Low-energy driven ring-opening behavior of benzocyclobutene derivatives

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Abstract

It’s urgent to develop benzocyclobutene (BCB)-based polymers with low curing temperatures for temperature-sensitive applications such as liquid crystal display (LCD) and flexible electronics. Herein, the effect of substituents on the ring-opening behavior of BCB derivatives was investigated. The ring-opening activation energy barriers (ΔGA) of BCB derivatives with one or two substituents on the four-membered alkyl ring were systematically calculated using the B3LYP function. Both mono- and di-substituted BCBs adopted the conrotatory ring-opening process, obeying the Woodward-Hoffmann’s Rules upon heating. The mono-/di-substituted BCBs exhibited 8.2 – 69% lower ΔGA compared with BCB, attributed to the electronic effects of the substituents. Disubstituted BCBs with both electron-donating and electron-withdrawing groups, e.g., 1-NH₂-8-NO₂-BCB, demonstrated the lowest ΔGA. In addition, BCB derivatives with amide/ester/acyloxy group modified on C1 position were synthesized as model molecules, and their ring-opening temperature can be decreased by 20 °C compared to the unsubstituted one, also consistent with our calculation results. This work combined the theoretical calculation method with experimental results to provide valuable insights into the design and synthesis of BCB derivatives and next-generation BCB functional packaging materials with low ring-opening temperatures.

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Keywords

Benzocyclobutene | Low curing temperature | Activation energy barrier | Electronic effect | Captodative effect

Comprehensive Summary

It’s urgent to develop benzocyclobutene (BCB)-based polymers with low curing temperatures for temperature-sensitive applications such as liquid crystal display (LCD) and flexible electronics. Herein, the effect of substituents on the ring-opening behavior of BCB derivatives was investigated. The ring-opening activation energy barriers (ΔGA) of BCB derivatives with one or two substituents on the four-membered alkyl ring were systematically calculated using the B3LYP function. Both mono- and di-substituted BCBs adopted the conrotatory ring-opening process, obeying the Woodward-Hoffmann’s Rules upon heating. The mono-/di-substituted BCBs exhibited 8.2 – 69% lower ΔGA compared with BCB, attributed to the electronic effects of the substituents. Disubstituted BCBs with both electron-donating and electron-withdrawing groups, e.g., 1-NH₂-8-NO₂-BCB, demonstrated the lowest ΔGA. In addition, BCB derivatives with amide/ester/acyloxy group modified on C1 position were synthesized as model molecules, and their ring-opening temperature can be decreased by 20 °C compared to the unsubstituted one, also consistent with our calculation results. This work combined the theoretical calculation method with experimental results to provide valuable insights into the design and synthesis of BCB derivatives and next-generation BCB functional packaging materials with low ring-opening temperatures.
Background and Originality Content

Electrocyclic reaction as one of the widely used synthetic methods in organic chemistry,\(^1\) exhibits excellent regio- and stereo-control in construction of polycyclic scaffolds like cyclopentanes, lactones, and cyclohexanes. The different ring-opening stereochemical pathways are commonly described in terms of conrotatory and disrotatory. In 1950s, The Frontier Molecular Orbital Theory (FMO)\(^2\) proposed by Fukui successfully explained the reactivity and regioselectivity phenomena of electrocyclic reaction. Later, in 1969, Woodward and Hoffmann summarized the rule of stereoselectivity for pericyclic reactions by the principle of symmetry conservation of molecular orbitals.\(^3\) The thermal-induced ring-opening of cyclobutene is a typical case of electrocyclic reaction,\(^4\) and numerous studies have investigated the effect of substituents on the ring-opening energy barrier of cyclobutene and the torqueselectivity during the ring-opening process.\(^5\) However, as a member of strained four-membered cyclic ring family, benzocyclobutene (BCB) with 4π-electron system stabilizing the cyclobutene ring can also undergo the ring-opening reaction under heating conditions, but has received little attention.\(^6\)

