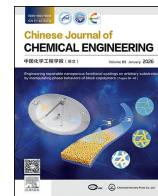




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Full Length Article

Cocrystal engineering for efficient separation of 4-bromo-3-methylphenol: Design of experiments, characterization, crystal structure and calculation

Chunxiao Wang, Shuai Wang, Hongsen Zhang, Chao Li^{*}, Renzhong Qiao^{*}

State Key Laboratory of Chemical Resource Engineering, Beijing University of Chemical Technology, Beijing 100029, China

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ABSTRACT

4-Bromo-3-methylphenol (BMP) is an important chemical intermediate with wide applications in the fields of medicine and pesticides. The synthesis of BMP from *m*-cresol via bromination is easy to carry out on an industrial scale. However, due to the formation of regioisomeric impurities during bromination and the low melting point of BMP, the separation process is prone to the formation of oily substances, resulting in low yield and purity. In this work, a new cocrystallization engineering approach was proposed to separate and purify BMP. Through design of experiments, the cocrystallization process of BMP and triethylenediamine (DABCO) was optimized using a minimum-run resolution IV screening design combined with response surface methodology. In addition, the obtained 2BMP-DABCO powder was characterized by thermal analysis, powder X-ray diffraction, infrared spectroscopy, and scanning electron microscopy. Single crystals of 2BMP-DABCO were grown from acetone by slow evaporation, and detailed structural information was obtained through single-crystal X-ray diffraction. The self-assembly mechanism was further clarified by density functional theory calculations. This study provides a simple, robust, and scalable method for the production of BMP and offers a reference for the separation and purification of phenolic substances.

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1. Introduction

4-Bromo-3-methylphenol (BMP) is an important chemical intermediate and is used as a starting material in the commercial route of crisaborole [1,2]. Additionally, it is widely applied as a basic synthetic building block in the development of new drugs [3–6]. The industrial synthesis of BMP is mainly achieved by brominating *m*-cresol [7]. Due to the positioning effect of the phenolic hydroxyl group and the methyl group, a large amount of regioisomeric impurities with similar properties are produced. Moreover, the low melting point of BMP (61–63 °C) further leads to the formation of an oily state during separation, resulting in low yield [8]. To obtain BMP with a high yield and high purity, methods such as low-temperature separation, multiple recrystallization, and distillation have been employed. However, the low separation

yield of BMP, the complex production equipment chain, and the large amount of organic solvents used remain unavoidable issues. Commercial BMP (purity >98%) is priced at approximately 400 USD·kg^{−1}. Therefore, developing a low-cost, simple, and environmentally friendly production process for BMP is crucial.

In recent years, the cocrystal strategy has been widely employed to improve the physicochemical properties of substances, such as melting point, density, color, solubility, dissolution rate, stability, and bioavailability [9–12]. In this work, we propose a novel cocrystal-based process for the separation of BMP. This process can achieve high-purity BMP with a high yield, and also offers the advantages of low energy consumption and reduced solvent usage. Specifically, amine compounds capable of forming cocrystal precipitates with BMP were systematically screened using the one-factor-at-a-time (OFAT) method. Triethylenediamine (DABCO) was identified as the most suitable amine to form a cocrystal with BMP. Subsequently, the design of experiments (DoE) was further employed to identify the key quality attributes and critical process parameters in the 2BMP-DABCO production process [13,14]. Moreover, single crystals of 2BMP-DABCO were

^{*} Corresponding authors.

E-mail addresses: lichao@mail.buct.edu.cn (C. Li), qiaorz@mail.buct.edu.cn (R. Qiao).

successfully obtained and comprehensively characterized by crystallographic data, thermal analysis, and various spectroscopic techniques. To further elucidate the separation mechanism of BMP, density functional theory (DFT) calculations and interaction region indicator (IRI) analysis were performed on the 2BMP-DABCO structure. This study demonstrates that the novel cocrystal process is suitable for the separation of BMP and provides guidance for industrial production.

2. Experimental

2.1. Materials

Amine compounds are shown in Fig. 1. Hexamethylenetetramine (HMTA) (>98% purity) was obtained from Sinopharm Chemical Reagent, China. The other amine compounds (>98% purity) were obtained from Energy Chemical, China. Acetone, toluene, and *n*-heptane were obtained from Fuyu Chemical, China. The crude BMP was self-made (purity: 89.2%).

2.2. OFAT amine screening experiments

The cocrystal purification of BMP mainly includes three unit operations: cocrystallization, separation, and decomplexation. Among the eight amines initially screened, DABCO, HMTA, piperazine, urea, and ethylenediamine were used in precipitation experiments with crude BMP at a molar ratio of 1:2, while pyridine, aniline, and tetraethylammonium hydroxide were used in precipitation experiments with crude BMP at a molar ratio of 1:1. The solvent used in all experiments was toluene, and the concentration of crude BMP was $1.0 \text{ mol} \cdot \text{L}^{-1}$. The generated cocrystal precipitates were added to water at 80°C for decomplexation. After the system transitioned into an oil–water two-phase system, BMP was obtained by separation.

2.3. Design of experiments for 2BMP-DABCO

Based on the preliminary assessment, the potential key parameters and their corresponding ranges for the precipitation of crude BMP using DABCO are shown in Table 1. Following the experimental design guidelines [15], a minimum-run resolution IV screening design was employed to identify the key parameters influencing the yield of 2BMP-DABCO. This is an efficient experimental design method that achieves resolution IV with the fewest number of experiments, ensures that the main effects are not confounded with second-order interactions, and allows for the simultaneous identification of significant main effects. Therefore, it is particularly suitable for the initial stage of experimental optimization [16]. Since the purity of 2BMP-DABCO in the

Table 1

Overview of DoE factors in the precipitation of BMP using DABCO.

Factors/units	Actual levels of coded factors		
	−1	0	1
Volume of toluene/ $\text{ml} \cdot \text{g}^{-1}$	2	3	4
Volume of <i>n</i> -heptane/ $\text{ml} \cdot \text{g}^{-1}$	4	7	10
Heating dissolution temperature/ $^\circ\text{C}$	50	65	80
Temperature of crystal growth/ $^\circ\text{C}$	0	15	30
Stirring duration/h	1	3	5
The amount of seed crystals/%	0.05	0.15	0.25
Stirring speed/ $\text{r} \cdot \text{min}^{-1}$	60	90	120

screening experiments was above 97%, purity was not selected as a response variable. The experimental design and results were analyzed using Design-Expert software. The experimental data and results of the analysis of variance (ANOVA) are summarized in Table S1–S2 (in Supplementary Material). After determining the key factors, the Box–Behnken design (BBD) was adopted to estimate the relationship between the yield of 2BMP–DABCO and the key factors, including the volume of toluene (x_1), the volume of *n*-heptane (x_2), and the temperature of crystal growth (x_3). The relationship between the yield of 2BMP–DABCO and these factors can be described by the following quadratic polynomial Eq. (1), where k represents the number of experimental data points, β_0 , β_i , β_{ii} , and β_{ij} represent the model coefficients. Additionally, x_i and x_j denote the values of the encoded independent variables, and ε represents the model's random error [17]. The experimental data are presented in Table S3. Residual analysis verifies the accuracy of the quadratic model (Fig. S1). In the simplified quadratic model, the effects of individual factors on the yield of 2BMP–DABCO are shown in Fig. S2. The accuracy of the model was evaluated using the coefficient of determination (R^2), while the significance of each regression coefficient in the proposed model was examined by calculating the p -value (probability value).

$$\text{Yield\%} = \beta_0 + \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^k \beta_{ii} x_i^2 + \sum_{i \leq j}^k \sum_j^k \beta_{ij} x_{ij} + \varepsilon \quad (1)$$

2.4. Characterization and analysis of 2BMP-DABCO powder

The morphology of the 2BMP-DABCO powder was observed using a field emission scanning electron microscope (FESEM, Sigma 360, ZEISS, Germany).

