

Article

Preparation and Characterization of Carboxylic Acid Adducts of Gabapentin

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Abstract. Gabapentin, $C_9H_{17}NO_2$, 2-[1-(aminomethyl)cyclohexyl]acetic acid, is used as an anticonvulsant drug to help control partial seizures in the treatment of epilepsy and to manage postherpetic neuralgia after 'shingles'. Cocrystals of gabapentin with a series of hydroxyl carboxylic acids and a cocrystal of gabapentin with oxalic acid were previously reported. The adduct with salicylic acid was prepared, along with adducts of two dicarboxylic acids, succinic acid and adipic acid, and an adduct with 1,2,4,5-benzenetetracarboxylic acid. Formation of new materials is demonstrated by new unique physical properties, including lower melting points (102.8-105.1 °C, 90.0-93.0 °C, and 152.4-154.8 °C for succinic acid, adipic acid, and 1,2,4,5-benzenetetracarboxylic acid products, respectively) than those of the individual starting materials. Shifts in infrared bands for $\nu(O-H)$, $\nu(N-H)$, and $\nu(C=O)$ bands confirm adduct formation and indicate the nature of the interactions between the two components in the lattice.

Keywords: Cocrystal, gabapentin, 2-[1-(aminomethyl)cyclohexyl]acetic acid, adducts.

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1. Introduction

Gabapentin, $C_9H_{17}NO_2$, 2-[1-(aminomethyl)cyclohexyl]acetic acid is a drug used as an anticonvulsant to help control partial seizures in the treatment of epilepsy. It reduces the number of seizures by increasing the amount of a closely related chemical called γ -aminobutyric acid (GABA) in the brain. It is also used in adults to manage a condition called postherpetic neuralgia, the pain that occurs after “shingles”.

Pharmaceutical cocrystallization is of great interest in the field of drug development. Formation of cocrystals of pharmaceutical solids can often improve physicochemical properties, such as solubility, stability, bioavailability, hygroscopicity, and compaction behavior [1]. In the simplest sense cocrystals are crystalline molecular complexes containing two or more species with essentially molecular properties bound together in a single crystal lattice through noncovalent interactions [2-3]. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of periodic molecular networks with only one molecular component (single component crystals and their polymorphs) or with multiple molecular components (cocrystals or multiple component crystals, including solvates) in the crystalline state. The design of experiments to exploit formation of extended networks based on noncovalent interactions is a goal of crystal engineering.

Gabapentin contains strong hydrogen bond donor and strong hydrogen bond acceptor groups (see Fig. 1) which makes its participation in such networks possible. Four crystalline forms of gabapentin have been reported [4-6], attesting to its flexibility in forming supramolecular structures. Form I is gabapentin monohydrate, and Forms II, III, and IV are the α -gabapentin, β -gabapentin, and γ -gabapentin polymorphs, respectively. Compounds containing carboxylic acid functional groups can readily interact with the $-NH_2$ and $-COOH$ fragments of un-ionized gabapentin, or the $-NH_3^+$ and $-COO^-$ fragments of Zwitterionic gabapentin (Fig. 1) to form network synthons as seen in previous studies with GABA and gabapentin with carboxylic acids [7-10]. Melting points of the four known forms of gabapentin are given in Table 1.