The thermal-induced ring-opening process of BCB\(^7\) also follows the stereoselective rule of the electrocyclic reaction. Moreover, the ring-opening reaction proceeds via a conrotatory pathway to yield the unstable diene o-quinodimethane (Scheme 1), due to the loss of aromaticity after ring-opening.\(^5e, 8\) During the ring-opening process, the C\(_1\)-C\(_8\) σ bond and the C\(_2\)-C\(_7\) π bond are cleaved, and two new π bonds are formed: C\(_1\)-C\(_2\) and C\(_7\)-C\(_8\). Resins containing multiple BCB functional groups are thermosetting materials, derived from Diels–Alder (D-A) reaction by exploiting the high reactivity of o-quinodimethane.\(^9\) After fully cured, BCB resins demonstrated high thermal stability, excellent mechanical and low-dielectric properties,\(^10\) and have been widely used as an advanced packaging material for the microelectronic industry.\(^11\)

BCB resins have been reported as an organic passivation layer and packaging material in liquid crystal displays (LCDs), owing to its moderate curing temperature (\(\leq 250^\circ\text{C}\)),\(^11a, 12\) As LCDs keep developing towards multifunctional and flexible wearable devices, the flexible substrate cannot withstand the high curing temperature, which may damage the internal components of electronic products, thereby limiting the further applications of BCB resins. It was found that modifying the phenyl ring of BCB derivatives had no significant effect on reducing its ring-opening temperature (peak temperature of DSC curves), whereas modifications on the four-membered alkyl ring could substantially influence the ring-opening activation energy.\(^11d, 13\) Chino et al. synthesized four BCB derivatives with electron-donating groups (methoxy, hydroxy, acetoxy, (trimethylsilyl)oxy groups on C\(_1\)) and three ones with electron-withdrawing groups (cyanoo, chloro-, bromo-groups on C\(_1\)). All of them demonstrated low ring-opening temperatures (< 200 °C).\(^14\) Dobish et al. reported a polyacrylate modified with 1-alkoxy substituted BCB as the pendant side chains, successfully reducing the cross-linking temperature by 100 °C for the formation of intra-molecular nanoparticles.\(^11e\) Hayes et al. synthesized 1-alkoxyl/hydroxyl/carbonyl group substituted BCB derivatives, exhibiting ring-opening temperatures as low as 148 - 231 °C, and believed that there might be an electronic relationship between the structure of BCB ring and the temperature at which electrocyclic ring opening occurred.\(^11d\)

As early as 1978, Roth et al. experimentally linked the thermal ring-opening reaction of BCB to D-A reaction to obtain a ring-opening activation energy barrier (Δ\(G_A\)) of 39.9 kcal/mol for BCB.\(^15\) Chino et al. characterized the Δ\(G_A\) as the enthalpy change, and utilized semi-empirical molecular orbital calculations to determine the barrier, as well as predicted the ring-opening temperatures of monosubstituted BCBs at C\(_1\)-position.\(^16\) Nava et al. analyzed the effects of three factors on the stability of the closed and open ring forms of cyclobutene and BCB: hyperconjugation, π-delocalization and ring strain.\(^5e\) Even so, the stereoelectronic effect of substituents on the four-membered ring should be the interior cause to influence the stability of BCB.\(^17\) To the best of our knowledge, how substituents influence the ring-opening behavior of BCBs has not been systematically studied yet. In this work, density functional theory (DFT) calculations were employed to reveal the effects of different types (electron-withdrawing/donating groups) and numbers (one or two) of substituents on C\(_1\) and C\(_8\) position of BCBs on their corresponding ring-opening tendencies. Furthermore,
a series of BCB model compounds with amide/ester/acyloxy modifications on C1 position were synthesized, to validate the theoretical calculation results (Scheme 1). Our findings provide a theoretical support for the research and development of novel low-temperature curable BCB resins, and expand its potential applications on flexible electronics,\textsuperscript{13, 18} interfacial bonding materials,\textsuperscript{19} etc.