Simultaneous thermogravimetric (TG) and differential scanning calorimetry (DSC) analyses were conducted using the TG-DSC 3+ (Mettler, Switzerland). The heating rate was set at $10^\circ\text{C} \cdot \text{min}^{-1}$, and all experiments were performed under a nitrogen atmosphere.

Powder X-ray diffraction (PXRD, D8 ADVANCE X, Bruker, Germany) was used to confirm the crystal forms present in the BMP, DABCO, and 2BMP-DABCO powders. Measurements were taken over the range of 3° – 90° 2θ using a $\text{Cu K}\alpha$ X-ray source ($\lambda = 0.15405 \text{ nm}$, 40 kV, 40 mA).

A Thermo Nicolet 6700 Fourier transform infrared (FT-IR) spectrometer (Thermo Scientific, USA) was used to acquire the IR spectra of the samples, which were prepared as KBr pellets.

2.5. Preparation of single crystal

Slow evaporation of the solvent provided single crystals. 2BMP-DABCO powder (1.0 g, 2.1 mmol) was added to acetone (7.0 ml) in a test tube at 25°C . After a clear solution was formed, the test tube was covered with a pin-holed sealing film and left at 25°C for slow evaporation. Colorless single crystals were obtained after 10 days.

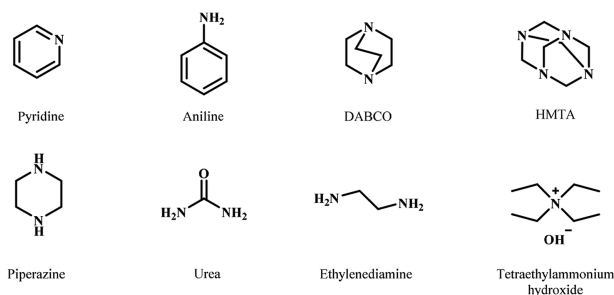


Fig. 1. The chemical structures of amine compounds used in the preliminary screening.

2.6. Single-crystal X-ray diffraction (SCXRD)

The SCXRD analysis of 2BMP-DABCO was carried out on a single-crystal diffractometer (Gemini E, Rigaku, Japan) using Mo K_{α} radiation. The collected single-crystal data were processed and analyzed using the OLEX2 software [18]. A summary of the crystallographic data for 2BMP-DABCO is presented in Table S4. Additionally, the Hirshfeld surface analysis, 2D fingerprint plots, and energy frameworks were generated using CrystalExplorer 17.5 based on the CIF data file of 2BMP-DABCO [19].

2.7. DFT calculations

The Gaussian 16W was used for DFT calculations on cocrystals and their individual components. The structures were optimized at the B3LYP/6-311G(d, p) level, and the single-point energies were calculated using the M06-2X/def2-TZVP method [20,21]. The molecular electrostatic potential surface (MEPS) was generated using Multiwfn and visualized with VMD [22–24]. Additionally, the interaction region indicator (IRI) was analyzed to provide deeper insights into intermolecular weak interactions. The wave function

of IRI is expressed by Eq. (2), where ρ denotes the electron density, $\mathbf{r}$ represents the coordinate vector, and α is an adjustable parameter with a default value of 1.1 [25].

$$\text{IRI}(\mathbf{r}) = \frac{|\nabla \rho(\mathbf{r})|}{[\rho(\mathbf{r})]^{\alpha}} \quad (2)$$

3. Results and Discussion

3.1. Results of OFAT experiments

Based on the reported cocrystals of amines and phenols, eight inexpensive and easily removable amines were initially selected for single-factor BMP precipitation studies (Fig. 2(a)) [26–30]. The precipitation of BMP depends on the formation of hydrogen bonds. Toluene was selected as the initial solvent for the OFAT experiment with amines. Among the screened amines, HMTA, DABCO, and urea can directly precipitate BMP. The ^1H NMR results confirmed that HMTA and DABCO combine with BMP in a 1:2 ratio, while urea combines with BMP in a 1:1 ratio (Fig. 2(b)). In the cocrystal precipitation scheme of BMP, the purity of the cocrystals formed with