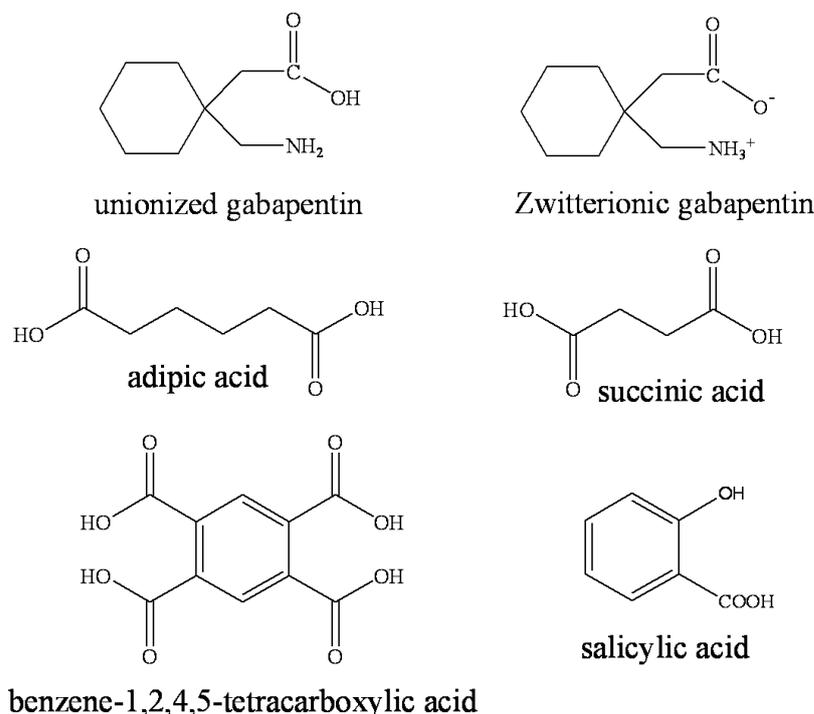


Fig. 1. Structural diagrams of gabapentin and the organic acids used in this study.

Cocrystallization of gabapentin with oxalic acid was reported in 2008 [9] and with a series of hydroxyl carboxylic acids in 2009 [10]. The 2008 study included a survey of the Cambridge Structural Database, CSD that identified over 12,000 instances of the particular bonding pattern as illustrated in Figure 2(a). The largest fraction of the CSD hits involves four individual moieties that are not covalently connected. Many involve two chemically different species, and thus, are cocrystalline or other multicomponent systems. In graph set notation this pattern is designated $R_4^2(8)$, where R identifies it as a ring, a cyclic pattern of bonds,

the subscript denotes the number of hydrogen bond donors involved in the set, and the superscript denotes the number of hydrogen bond acceptors involved in the set [11]. An individual pattern of such supramolecular interactions is often called a synthon (or sometimes a supramolecular synthon), and can be understood as a logical extension of the concept of functional group originating in organic chemistry. While it is not necessary for a synthon to be symmetric, both synthons illustrated in Fig. 2 are often found in the solid state positioned about a crystallographic inversion center or exhibiting pseudo centrosymmetry. The CSD survey finds 918 hits for structures exhibiting the $R_4^2(8)$ synthon in which the donor is an amino group ($-\text{NH}_2$) and the acceptor is a carbonyl group ($>\text{C}=\text{O}$). Ammonium donor ($-\text{NH}_3^+$) and carboxylate acceptor ($-\text{COO}^-$) forms are also well represented in the CSD survey. The gabapentin oxalate report itself has an example of a crystallographically centrosymmetric $R_4^2(8)$ synthon involving the ionized forms.

Table 1. Melting points of gabapentin polymorphs and gabapentin monohydrate.

Form	Species	Melting point (°C)	Reference
I	gabapentin monohydrate	156.0-156.7	[4]
II	α -gabapentin	160.0-162.0, 155.0-166.0 ^a	[5-6]
III	β -gabapentin	156.0-158.0, 155.0-168.0 ^a	[5-6]
IV	γ -Gabapentin	150.0-168.0 ^a	[6]

^aMelting point measured by DSC [6].

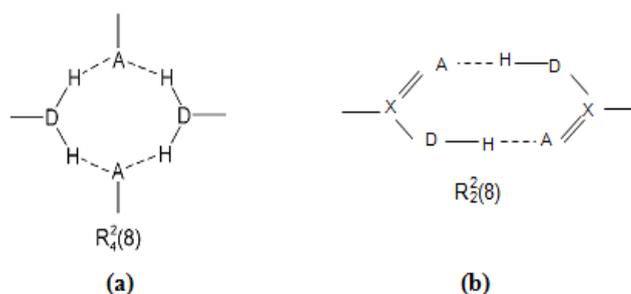


Fig. 2. Graph set notation for two simple synthons relating to carboxylic acids. a) an $R_4^2(8)$ synthon and b) the $R_2^2(8)$ synthon as found in a carboxylic acid dimer. D represents a hydrogen bond donor and A represents a hydrogen bond acceptor.

The present work reports preparation of adducts of gabapentin with two dicarboxylic acids, succinic acid and adipic acid, and an adduct with benzene-1,2,4,5-tetracarboxylic acid. Also, another adduct of gabapentin with salicylic acid was found while preparing the reported adduct from a modified solvent system. Formation of new materials is demonstrated by new unique physical properties, including melting points and morphologies. Shifts in infrared bands confirm adduct formation and indicate the nature of the interactions between the two components in the lattice.