**Scheme 1** a) Scheme of ring-opening reaction of BCB and its possible energy changes. b) Design of the mono-/di-substituted BCB derivatives.

**Results and Discussion**

**Mechanism of thermal-induced ring-opening of BCB derivatives**

The thermal-induced ring-opening process of BCB to o-quinodimethane generally follows the principle of molecular orbital symmetry.\textsuperscript{,3} According to the stereoselectivity rule of the electrocyclization reaction, o-quinodimethane owns eight $\pi$-electrons, and BCB adopts the conrotatory ring-opening pathway under heating condition. In 2000, Sakai employed \textit{ab initio} molecular orbital methods to investigate the transition state of the reaction (o-quinodimethane to BCB) on both conrotatory and disrotatory paths, revealing a minimal difference in activation energy between them (less than 8 kcal/mol).\textsuperscript{20} The planarity of the BCB system significantly influences the ring-opening mechanism. Due to the partial connection of the alkyl ring to a rigid benzene ring, the system possesses a high degree of planarity that favors alkyl ring-opening through a conrotatory pathway. Lee et al. have confirmed that as the planarity of a system increases, conrotatory ring-opening becomes more favorable.\textsuperscript{5c}

The elucidation of ring-opening pathways for substituted BCB derivatives is crucial. Upon introducing a substituent to the alkyl ring of BCB, two torsional pathways can be taken: inward and outward. The specific pathway is determined by the electronic effect between the porbital of the substituent and the orbital of the broken $\sigma$ bond (C$_1$-C$_8$ bond) at the transition state. By conducting calculations (Figure 1), it was determined that the $\sigma$-bond (C$_1$-C$_8$) was broken at the highest occupied molecular orbital (HOMO) of transition state, with the lowest unoccupied molecular orbital (LUMO) of the $\sigma^*$ orbital. In case of an electron-donating group, such as NH$_2$, presented as a substituent at C$_1$ position, the HOMO orbital experienced strong repulsion due to the filled $p$ orbital of the substituent interacting with the orbital of the broken $\sigma$ bond during inward pathway. For LUMO orbitals, rotation of the substituent inward results in the formation of a node-like structure between the $p$ orbital of the substituent and the orbital of the broken bond, causing the transition state to become unstable.

However, this pathway cannot be applied to electron-withdrawing groups. In 1992, Jefford et al. experimentally and theoretically explored the torquoselectivity of ring opening of 1-substituted BCBs, such as 1-CN-BCB and 1-COOH-BCB, utilizing D-A reaction of BCB derivatives with maleic anhydride, and inferred the o-quinodimethane conformation accordingly. It was found that 1-CN-BCB, 1-COOH-BCB and 1-COOMe-BCB were ring-opened outwards, whereas the 1-formyl substituted one turned inwards.\textsuperscript{7} Therefore, further investigation was required to understand the reasons behind the torquoselectivity of ring-opening for different substituents. In order to shed light on this matter, nine different substituents with different electronic effects were selected to verify the ring-opening pathway. Through DFT calculations, the conrotatory pathway can be determined.
Previous experimental and theoretical studies found that a high activation energy barrier was required in the thermal-induced ring-opening of BCB due to the loss of aromaticity.\textsuperscript{5a, 15, 17} Meanwhile, the ring-opening temperature of BCB derivatives should be associated with the ring-opening activation energy barrier ($\Delta G_A$). The higher $\Delta G_A$ corresponded to the higher ring-opening temperature, and vice versa. Four electron-donating groups (NH\textsubscript{2}, OH, OCOCH\textsubscript{3}, CH\textsubscript{3}), three electron-withdrawing groups (NO\textsubscript{2}, CN, COOH), and two halogen substituents (Br, F) were selected to study the effect of substituents at the C\textsubscript{1} position on $\Delta G_A$. The ring-opening temperatures of 1-Br-BCB, 1-OH-BCB, 1-COOH-BCB were defined by differential scanning calorimetry (DSC) (Table S1, Figure S1). Among them, the ring-opening temperature of 1-COOH-BCB was basically consistent with the reported one. Whereas, the ring-opening temperature of 1-OH-BCB, presenting at 156 °C, was much higher than the previous report of 80 °C.\textsuperscript{17} Besides, according to Chino’s report,\textsuperscript{16} 1-Br-BCB demonstrated an endothermic peak, not matched with the regular exothermic effect of ring-opening reaction and D-A reaction. But 1-Br-BCB based on our synthetic procedure exhibited an exothermic peak with ring-opening temperature of 150 °C. The $\Delta G_A$ of unsubstituted BCB was obtained as 37.20 kcal/mol at B3LYP/6-311G(d,p) with dispersion correction introduced, which was consistent with the experimental value (40 kcal/mol).\textsuperscript{5c, 15} A positive correlation between temperature and energy barrier was determined (Table S1). Extensive calculations were performed at this level, and the results were shown in Figure 2a and 2b.