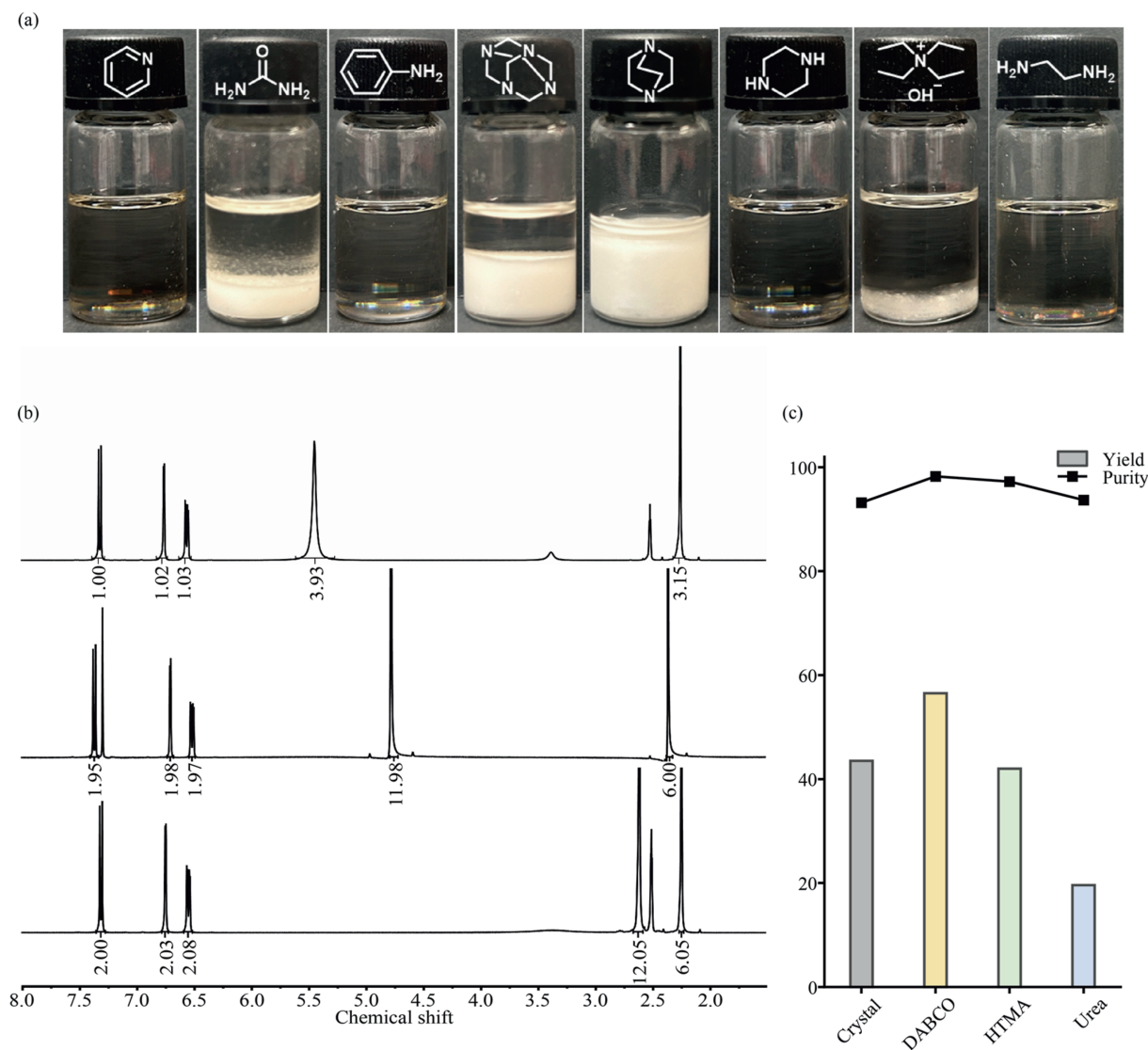


Fig. 2. (a) Photographs of BMP precipitated by eight kinds of amine compounds; (b) ^1H NMR spectra of BMP precipitated by urea, HMTA, and DABCO; (c) yield and purity of BMP obtained by direct crystallization and precipitation with DABCO, HMTA, and urea.

HMTA and DABCO is significantly higher than that of the cocrystals formed with urea, which is speculated to be related to the symmetry of the cocrystals. The HPLC results indicated that there was no significant difference in purity between the urea-precipitated BMP and the directly crystallized BMP, suggesting that this binding mode was ineffective in removing regioisomeric impurities. In addition, the five main impurities in BMP were each subjected to precipitation experiments with BMP and DABCO at a molar ratio of 1:1:1. None of them formed precipitates (Fig. S3), further confirming the importance of symmetrical crystallization in the separation and purification process of BMP. DABCO was identified as the most suitable amine for the cocrystallization precipitation of BMP due to its excellent water solubility ($400 \text{ mg} \cdot \text{ml}^{-1}$ at 25°C), which allows it to be easily removed during the workup process. Further screening of solvents led to the initial selection of the toluene/*n*-heptane mixed system to avoid the influence of the solvents on the formation of cocrystal hydrogen bonds.

3.2. Optimization of the 2BMP-DABCO cocrystal

Seven potential key process parameters in the precipitation of BMP using DABCO were systematically studied. In the minimum-run resolution IV screening design model, the 2BMP-DABCO yield varied between 52% and 92% (Table S1), thereby validating the importance of the selected parameters and their ranges. The model exhibited a *p*-value of less than 0.0001, which underscores its statistical significance. Based on the Half-normal plot and the Pareto chart (Fig. 3(a)–(b)), it was evident that the volume of toluene, the volume of *n*-heptane, and the cocrystal growth temperature were the critical factors influencing the yield of 2BMP-DABCO.

Based on the influence trends of each factor level on the yield of 2BMP-DABCO, a response surface methodology was designed and implemented. The experimental results were subsequently modeled using the least squares regression method. ANOVA (Table 2) revealed that the quadratic model was highly significant (*p*-value < 0.0001), indicating that the corresponding model terms were statistically significant. The precision and reliability of the experiment were validated by the coefficient of variation (CV), which was only 1.27%, confirming high precision and reliability. The R^2 value was 0.9875, indicating a strong linear relationship between the variables. Additionally, the adjusted R^2 was 0.9688, closely aligning with the R^2 value, thereby substantiating the reliability of the regression model fitting. The quadratic model for the yield of 2BMP-DABCO is presented in Eq. (3). The coefficient of x_1 (−2.96) indicates that increasing the volume of the good solvent, toluene, negatively affects the yield. Conversely, the coefficient of x_2 (+2.69) suggests that increasing the volume of the anti-solvent, *n*-heptane, positively influences the yield. The coefficient of x_3 (−3.18) shows that an increase in temperature has a detrimental effect on the yield. The interaction term x_1x_2 has a coefficient of +5.95, which is significantly higher than those of x_1x_3 (−3.77) and x_2x_3 (+1.48), indicating that the yield is predominantly influenced by the interplay between the volume of the good solvent and the anti-solvent.

$$\text{Yield\%} = 89.90 - 2.96x_1 + 2.69x_2 - 3.18x_3 + 5.95x_1x_2 - 3.77x_1x_3 + 1.48x_2x_3 - 1.35x_1^2 - 5.00x_2^2 - 2.87x_3^2 \quad (3)$$

Fig. 3(c) illustrates the correlation between experimental data and predicted results, demonstrating that, within the studied parameter range, linear fitting accurately describes the

