 2.03                             | NI*  | 4  |
| Form δ    | 0.105      | 1.49                             | 7    | 2  |
| Form ε    | 0.107      | 1.73                             | 8    | 1  |
| Form ζ    | 0.811      | 4.69                             | 92   | 2  |
| Form η    | 0.135      | 1.47                             | 6    | 2  |
| Form θ    | 0.038      | 2.61                             | NI*  | 20 |
| Form ι    | 0.202      | 2.39                             | 11   | 1  |

*NI: The structure was not included in this CSP search.
8. Thermal Stability and Polymorphic Conversion

Supplementary Figure 10. Differential scanning calorimetry (DSC) curves of four NIC polymorphs. All measurements were performed at a heating rate of 10 °C/min (n=4)

Supplementary Table 5. Melting point ($T_m$) and melting enthalpy ($\Delta H_m$) of NIC polymorphs. The values of $T_m$ and $\Delta H_m$ were determined by using DSC at a heating rate of 10 °C/min (n=4). $T_m$ values were also measured by using hot-stage combined with a polarized optical microscopy (POM)

| Crystal form | $T_{m, peak}(DSC)$ (°C) | $\Delta H_m$ (kJ/mol) | $T_{m}(POM)$ (°C) |
|--------------|-------------------------|-----------------------|-------------------|
| α            | 131.9±0.2               | 20.0±0.7              | 129               |
| β            | 118.9±0.3               | 17.5±0.4              | 116.5             |
| γ            | 113.8±0.1               | 17.0±0.1              | 115               |
| δ            | -                       | -                     | 114               |
| ε            | 110.6±0.1               | 16.4±0.1              | 110.5             |
| ζ            | -                       | -                     | 109.5             |
| η            | -                       | -                     | 108               |
| θ            | -                       | -                     | 104.5             |
| ι            | -                       | -                     | 103               |
Supplementary Figure 11. PXRD patterns of the polymorphic conversion from metastable polymorphs to stable polymorph α. (a) β-to-α phase conversion; (b) γ-to-α phase conversion; (c) θ-to-α phase conversion; (d) ε-to-α phase conversion.
Supplementary Figure 12. Polymorphic conversion from Form θ to Form β. (a-c) POM images; (d) Raman spectra.

Supplementary Figure 13. Polymorphic conversion from Form θ to Form γ. (a-c) POM images; (d) Raman spectra.
Supplementary Figure 14. Polymorphic conversion from Form θ to Form ε. (a-c) POM images; (d) Raman spectra.

Supplementary Figure 15. Polymorphic conversion from Form ε to Form β. (a-c) POM images; (d) Raman spectra.
Supplementary Figure 16. Polymorphic conversion from Form ε to Form γ. (a-c) POM images; (d) Raman spectra

Supplementary Figure 17. Time-resolved FTIR spectra showing the η-to-α polymorphic conversion
Supplementary Figure 18. Cross-nucleation of Form $\zeta$ on Form $\delta$ and the following $\zeta$-to-$\gamma$ polymorphic conversion at 105 °C. (a) A NIC melt was quenched at room temperature to nucleate Form $\delta$ and then this sample was transferred to a hot-stage preset as 105 °C to cross-nucleate Form $\zeta$; (b) Form $\delta$ transformed to Form $\gamma$ and this newly-formed Form $\gamma$ triggered the $\zeta$-to-$\gamma$ polymorphic conversion.

Supplementary Figure 19. Polymorphic conversion from Form $\iota$ to Form $\epsilon$. (a) Initial; (b) 8s; (c) 13 s.
9. Supplementary Methods

The methods for preparing crystallographically pure samples of the NIC polymorphs are described below.

Form α. The commercially available sample of NIC was Form α.

Form β. To prepare a crystallographically pure Form β, Form θ was first prepared at 60-70 °C, possibly concomitant with Forms δ and ζ. After Form θ partially converted to Form β, the sample was heated to a temperature just below the melting point of Form β to melt Form θ and other possibly present metastable polymorphs, followed by cooling to 100 °C to grow pure Form β.

Form γ. To prepare a crystallographically pure Form γ sample, an NIC melt was quenched at 30-80 °C to nucleate Form δ. After Form δ partially converted to Form γ, this sample was heated just below the melting point of Form γ to melt Form δ and other possible metastable polymorphs. Then, the seeds of Form γ were grown at 105 °C, yielding a pure Form γ sample.

Form δ. A crystallographically pure Form δ sample can be obtained by crystallizing an NIC melt at room temperature. However, this Form δ sample rapidly converted to Form γ.

Form ε. Crystallization of an NIC melt at 70-80 °C could yield a crystallographically pure Form ε sample or a Form ε sample concomitant with Forms δ and θ.

Form ζ. Form ζ usually cross-nucleates on the surface of Form γ between 90-95 °C or Form δ between 90-105 °C. A crystallographically pure ζ-NIC sample could be obtained by seeding ζ-NIC seeds in a fresh melt droplet at 105 °C.

Form η. Cold crystallization at 104 °C randomly yielded pure Form η or a concomitant sample containing other polymorphs. The nucleation probability of Form η was found to be extremely low.

Form θ. A crystallographically pure Form θ sample can be obtained by nucleating an NIC melt at 60 °C and consuming all materials without polymorphic conversion to Form β. Form θ often concomitantly nucleates with Forms δ and ζ and then converts to Form β. Therefore, obtaining pure θ is a probabilistic event.

Form l. Seeding iso-nicotinamide (iso-NIC) Form l at the edge of an NIC melt sample between 70-95 °C randomly triggered the nucleation of Form α and/or Form l. Because Form α always nucleates from the site of seeding and converts Form l, it is difficult to obtain pure Form l.