The substituents on the alkyl ring can effectively reduce $\Delta G_A$, and $\Delta G_A$ is related to the electronic activities of the substituents. The introduction of the strong electron-donating NH\textsubscript{2} group at C\textsubscript{1} position (1-NH\textsubscript{2}-BCB), resulted in the lowest $\Delta G_A$ value, which was 13.13 kcal/mol (35.3%) lower than that of unsubstituted BCB. The $\Delta G_A$ of 1-OH-BCB and 1-OCOCH\textsubscript{3}-BCB were 27.59 and 31.82 kcal/mol, which were 9.61 and 5.38 kcal/mol (25.8%, 14.5%) lower than that of unsubstituted BCB, respectively. A clear correlation can be observed between the electron-donating abilities of substituents and the corresponding $\Delta G_A$ values: substituents with higher electron-donating ability exhibited lower $\Delta G_A$ values, which was consistent with the substituent effect of thermal ring-opening of cyclobutene.\textsuperscript{5a} Furthermore, a strong linear relationship existed between the electron-donating ability of the substituents and the corresponding $\Delta G_A$ values.

Different from the electron-donating effect, although the introduction of electron-withdrawing group at the C\textsubscript{1} position of BCB can also result in a decrease of $\Delta G_A$, no direct relationship was found between the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{HOMO and LUMO orbitals of the transition states of 1-NH\textsubscript{2}-BCB and 1-NO\textsubscript{2}-BCB.}
\end{figure}
electron-withdrawing ability of the substituents and $\Delta G_A$ values. Compared with 1-COOH-BCB (with $\Delta G_A$ of 34.15 kcal/mol) and 1-NO$_2$-BCB (with $\Delta G_A$ of 33.4 kcal/mol), 1-CN-BCB decreased $\Delta G_A$ to 31.08 kcal/mol, 6.12 kcal/mol (16.5%) lower than the unsubstituted BCB. As for the two halogen substituents, 1-Br-BCB was about 33.59 kcal/mol, and comparatively the $\Delta G_A$ of 1-F-BCB was 0.36 kcal/mol lower than that of 1-Br-BCB, owing to its stronger electron-withdrawing ability.

The Gibbs free energy change ($\Delta G_R$) of the ring-opening reaction can actually evaluate the stabilities of initial (cyclic ring) and final (conjugated diene) state. From 1-NH$_2$-BCB to 1-CH$_3$-BCB, as the electron-donating ability decreased, $\Delta G_R$ gradually increased from 1.46 to 8.94 kcal/mol. On the other hand, for electron-withdrawing groups, the $\Delta G_R$ increased from 3.01, 4.23 to 9.85 kcal/mol with increasing electron-withdrawing abilities from 1-COOH-BCB, 1-CN-BCB to 1-NO$_2$-BCB. Besides, the $\Delta G_R$ of the two halogen-substituted BCBs (1-F-BCB and 1-Br-BCB) were higher than that of unsubstituted BCB (9.63 kcal/mol). Based on the above calculation results, the stronger electron-donating or weaker electron-withdrawing ability the substituent group owned, the more stable the ring-opened diene intermediate was.