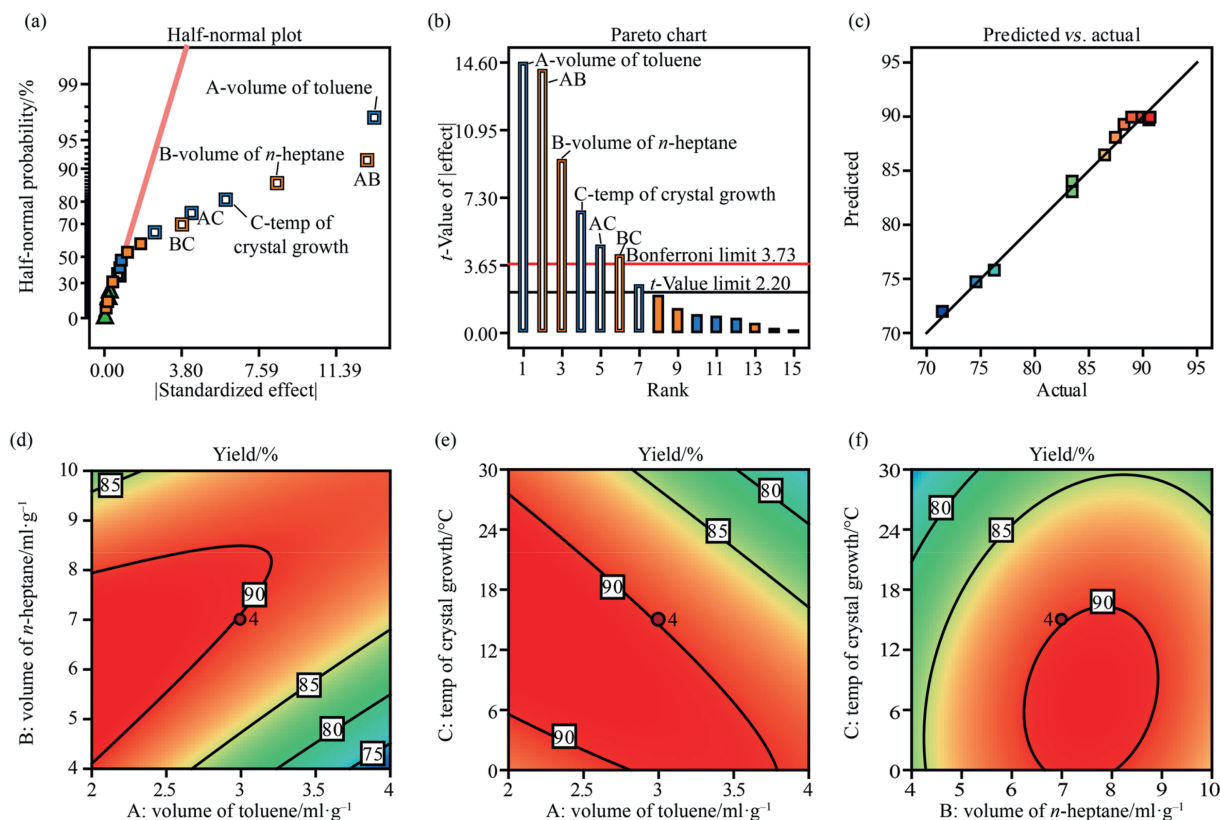


Fig. 3. (a) Half-normal plot, (b) Pareto chart, (c) comparison of predicted values with experimental results; contour plots for 2BMP-DABCO yield depending on (d) volume of toluene and volume of *n*-heptane, (e) volume of toluene and temperature of crystal growth, and (f) volume of *n*-heptane and temperature of crystal growth.

Table 2
ANOVA analysis of quadratic model for 2BMP-DABCO yield.

Source	Sum of squares	df	Mean square	F-value	p-value	
Model	556.31	9	61.81	52.74	<0.0001	Significant
x_1 -volume of toluene	70.21	1	70.21	59.90	0.0002	
x_2 -volume of <i>n</i> -heptane	57.78	1	57.78	49.30	0.0004	
x_3 -crystal growth temperature	80.64	1	80.64	68.80	0.0002	
x_1x_2	141.61	1	141.61	120.82	<0.0001	
x_1x_3	57.00	1	57.00	48.63	0.0004	
x_2x_3	8.70	1	8.70	7.42	0.0344	
x_1^2	7.29	1	7.29	6.22	0.0469	
x_2^2	100.00	1	100.00	85.32	<0.0001	
x_3^2	33.06	1	33.06	28.21	0.0018	
Residual	7.03	6	1.17			
Lack of fit	5.33	3	1.78	3.14	0.1864	Not significant
Pure error	1.70	3	0.5667			
Cor total	563.34	15				

$R^2 = 0.9875$, adjusted $R^2 = 0.9688$, predicted $R^2 = 0.8432$ and CV = 1.27%.

relationship between the variables. Fig. 3(d)–(f) illustrate the effects of the volume of toluene, the volume of *n*-heptane, and the cocrystal growth temperature on the yield of 2BMP-DABCO. Specifically, at a constant temperature of 15 °C, there is an interaction between the volumes of toluene and *n*-heptane. The dense contour lines in the lower right corner of Fig. 3(d) indicate that when the amount of anti-solvent *n*-heptane is low, increasing the toluene volume significantly decreases the yield. When the *n*-heptane volume is maintained at 7 ml·g^{−1}, the dense contour lines in the upper right corner of Fig. 3(e) reveal a clear interaction. The downward slope of the contour lines suggests that lower temperatures have a positive effect on the yield. The elliptical shape of the contour plot in Fig. 3(f) depicts the effects of the temperature of cocrystal growth and the volume of *n*-heptane on the yield. With toluene held constant at 3 ml·g^{−1}, the yield initially increased and then decreased with increasing volume of *n*-heptane, suggesting that an excess of *n*-heptane may adversely affect the yield. The RSM prediction results suggest that the highest yield of 2BMP-DABCO (92%) is achieved when the toluene volume is 2.0 ml·g^{−1}, the *n*-heptane volume is 5.6 ml·g^{−1}, and the cocrystal growth temperature is 14.8 °C (Fig. S4).

These conditions were validated through three replicate experiments, achieving an average purity of 99.3% and a yield of 91% for 2BMP-DABCO (Table S5). Furthermore, during the scale-up reaction (using 5 kg of *m*-cresol; the synthetic process is described in the Supplementary Material), after removing DABCO twice with water at 80 °C, the total yield was 87%, and the purity was 99.9%. These results demonstrate that the established predictive model exhibits high reliability and practicality.

3.3. Inherent properties

To evaluate the thermal stability of BMP, DABCO, and 2BMP-DABCO, DSC experiments were conducted on powdered samples. The melting point of 2BMP-DABCO was observed at a peak temperature of 110.8 °C, which is significantly higher than those of BMP and DABCO, as shown in Fig. 4(a). In addition, the DSC thermogram of the physical mixture of BMP and DABCO appears to be a simple superposition of the individual DSC thermograms of BMP and DABCO, indicating that the intermolecular interaction between BMP and DABCO in this mixture is very weak. To correlate the observations in the DSC thermogram with the thermal decomposition behavior of 2BMP-DABCO, TG analysis was conducted. As shown in Fig. 4(b), 2BMP-DABCO begins to decompose at approximately 120 °C, exhibiting a mass loss of 79.5% during this process. In contrast, both BMP and DABCO exhibit significantly lower onset decomposition temperatures and higher mass losses

compared to those of 2BMP-DABCO. The DTG curve is obtained by taking the first derivative of the TG curve [31]. The maximum decomposition temperature of 2BMP-DABCO was calculated to be 188.5 °C, significantly higher than that of DABCO at 169.5 °C and that of BMP at 112.3 °C (Fig. S5). According to the DSC, TG, and DTG analyses, it can be inferred that the thermal stability of 2BMP-DABCO is significantly higher than that of BMP and DABCO.

PXRD is the preferred method for characterizing the formation of novel crystal morphologies [32]. Fig. 4(c) displays the superimposed PXRD patterns of BMP, DABCO, the physical mixture of BMP and DABCO, and 2BMP-DABCO. The PXRD pattern of the physical mixture of BMP and DABCO appears to be a simple superposition of the individual PXRD patterns of BMP and DABCO, suggesting minimal intermolecular interaction between BMP and DABCO in this mixture [33]. In contrast, the PXRD pattern of 2BMP-DABCO exhibits distinct characteristic peaks that are absent in the physical mixture, indicating the formation of a new crystalline phase. Specifically, the characteristic peaks of the 2BMP-DABCO appear at 2θ angles of 7.5°, 15.8°, 17.1°, 22.6°, and 30.8°. In addition, the simulated PXRD pattern of the 2BMP-DABCO single crystal and the experimental PXRD pattern are shown in Fig. S6. The newly observed PXRD peaks are in agreement with the simulated PXRD pattern, confirming that BMP and DABCO formed the 2BMP-DABCO cocrystal during the experiment. However, there is a deviation between the experimental PXRD pattern and the simulated pattern, which may be attributed to the preferred orientation of the crystal [11].