2. Experimental

2.1. Chemicals and Solvents

Commercial chemicals: adipic acid (Acros Organics 99%, laboratory grade), succinic acid (Carlo Erba 99.5%, AR grade), benzene-1,2,4,5-tetracarboxylic acid, pyromellitic acid, (Acros Organics 96%, laboratory grade), and salicylic acid (Mallinckrodt, AR grade), methanol (Carlo Erba 99.9%, AR grade), and DI water.

Separation of gabapentin: Dissolve 7.49 g, the content of 20 capsules, of Gabapentin drug (The Government Pharmaceutical Organization, Thailand, 300 mg gabapentin/capsule) in 400 mL of methanol:H₂O (3:1 v/v)

and warm at 40 °C with stirring (400 rpm) for 40 min. Filter the hot solution and rinse the solids with cold DI water. Heat the filtrate at 50 °C until the volume is reduced to 130 mL. Cool and let stand at room temperature for 3 days to crystallize. The colorless crystals were separated by vacuum filtration on a Buchner funnel and washed with 1 mL of cold DI water giving 5.10 g of gabapentin monohydrate (77% recovery).

2.2. Cocrystallization

Gabapentin monohydrate (378 mg, 2 mmol) and adipic acid (146 mg, 1 mmol) were ground together 10 min, dissolved in 5 mL of methanol:H₂O (2:1 v/v), and warmed at 37 °C 20 min with stirring, reducing the volume to 2.5 mL. Crystalline product was obtained after 5 weeks of controlled evaporation at room temperature. Similar methodology was used for reactions of 2:1 mole ratio gabapentin with succinic acid, of 1:1 mole ratio gabapentin with benzene-1,2,4,5-tetracarboxylic acid, and of 1:1 mole ratio gabapentin with salicylic acid.

2.3. Characterizations

Crystal morphologies were observed with scanning electron microscopy (SEM) using a JSM 6400 electron microscope (JEOL, Japan). Infrared (IR) spectra were acquired on a Perkin-Elmer model spectrum GX Fourier transform infrared spectrophotometer in wave number range 400-4000 cm⁻¹ from KBr pellets. Melting points were measured with a Stuart Model SMP 30 melting point apparatus (Bibby Scientific, UK).

3. Results and Discussion

Gabapentin was separated from commercially available drug capsules with high recovery using a methanol:H₂O mixed-solvent system. Gabapentin crystals show rectangular crystal morphology as shown in Fig. 3. The product was characterized by melting point and IR spectroscopy. The measured melting point is 154.0-155.6 °C, which corresponds to the melting point of gabapentin monohydrate (Table 1, Form I) as well as to that of β-gabapentin (Form III).

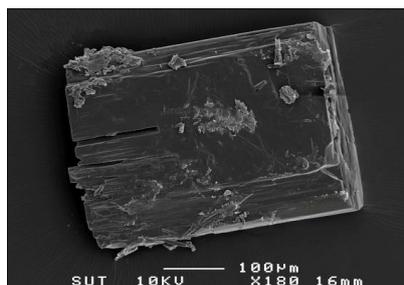


Fig. 3. SEM image of gabapentin crystal.

The infrared spectrum of the crystalline product is presented in Fig. 4. The N–H stretching band, $\nu(\text{N-H})$, appears at 3286 cm⁻¹ and the bending bands, $\delta_{\text{as}}(\text{N-H})$ and $\delta_{\text{s}}(\text{N-H})$, at 1615 cm⁻¹ and 1544 cm⁻¹, respectively. A $\nu(\text{N-H})$ band at 2144 cm⁻¹ corresponds to the additional vibrational band that often appears at about 2100 cm⁻¹ when amine is converted to ammonium. Further, the $\nu(\text{C=O})$ band is shifted lower at 1662 cm⁻¹, compared to the typical $\nu(\text{C=O})$ vibration of a carboxylic acid (1700-1730 cm⁻¹), consistent with the partial delocalization that often occurs in a carboxylate ion. The $\nu(\text{C-O})$ band of carboxylate shows at 1400 cm⁻¹. The band at 3389 cm⁻¹ is assigned to $\nu(\text{O-H})$ of water, suggesting the product is gabapentin monohydrate. The total spectrum is quite similar to gabapentin form I reported in the previous work [12], confirming the product to be gabapentin monohydrate.