Ring-opening of $C_1$ and $C_8$-position disubstituted BCB derivatives

To further understand the electronic effect on the ring-opening of BCB, eight substituents with different electronic effects, including NH$_2$, OH, OCOCH$_3$, CH$_3$ as electron-donating groups, and NO$_2$, CN, Br, COOH as electron-withdrawing groups, were selected to modify the $C_1$ and $C_8$ positions of BCB. All possible arrangements of substituents were considered. The results were shown in Figure 2c and 2d. Interestingly, four distinct conclusions can be drawn regarding the relationship between the $\Delta G_A$ of these disubstituted BCBs and its corresponding substituent effects.

1) The $\Delta G_A$ of the disubstituted BCB was lower than that of the corresponding monosubstituted BCB. Specifically, when $R_1$ was fixed as NH$_2$ and $R_2$ varied from NH$_2$ to NO$_2$ (named as 1-NH$_2$-8-$R_2$-BCB), $\Delta G_A$ decreased from 21.49 kcal/mol to 11.54 kcal/mol, less than that of 1-NH$_2$-BCB (24.06 kcal/mol). A similar trend was observed when $R_1$ was fixed as OH and other groups. (Figure 2c).

2) The $\Delta G_A$ of the disubstituted BCB with an electron-donating group was lower than that with electron-withdrawing groups. In the diagonal position in Figure 2c ($R_1 = R_2$), from 1-NH$_2$-8-NH$_2$-BCB to 1-NO$_2$-8-NO$_2$-BCB, as the electron-withdrawing ability of $R_1$ and $R_2$ increased simultaneously, $\Delta G_A$ increased. From 1-NO$_2$-8-NH$_2$-BCB to 1-NO$_2$-8-NO$_2$-BCB, where $R_1$ was fixed as NO$_2$, as the electron-withdrawing ability of $R_2$ increased, $\Delta G_A$ increased gradually. Similar trends were observed when $R_2$ was fixed as other electron-withdrawing groups.
Further, when $R_1$ changed from CH$_3$ to NH$_2$ and $R_2$ was fixed as NH$_2$ (i.e., 1-CH$_3$-8-NH$_2$-BCB to 1-NH$_2$-8-NH$_2$-BCB), the $\Delta G_A$ of disubstituted BCB decreased from 21.49 to 16.55 kcal/mol, indicating a decrease in $\Delta G_A$ with increasing electron-donating ability of substituents.

(3) An extra reduction of $\Delta G_A$ was observed, known as the “captodative effect”, when $R_1$ was an electron-donating group (NH$_2$, OH, OCOCH$_3$, CH$_3$) and $R_2$ was an electron-withdrawing group (NO$_2$, CN and COOH).

“Captodative effect” ($\Delta G_{AC}$): $\Delta G_{AC} = [\Delta G_A$ of BCB - $\Delta G_A$ of 1-R$_1$-8-R$_2$-BCB] - [\Delta G_A$ of BCB - $\Delta G_A$ of 1-R$_1$-BCB] - [\Delta G_A$ of BCB - $\Delta G_A$ of 1-R$_2$-BCB]. For example, $\Delta G_{AC}$ of 1-NH$_2$-8-NO$_2$-BCB = (37.2 -11.54) - (37.2 -24.07) - (37.2 -33.4) = 8.73 kcal/mol.

All BCB molecules with ”captodative effect” were listed in Figure 2d. Among them, $\Delta G_{AC}$ of 1-NH$_2$-8-NO$_2$-BCB was the largest. The $\Delta G_{AC}$ of 1-NH$_2$-8-R$_2$-BCB was larger than that of 1-OH-8-R$_2$-BCB, 1-OCOCH$_3$-8-R$_2$-BCB and 1-CH$_3$-8-R$_2$-BCB, respectively. The $\Delta G_{AC}$ increased with the electron-donating ability of $R_1$.