Fig. 4(d) displays the FT-IR spectra of BMP, DABCO, and 2BMP-DABCO. In the spectrum of BMP, the $\nu(\text{O-H})$ vibration appears as a broad peak at 3291 cm^{−1}. For 2BMP-DABCO, a broad band is observed between 2800 cm^{−1} and 2400 cm^{−1}, which can be attributed to the red shift caused by the intermolecular hydrogen bonding between BMP and DABCO. This spectral feature serves as compelling evidence for the formation of the cocrystal. In DABCO, the $\nu(\text{C-N})$ stretching vibration is observed at 1634 cm^{−1} [34]. In 2BMP-DABCO, the formation of hydrogen bonds causes the $\nu(\text{C-N})$ stretching vibration to redshift to 1579 cm^{−1}. The $\nu(\text{C-H})$ stretching vibrations of DABCO in 2BMP-DABCO are detected at 2965, 2941, and 2873 cm^{−1}. The $\delta(\text{C-H})$ bending vibration is observed at 1460 cm^{−1} [35,36].

In addition, the FESEM image shows that the 2BMP-DABCO powder has good morphological characteristics, with a smooth surface and a size ranging from 30 to 50 μm (Fig. 5).

3.4. Description of the crystal structure

Based on the SCXRD results, 2BMP-DABCO belongs to the *P*-1 space group in the triclinic system [unit cell dimensions: $a =$

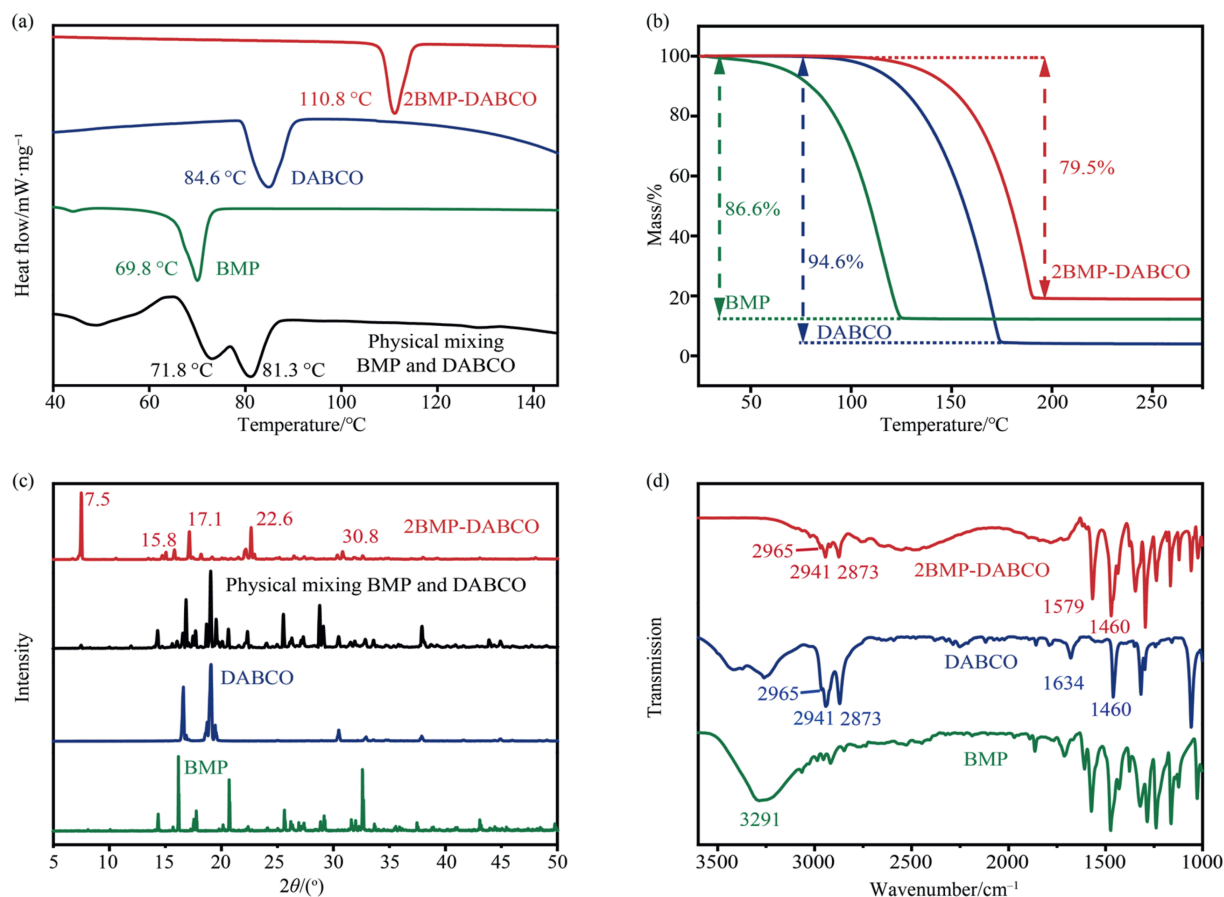


Fig. 4. (a) DSC, (b) TG, (c) PXRD, and (d) FT-IR curves of BMP, DABCO, and 2BMP-DABCO.

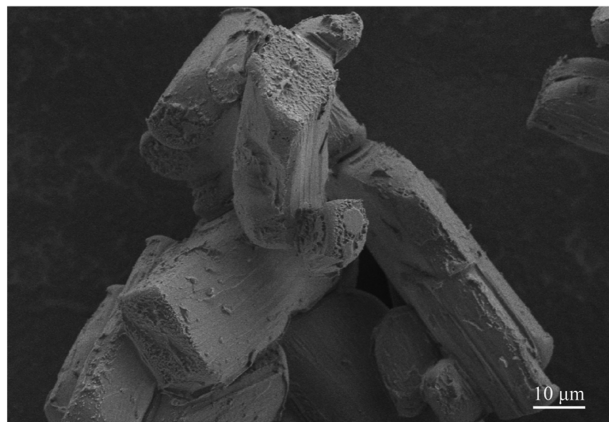


Fig. 5. The FESEM image of 2BMP-DABCO powder at a resolution of 10 μm .

$0.66366(10)$ nm, $b = 1.18154(18)$ nm, $c = 1.33281(14)$ nm, $\alpha = 82.560(11)^\circ$, $\beta = 77.771(11)^\circ$, $\gamma = 81.914(13)^\circ$, $V = 1.0059(2)$ nm³, $Z = 2$, and $\mu = 4.046$ mm⁻¹. As illustrated in Fig. 6(a), the symmetric unit comprises two BMP molecules and one DABCO molecule, which assemble into 2BMP-DABCO through hydrogen bonding interactions. As illustrated in Fig. 6(b), along the crystallographic b -axis, the H atoms of the DABCO molecule form a network of weak hydrogen bonds with the phenolic hydroxyl groups of the BMP molecules. Furthermore, weak hydrogen bonds are also observed between the methyl H atoms of the BMP molecules and the phenolic hydroxyl groups (Fig. 6(c)). For a detailed

examination of these weak hydrogen bonds, all relevant hydrogen bond data are summarized in Table 3. These interactions collectively contribute to the formation of an extensive hydrogen bond network along the crystallographic b -axis. Furthermore, the DABCO molecule is stabilized by C–H $\cdots\pi$ interactions with two BMP molecules from adjacent non-cocrystalline units [37], with interaction distances of 0.3668 nm and 0.3432 nm (Table 4). These C–H $\cdots\pi$ interactions are illustrated in Fig. 6(d). The unit cell structure of the 2BMP-DABCO complex is depicted in Fig. 6(e).