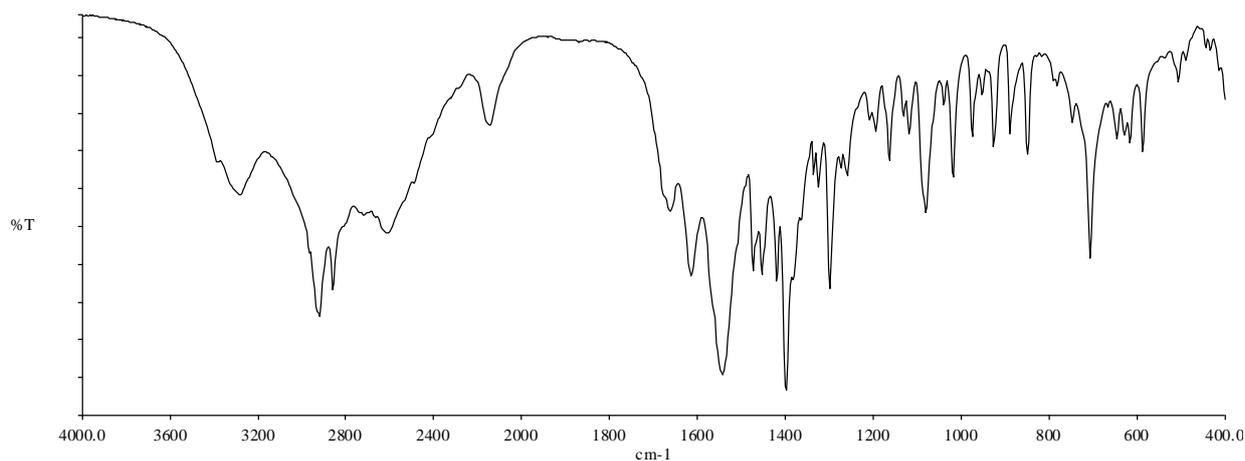


Fig. 4. IR spectrum of gabapentin monohydrate.

Morphologies of the solid products of the cocrystallization experiments, observed with SEM, are shown in Fig. 5. SEM images of adducts of gabapentin with adipic acid, succinic acid, and benzene-1,2,4,5-tetracarboxylic acid (Fig. 5(a-c)) show plate morphology while the crystalline product for the adduct of gabapentin with salicylic acid shows prism morphology.

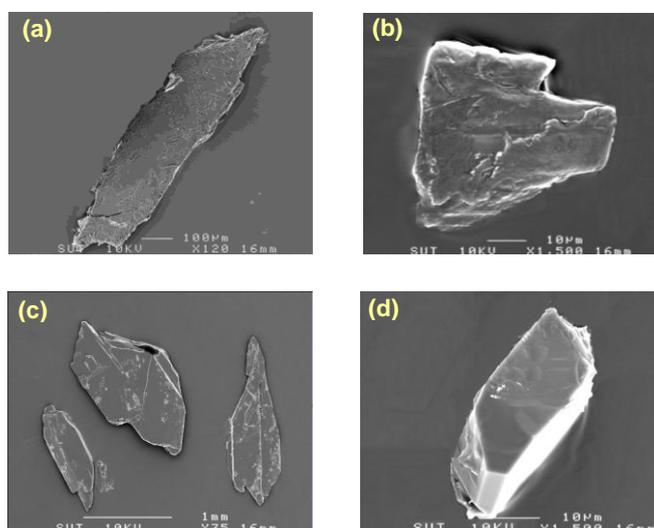


Fig. 5. SEM images of adducts of gabapentin with (a) adipic acid, (b) succinic acid, (c) benzene-1,2,4,5-tetracarboxylic acid, and (d) salicylic acid.

Formation of new materials is demonstrated by new unique physical properties, including lower melting points than the starting materials (Table 2). The melting points of the solid product adducts of gabapentin with succinic acid and with salicylic acid are quite similar and very much reduced, similar to the adduct with malic acid [10]. The melting point of the solid product from reaction of gabapentin with salicylic acid is lower (about 30 °C) than the 131 °C previously reported [10]. The narrow range of the current melting point determination suggests it is indeed a pure compound, and thus is a new adduct of gabapentin with salicylic acid.

Infrared spectra of the adducts were compared to the spectra of both gabapentin and the relevant carboxylic acid starting materials to determine the identity of the solids isolated from the cocrystallization experiments. The band positions and assignments for the solid products are summarized in Table 3.

The IR result for the gabapentin:salicylic acid adduct is consistent with the previous report [10], but shows new peaks at 1670-1690 cm^{-1} and 1633 cm^{-1} when compared to the previous work. These two peaks are assigned to $\nu(\text{C}=\text{O})$ of carboxylate group and $\delta(\text{N}-\text{H})$ of ammonium ion, respectively.