(4) In addition to the calculation of $\Delta G_A$, the $\Delta G_R$ for the ring-opening reaction of disubstituted BCBs were also determined (Figure S2). For a fixed $R_1$ and varying $R_2$ as electron-donating groups (NH$_2$, OH, OCOCH$_3$, CH$_3$), $\Delta G_R$ decreased gradually with the increase in the electron-donating ability, similar to the trend observed for $\Delta G_A$. Intriguingly, when $R_1$ = NH$_2$ and $R_2$ changed from NH$_2$, COOH, CN to NO$_2$, the $\Delta G_R$ of the four compounds were less than zero. Moreover, the $\Delta G_A$ of these four BCBs were the lowest among all the disubstituted BCBs, with values of 16.55, 13.46, 11.82, and 11.54 kcal/mol, respectively. This indicated that the ring-opening of these four disubstituted BCBs may spontaneously proceed towards $o$-dimethylquinone at 25 °C.

Ring-opening of monosubstituted BCB with complex electronic effect at C$_1$-position
For practical applications in microelectronic packaging, the low-temperature cured BCB units are still required to be chemically modified into a polymerizable monomer. Therefore, the simple electron-donating/withdrawing groups at C1 position may further undergo coupling reactions to yield intricate pendant bonds, demonstrating complex electronic and steric effects, such as ester, amide, ether, etc., which could have a substantial impact on the corresponding $\Delta G_A$.

**Scheme 2** Synthetic routes of compounds 3-8.

To investigate the $\Delta G_A$ of monosubstituted BCBs with complex electronic effect at C1 position and varying spatial structures, we designed eight BCB molecules and six of them (compounds 3-8) were synthesized (Scheme 2). The ring-opening temperatures of compounds 3-8 were further determined by DSC to verify their corresponding $\Delta G_A$ and the results were shown in Figure 3.

The DSC curves for compounds 3-8 showed very similar ring-opening temperatures at around 230 °C, which was only about 20 °C lower than that of pristine BCB (Figure 3b). Consistently, their calculated $\Delta G_A$ were also distributed around 31 kcal/mol, slightly lower than that of BCB (6.2 kcal/mol, 16.7%, Figure 3a). Notably, compounds 1 and 2 exhibited lower $\Delta G_A$ values of 25.42 and 27.13 kcal/mol, respectively, which were significantly lower than those of compounds 3-8. This effect can be attributed to the strong electron-donating effect of the NH$_2$ group. Based on the DFT calculations and DSC results, we found that modification on simple groups such as NH$_2$, OH, COOH, could greatly change the electronic effect. And spatial structure of different substituents had little effect on the $\Delta G_A$ and ring-opening temperatures of BCBs, consistent with Willson et al.'s report.$^{11d}$

**Figure 3** a) The calculated $\Delta G_A$ of compounds 1-8. b) DSC curves of compounds 3-8.

**Conclusions**

A systematic study of the substituent effect on the ring-opening behavior of BCB derivatives has been presented. The principal findings were as follows: the mono-/di-substituted BCBs, no matter with electron-donating groups or electron-withdrawing groups, demonstrated 8.2 – 69% lower $\Delta G_A$ than the unsubstituted one. The stronger electron-donating ability the substituents owned, the lower $\Delta G_A$ values it exhibited (e.g., 1-NH$_2$-BCB). The disubstituted BCBs with both an electron-donating group and an electron-withdrawing group at C1- and C8-position, respectively, exhibited the lowest $\Delta G_A$ of 11.54 kcal/mol, possibly due to the captodative effect between two substituents with distinct electronic attributes. Moreover, complex pendant chemical bonds, such as amide (CONHR), ester (COOR), acyloxy (OCOR), can substantially modify its electronic effect and $\Delta G_A$. These complex pendant substituents can reduce the ring-opening temperature by 20 °C compared to unsubstituted BCB, similar to the effects of electron-withdrawing groups. These results offer a theoretical basis for developing BCB-based functional materials with low curing temperatures and further promote the expansion of BCB application fields in high-temperature sensitive fields such as advanced displays and flexible electronics.
Experimental