3.5. Hirshfeld surface analysis and energy frameworks

Hirshfeld surface analysis offers a comprehensive and quantitative assessment of intermolecular interactions and contacts arising from supramolecular stacking in crystals. Additionally, it employs numerical calculation methods to provide an analytical approach for evaluating atomic valence and other properties [38]. The Hirshfeld surface of the BMP fragment within the 2BMP-DABCO complex is illustrated in Fig. 7(a). The d_{norm} surface represents a normalized contact distance derived from d_e (the distance to the nearest nucleus outside the Hirshfeld surface) and d_i (the distance to the nearest nucleus inside the Hirshfeld surface). The red regions indicate the strongest interaction forces, followed by blue and white regions, which correspond to progressively weaker interactions [39]. The shape index visualizes the electron density, with regions of low density represented by red areas and regions of high density depicted by blue areas. The red triangle surrounding the benzene ring on the surface highlights the C14–H14A $\cdots$ Cnt5 interaction. However, the absence of a large flat

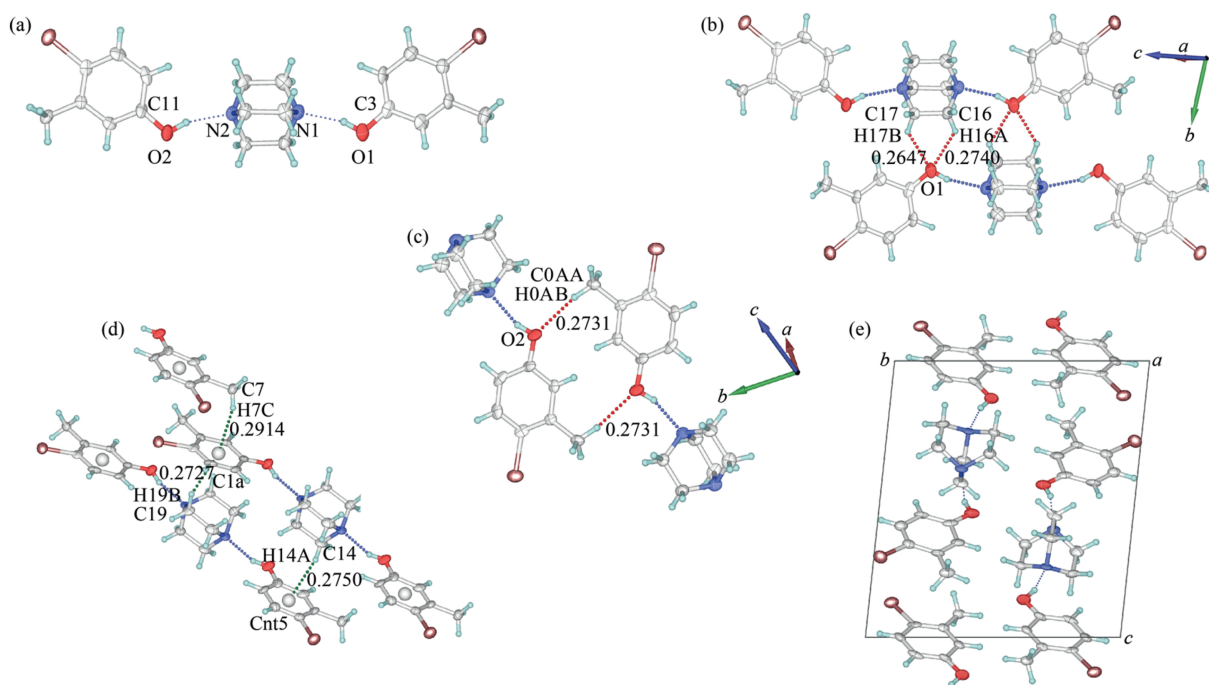


Fig. 6. (a) Symmetric unit of 2BMP-DABCO. (b) Hydrogen-bonded pattern in 2BMP-DABCO. (c) Weak hydrogen bonding interactions (red lines) between BMP molecules. (d) C–H $\cdots\pi$ interactions (green lines) in 2BMP-DABCO. (e) Packing diagram of 2BMP-DABCO along the axis.

Table 3

Hydrogen bonding contacts for 2BMP-DABCO.

D–H $\cdots$ A	D–H/nm	H–A $\cdots$ /nm	D–A $\cdots$ /nm	D–H $\cdots$ /($^{\circ}$)	Symmetry codes
O1–H1 $\cdots$ N1	0.084	0.187	0.26788(3)	161.3	–
O2–H2 $\cdots$ N2	0.084	0.189	0.26904(3)	157.8	–
C16–H16A $\cdots$ O1	0.099	0.265	0.34341(5)	136.6	2–X, –1–Y, 1–Z
C17–H17B $\cdots$ O1	0.099	0.274	0.34750(6)	131.4	2–X, –1–Y, 1–Z
C0AA–H0AB $\cdots$ O2	0.098	0.273	0.35508(6)	141.5	1–X, –1–Y, –Z

Table 4

C–H $\cdots\pi$ intermolecular interactions in 2BMP-DABCO.

C–H $\cdots$ Cg	H–Cg/nm	X $\cdots$ Cg/nm	X–H $\cdots$ Cg/($^{\circ}$)	Symmetry codes
C14–H14A $\cdots$ Cnt5	0.27497(4)	0.3432	126.5	–1+X, +Y, +Z
C19–H19B $\cdots$ C1a	0.27268(4)	0.3668	158.9	–1+X, +Y, +Z
C7–H7C $\cdots$ C1a	0.29145(4)	0.3605	128.3	–1+X, +Y, –1+Z

region in the curvedness suggests that significant $\pi\cdots\pi$ stacking interactions are not evident in the cocrystal. The segmented BMP segments illustrate specific intermolecular interactions, while the overall fingerprint encompasses all of these interactions. Fig. 7(b) shows the relative contribution of the Hirshfeld surface area for 2BMP-DABCO. The H $\cdots$ H intermolecular contacts contribute most significantly to the crystal structure, accounting for 47.6%. Other major contributors include C $\cdots$ H/H $\cdots$ C (19.8%) and Br $\cdots$ H/H $\cdots$ Br (18.2%) contacts. Additionally, minor contributions come from interactions such as O $\cdots$ H/H $\cdots$ O (10.1%) and Br $\cdots$ C/C $\cdots$ Br (2.2%).

Furthermore, an energy framework analysis was performed on 2BMP-DABCO. In this framework, the coulombic energy is represented by the red bars in Fig. 8(a), the dispersion energy is represented by the green bars in Fig. 8(b), and the total interaction energy is represented by the blue bars in Fig. 8(c) [40,41]. The results indicate that the 2BMP-DABCO cocrystal is primarily governed by strong electrostatic interactions, with a less pronounced dispersion effect from $\pi\cdots\pi$ interactions. Further analysis confirms that hydrogen bonding plays a crucial role in maintaining the

spatial arrangement of the 2BMP-DABCO cocrystal molecules during cocrystal formation.