Table 2. Melting points of reactants and multicomponent crystalline products.

	Material	Melting point (°C)
reactants	gabapentin	154.0-155.6
	adipic acid	152.0
	succinic acid	185.0
	benzene-1,2,4,5-tetracarboxylic acid	281.0
	salicylic acid	159.0
adducts	gabapentin:adipic acid	90.0-93.0
	gabapentin:succinic acid	102.8-105.1
	gabapentin:benzene-1,2,4,5-tetracarboxylic acid	152.4-154.8
	gabapentin:salicylic acid	102.0-105.0

Gabapentin:adipic acid adduct: The IR spectrum contains peaks due to both reactant species. Peaks at 2930 and 2859 cm^{-1} are assigned to the $\nu(\text{C-H})$ of gabapentin. The $\nu(\text{N-H})$ band of gabapentin is shifted to lower energy (3229 cm^{-1} , $\Delta\nu_{(\text{N-H})} = 57 \text{ cm}^{-1}$) indicating the $-\text{NH}_3^+\cdots\text{O}^-$ interaction of the ionized ammonium of gabapentin with a carboxylate group. The $\nu(\text{C=O})$ of a carboxylic acid group at 1702 cm^{-1} is shifted to higher energy compared to both reactants, indicating an $-\text{O-H}\cdots\text{O}^-$ interaction of the carboxylic acid group of gabapentin with a carboxylate of adipic acid with the possibility that an $\text{R}_4^2(8)$ hydrogen bond synthon has formed. The band at 1645 cm^{-1} corresponds to $\nu(\text{C=O})$ of carboxylate groups. While similar discussion of 2:1 gabapentin:oxalic acid adducts has been reported [9], the possibility of formation does not prove the synthon has formed as is illustrated by the GABA:oxalic acid study [7, 8] which contains the ionized ammonium and carboxylate forms, but does not contain the $\text{R}_4^2(8)$ hydrogen bond synthon.

Gabapentin:succinic acid adduct: The IR spectrum shows peaks at 2935 and 2859 cm^{-1} due to $\nu(\text{C-H})$ and peaks at 1714 and 1644 cm^{-1} attributed to $\nu(\text{C=O})$ of carboxylic acid and carboxylate, respectively. The $\nu(\text{N-H})$ band was observed as a weak broad band at 3258 cm^{-1} , shifted 51 cm^{-1} to lower energy when compared to the gabapentin spectrum, indicating an $-\text{NH}_3^+\cdots\text{O}^-$ interaction of the ionized ammonium of gabapentin with a carboxylate of succinic acid. The $\nu(\text{C=O})$ peak shifted to higher energy at 1725 cm^{-1} when compared to the succinic acid spectrum, similar to $\nu(\text{C=O})$ in the gabapentin:adipic acid adduct suggesting similar formation of hydrogen bond synthons in the structures.

Gabapentin:benzene-1,2,4,5-tetracarboxylic acid adduct: The $\nu(\text{O-H})$ bands at 3532 and 3389 cm^{-1} are observed in the product spectrum with no peak shift compared to the benzene-1,2,4,5-tetracarboxylic acid spectrum, suggesting the carboxylic acid groups do not change to the carboxylate form. There are two $\nu(\text{C=O})$ bands at 1690-1712 cm^{-1} region indicating different types of hydrogen bond formation between the carboxylic acid groups of benzene-1,2,4,5-tetracarboxylic acid with Zwitterionic gabapentin. Vibrational bands at 1590 and 1626 cm^{-1} are assigned to $\delta(\text{N-H})$ of the ionic $-\text{NH}_3^+$ and $\nu(\text{C=O})$ of carboxylate, respectively. Similar discussion of 1:1 gabapentin:trimesic acid adducts has been previously reported [13].

Gabapentin:salicylic acid adduct: The $\nu(\text{N-H})$ band at 3253 cm^{-1} is shifted 33 cm^{-1} to lower energy compared to free gabapentin. A very broad peak in the 3300-2700 cm^{-1} region indicates hydrogen bond interactions between the $-\text{NH}_3^+$ group of gabapentin and a $-\text{COO}^-$ carboxylate group. Two $\nu(\text{C=O})$ peaks at 1677 and 1713 cm^{-1} shifted to higher frequencies compared to the reactants indicates that the carbonyl group is involved in hydrogen bond interaction(s). A previous report on a 1:1 adduct of gabapentin and salicylic acid [10] shows intramolecular interaction between $-\text{O-H}$ and a carboxylate group in salicylic acid, and intermolecular $-\text{NH}_3^+\cdots\text{O}^-$ interactions between ionized ammonium of gabapentin with the carboxylate group of ionized salicylic acid. The solid product from the previous work shows a significantly higher melting point than the product of this work. The current product also shows additional peaks at 1670-1690 cm^{-1} and 1633 cm^{-1} in the IR spectrum. These two peaks are assigned to $\nu(\text{C=O})$ of carboxylate group and

$\delta(\text{N-H})$ of ionized ammonium, respectively. These results indicate the formation of a new gabapentin:salicylic acid adduct.