Compound 3: 100mg 1-OH-BCB and 78mg propionic acid were added in a 25mL round-bottomed flask, then 5mL dry DCM was injected. And 191mg EDC and 122mg DMAP were added whereupon it was cooled. The mixture was stirred overnight under a nitrogen atmosphere at room temperature. After the reaction was completed, the solution was washed with 0.1mol/L HCl solution (60mL) and DCM (20mL × 3). Repeat with saturated salt and DCM. The organic layer was dried over MgSO₄ and evaporated in vacuo. Compound 7 was obtained as a colorless liquid with a yield of 80.5%. ¹H NMR (300 MHz, Chloroform-d) δ 7.32 (dq, J = 8.3, 4.2 Hz, 1H), 7.24 (s, 1H), 7.15 (d, J = 7.2 Hz, 1H), 5.93 (d, J = 4.7 Hz, 1H), 3.67 (dd, J = 14.5, 4.6 Hz, 1H), 2.39 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-d) δ 174.50, 144.35, 142.76, 129.94, 127.51, 123.57, 123.20, 77.25, 71.48, 38.95, 27.52, 9.06.

Compound 4: 100mg 1-OH-BCB, 175mg benzoyl chloride were added in a 25mL round-bottomed flask. Then 5mL dry DCM was injected, cooled in an ice bath for 5 min, 168mg Et₃N and 2mL dry DCM were added to another flask. And acyl chloride, diluted by 2mL dry DCM, was dropwis under ice bath. The reaction solution was stirred at room temperature overnight. After the reaction was finished, the reaction solution was washed with saturated salt water (60mL) and DCM (20mL × 3). The organic layer was dried over MgSO₄ and evaporated in vacuo, then it was diluted by 2mL dry DCM, cooled in an ice bath for 5 min, 168mg Et₃N and 2mL dry DCM were added to another flask. And acyl chloride, diluted by 2mL dry DCM, was dropwised under ice bath. The reaction solution was stirred at room temperature overnight. After the reaction was finished, the reaction solution was washed with saturated salt water (60mL) and DCM (20mL × 3). The organic layer was dried over MgSO₄ and evaporated in vacuo. A light yellow solid was obtained.

Compound 5: 300mg 1-COOH-BCB and 8mL sulfoxide chloride were added in a 25 mL round-bottomed flask. The mixture was refluxed at 80°C for 3 h until no bubbles were generated. The excess sulfoxide chloride was evaporated in vacuo, then it was diluted by 2mL dry DCM. 219mg n-butylamine, 310mg sulfoxide chloride were added in a 25 mL round-bottomed flask. The mixture was refluxed at 80°C for 3 h until no bubbles were generated. The excess sulfoxide chloride was evaporated in vacuo, then it was diluted by 2mL dry DCM, cooled in an ice bath for 5 min, 168mg Et₃N and 2mL dry DCM were added to another flask. And acyl chloride, diluted by 2mL dry DCM, was dropwised under ice bath. The reaction solution was stirred at room temperature overnight. After the reaction was finished, the reaction solution was washed with saturated salt water (60mL) and DCM (20mL × 3). The organic layer was dried over MgSO₄ and evaporated in vacuo. A light yellow solid was obtained with a yield of 81.7%. ¹H NMR (300 MHz, Chloroform-d) δ 8.12 – 8.06 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 6.18 (dd, J = 4.6, 2.0 Hz, 1H), 3.78 (dd, J = 14.5, 4.5 Hz, 1H), 3.39 (d, J = 13.7 Hz, 1H). ¹³C NMR (75 MHz, Chloroform-d) δ 166.58, 144.31, 142.80, 133.04, 130.06, 129.72, 128.35, 127.58, 123.73, 123.25, 77.24, 72.02, 39.09.