3.6. MEPS analysis

Most hydrogen-bonding interactions are electrostatic in nature and can be effectively illustrated and analyzed using MEPS [9,42,43]. As illustrated in Fig. 9, the first global maximum for BMP is located at the H1 site (+54.59 kcal $\cdot$ mol $^{-1}$, 1 kcal = 4.18 kJ), whereas the global minima for DABCO are observed at N1 and N2 (–33.46 kcal $\cdot$ mol $^{-1}$). The first global minimum of BMP occurs at O1 (–21.77 kcal $\cdot$ mol $^{-1}$), while the first global maximum of DABCO occurs at H3 (+10.61 kcal $\cdot$ mol $^{-1}$). In cocrystal systems, based on the hierarchical and rule-based interactions between functional groups, the primary interaction sites should initially form as pairs of minimum and maximum MEPS, followed by secondary interactions. Following this principle, the interactions between O–H $\cdots$ N and C–H $\cdots$ O are predicted, which are consistent with the single crystal results.

3.7. IRI analysis

The IRI facilitates the intuitive visualization of chemical bonds and weak interactions within a chemical system. Its primary advantage is the equal representation of diverse interactions [25]. Fig. 10(a) illustrates the weak intermolecular interactions within a single 2BMP-DABCO cocrystal structure, with the bonding regions

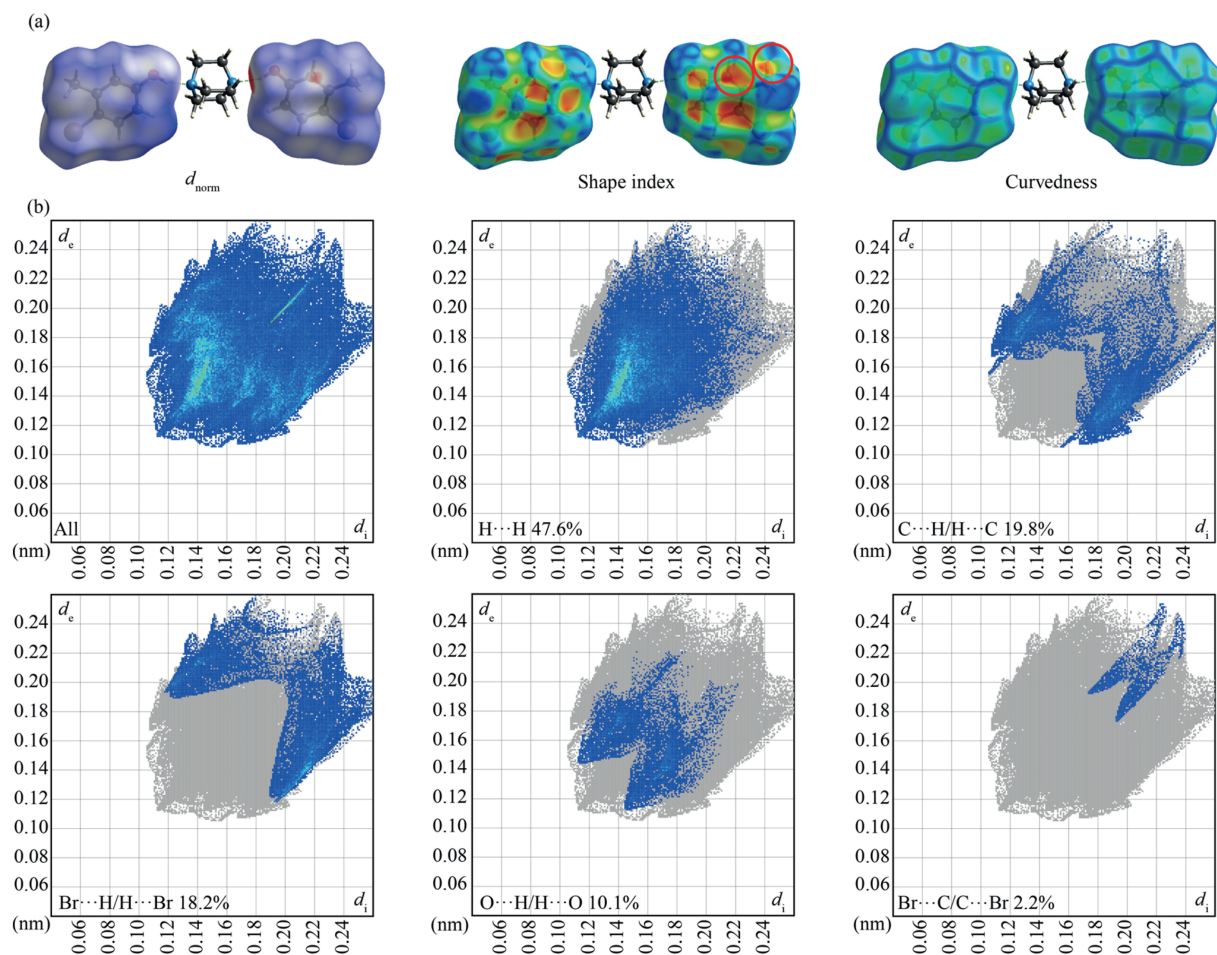


Fig. 7. (a) Hirshfeld surfaces for the 2BMP-DABCO cocrystal mapped over d_{norm} , shape index, and curvedness. (b) 2D fingerprint plots for the 2BMP-DABCO cocrystal.

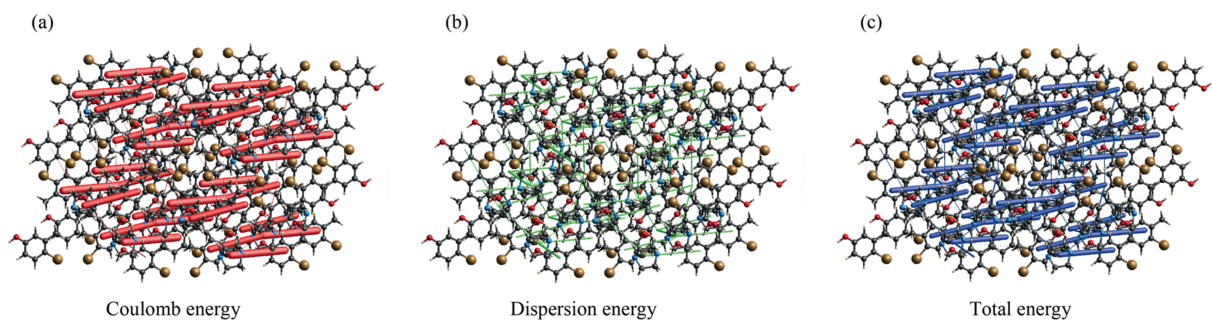


Fig. 8. The energy framework analysis of 2BMP-DABCO: (a) coulomb energy, (b) dispersion energy, and (c) total energy.