Compound 6: 300mg 1-COOH-BCB and 226mg phenylamine were added in a 25 mL round-bottomed flask, then 10mL dry DCM was injected. And 389mg EDC and 248mg DMAP were added whereupon it was cooled. The mixture was stirred overnight under a nitrogen atmosphere at room temperature. After the reaction was completed, the solution was washed with 0.1mol/L HCl solution (60mL) and DCM (20mL × 3). Repeat with saturated salt and DCM. The organic layer was dried over MgSO₄ and evaporated in vacuo. Compound 8 was obtained as light yellow liquid with a yield of 66%. ¹H NMR (400 MHz, DMSO-d₆) δ 10.18 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.14 (d, J = 6.0 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 4.44 (dd, J = 5.3, 2.8 Hz, 1H), 3.42 (dd, J = 14.0, 2.8 Hz, 1H), 3.35 (dd, J = 14.0, 5.3 Hz, 1H). ¹³C NMR (75 MHz, Chloroform-d) δ 172.71, 144.90, 142.30, 137.64, 129.01, 128.83, 127.94, 127.47, 123.73, 123.22, 119.89, 77.25, 48.83, 35.69.

Compound 7: 200mg of 1-COOH-BCB, 730μL of MeOH were placed in a schlenk tube. Then 333μL of concentrated H₂SO₄ was added and refluxed overnight. After the reaction was completed, the reaction solution was washed with brine (60mL) and DCM (20mL × 3). The organic layer was dried over MgSO₄ and evaporated in vacuo. Compound 8 was obtained as colorless liquid with a yield of 66%. ¹H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.21 (m, 2H), 7.17 (d, J = 5.9 Hz, 1H), 7.10 (t, J = 4.3 Hz, 1H), 4.32 (t, J = 4.2 Hz, 1H), 3.74 (s, 3H), 3.50 – 3.46 (m, 2H). ¹³C NMR (75 MHz, Chloroform-d) δ 172.71, 144.22, 142.74, 128.21, 127.36, 122.92, 122.55, 77.24, 52.04, 45.79, 34.05.
flask. The mixture was refluxed at 80°C for 3 h until no bubbles were generated. The excess sulfoxide chloride was evaporated in vacuo, then it was diluted by 2mL dry DCM. 188 mg phenol, 280 mg triethylamine and 3 mL dry DCM were added to another flask. And acyl chloride, diluted by 2mL dry DCM, was dropwised under ice bath. The reaction solution was stirred at room temperature overnight. After the reaction was finished, the reaction solution was washed with brine(60mL) and DCM (20mL×3). The organic layer was dried over MgSO₄ and evaporated in vacuo. A colorless liquid was obtained with a yield of 71%. ¹H NMR (300 MHz, Chloroform-d) δ 7.36 (t, J = 7.7 Hz, 2H), 7.22 (d, J = 6.8 Hz, 3H), 7.16 – 7.04 (m, 3H), 4.54 (dd, J = 5.4, 3.0 Hz, 1H), 3.58 (qd, J = 14.3, 4.2 Hz, 2H). ¹³C NMR (75 MHz, Chloroform-d) δ 170.69, 150.81, 144.22, 142.40, 129.66, 129.43, 128.47, 127.57, 125.87, 123.08, 121.51, 115.27, 77.24, 46.05, 34.02.

Supporting Information
The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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References


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The Authors

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Left to Right: Ziwei Yuan, Quan Sun, Jinchong Xiao, Pingxia Zhang, Konstantin S. Levchenko, Dmitry Y. Demin, and Wenxin Fu

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The ring-opening behaviors of benzocyclobutene derivatives with one or two substituents on the four-membered ring were studied...