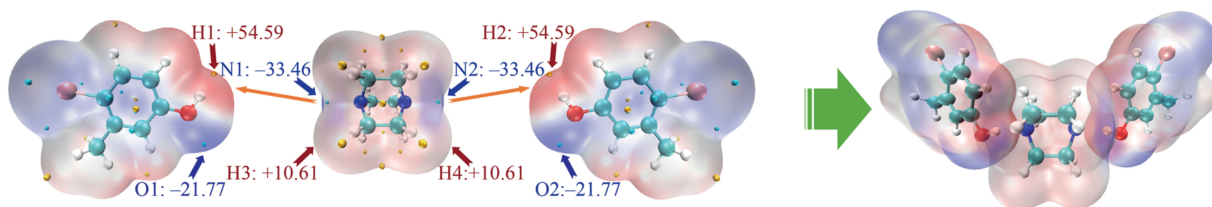


Fig. 9. Calculated MEPS analysis of BMP, DABCO, and 2BMP-DABCO.

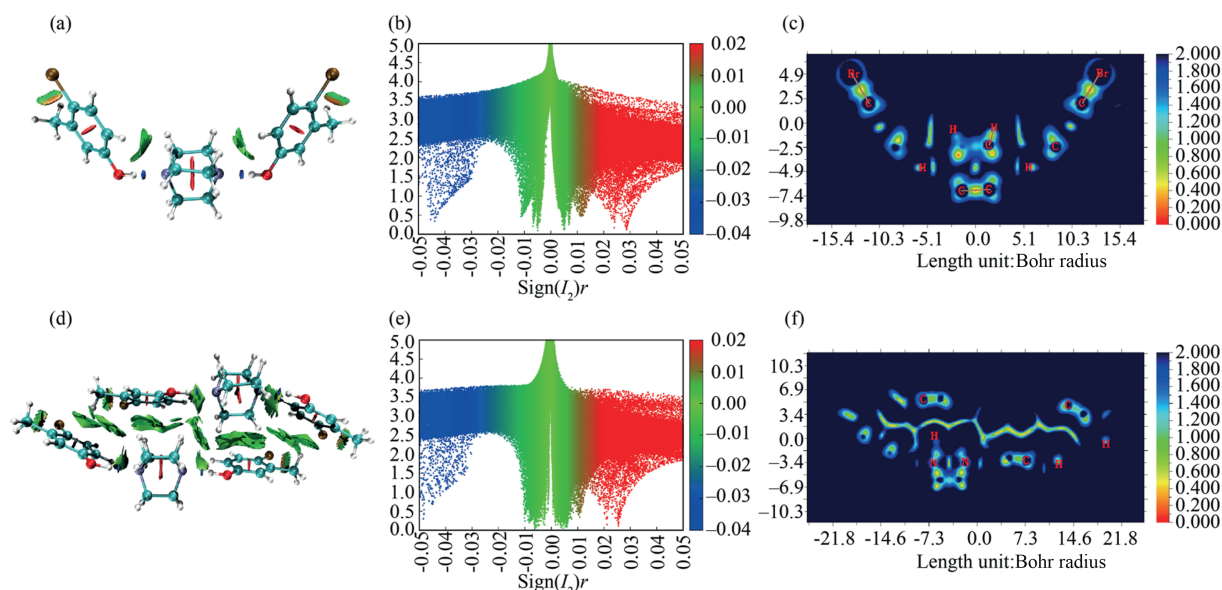


Fig. 10. Analysis of IRI in 2BMP-DABCO: (a) IRI of 2BMP-DABCO; (b) IRI vs. $\text{sign}(I_2)r$ scatter plot; (c) IRI plane color-filled diagram; (d) IRI of two molecules of 2BMP-DABCO stacked together; (e) IRI scatter plot of $\text{sign}(I_2)r$ for the stack of two 2BMP-DABCO molecules; and (f) the corresponding IRI plane color-filled diagram.

concealed. The intermolecular interactions in 2BMP-DABCO include strong hydrogen bonds and van der Waals forces. The $\text{sign}(I_2)r$ function is used to indicate the nature of these intermolecular interactions. Specifically, $\text{sign}(I_2)r$ not only reflects the electron density but also simultaneously captures both the type and strength of the interaction [44]. Fig. 10(b) illustrates the scatter plot of IRI versus $\text{sign}(I_2)r$ for 2BMP-DABCO. The central green region ($-0.02 < \text{sign}(I_2)r < 0.01$) signifies weak intermolecular interactions, primarily van der Waals forces. The right red region ($0.01 < \text{sign}(I_2)r < 0.05$) denotes repulsive intermolecular effects, such as steric hindrance. The left blue region ($-0.05 < \text{sign}(I_2)r < -0.02$) represents hydrogen bonding interactions between BMP and DABCO. Fig. 10(c) illustrates the IRI plane-filling diagram of the 2BMP-DABCO cocrystal, highlighting the presence of weak intermolecular forces within its structure. Fig. 10(d) depicts the stacking arrangement of two 2BMP-DABCO molecules, where significant van der Waals interactions are evident between the cocrystal molecules. The green region in the center of Fig. 10(e) specifically highlights these van der Waals interactions, showing a notable increase in peak density compared to Fig. 10(b). This observation aligns with the fact that the stacking process is primarily driven by $\text{C-H} \cdots \pi$ intermolecular interactions. Fig. 10(f) provides the IRI plane filling diagram of the stacked structure, clearly demonstrating the interactions between the H atoms in DABCO and the aromatic rings of BMP, as well as the interactions between the methyl H atoms in BMP and the aromatic rings of adjacent BMP molecules. In summary, the stacking of 2BMP-DABCO molecules is predominantly influenced by weak intermolecular interactions.

4. Conclusions

In this study, a novel cocrystallization process for the separation and purification of the low-melting-point compound BMP was proposed. This method of separation and purification is based on the formation of a structurally symmetrical cocrystal between DABCO and BMP in a 1:2 molar ratio. Thermal analysis shows that the thermal stability of 2BMP-DABCO is significantly higher than that of the corresponding monomers, thereby addressing the

drawback of oiling out in traditional recrystallization processes. Additionally, the symmetrical structure of the 2BMP-DABCO cocrystal is believed to facilitate the removal of regioisomeric impurities, and high-purity BMP is obtained after decomplexation. The key influencing factors of the cocrystallization process were investigated through a minimum-run resolution IV screening design, and the highest 2BMP-DABCO yield could reach 91% under the optimal reaction conditions obtained by RSM based on the Box–Behnken design. Additionally, SCXRD, PXRD, and FT-IR revealed that a 2BMP-DABCO cocrystal was formed through hydrogen bonds and $\text{C-H} \cdots \pi$ weak interactions during the precipitation of BMP and DABCO. MEPS indicated that 2BMP-DABCO exhibited paired global maximum and minimum points, and IRI analysis visually revealed the weak interactions in the 2BMP-DABCO. In summary, this study provides new insights into the commercial production of BMP and the separation and purification of phenolic substances.

CRediT Authorship Contribution Statement

Chunxiao Wang: Writing – original draft, Methodology, Conceptualization. Shuai Wang: Methodology, Conceptualization. Hongsen Zhang: Methodology, Investigation. Chao Li: Supervision, Resources, Conceptualization. Renzhong Qiao: Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cjche.2025.08.021>.

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