Table 3. IR spectral peak positions and assignment of gabapentin monohydrate and solid product peaks.

Gabapentin	Adduct of gabapentin with acid				Assignment
	Adipic acid	Succinic acid	Benzene-1,2,4,5-tetracarboxylic acid	Salicylic acid	
3389 sh		3481 vw	3532 w, sp		$\nu(\text{O-H})$ (3600-3200 cm^{-1})
3386 m, br	3229 m	3358 sh 3235 vw	3389 sh 3055 vw	3253 w	$\nu(\text{N-H})$ (3500-3100 cm^{-1})
2922 s, sp	2930 s, sp	2935 vs, sp	2934 m	2928 s	$\nu(\text{C-H})$ aliphatic (3100-2600 cm^{-1})
2861 m, sp	2860 m, sp	2859 m, sp	2866 w	2861 m	
2716 vw	2668 vw	2589 w	2646 vw	2708 vw	
2609 w	2540 vw 1926 br	2505 sh	2508 vw	2505 vw	
2145 m					$\nu(\text{N-H})$ ammonium (near 2100 cm^{-1})
1663 w	1702 vs, sp	1715 vs, sp	1713 sh	1714 w, sp	$\nu(\text{C=O})$ carboxylic (1730-1700 cm^{-1}) $\nu(\text{C=O})$ carboxylate (asymmetric, 1600 cm^{-1})
1615 s, sp	1645 s, sp	1645 vw	1693 s	1677 m, sp	
1544 vs, sp					$\delta(\text{N-H})$ (1640-1550 cm^{-1})
1474 m, sp	1568 s, sp	1530 vs	1626 w	1632 vw	combination of $\nu(\text{C=C})$, $\delta(\text{O-H})$ (1650-1450 cm^{-1}), and $\nu(\text{C=O})$ carboxylate (symmetric, 1400 cm^{-1})
1455 m, sp	1488 s, sp	1456 m, sp	1592 sh	1594 m, sp	
1420 m, sp	1465 w, sp	1404 m, sp	1487 m	1556 w	
1400 vs, sp			1443 sh 1413 m, sp	1513 w 1483 vs, sp 1454 s, sp	
1326 w, sp	1368 w, sp	1321 s	1369 vw, sp	1390 m, sp	Combination of $\delta(\text{C-O})$, $\delta(\text{C-N})$, $\delta(\text{C-C})$ (1350-900 cm^{-1}) and $\nu(\text{C-O})$ carboxylic (1320-1210 cm^{-1})
1300 vs, sp	1314 w	1305 s	1340 w, sp	1357 w	
1260 w	1276 vs, sp	1213 w	1305 w, sp	1327 vw	
1209 vw	1232 w, sp	1177 vs, sp	1268 vs	1305 m, sp	
1196 w, sp	1190 vs, sp	1127 w	1222 vw	1252 s	
1165 m, sp	1125 m, sp	1085 w, sp	1196 vw	1220 vw	
1119 w, sp	1079 m, sp	1057 vw, sp	1116 m, sp	1201 w, sp	
1082 s, sp	1059 w, sp	999 m, sp	1053 w	1175 m	
1020 s, sp	982 m, sp	950 w	957 m	1157 vw	
976 m, sp	909 m, sp	883 w	921 m	1140 w, sp	
927 m, sp	850 w, sp	798 w, sp	889 m	1087 w, sp	
890 m, sp	800 w, sp	775 w, sp	865 vw	1029 m, sp	
850 m, sp	762 w	740 w, sp	814 s, sp	974 vw	
708 vs, sp	708 vs, sp	696 vw	754 m, sp	926 w	
647 w, sp	625 m, sp	633 m, sp	693 w	859 m, sp	
627 w, sp	523 m, sp	608 m, sp	646 w	805 m, sp	
617 w, sp		597 w	579 w, sp	758 vs, sp	
589 w, sp			511 w, sp	702 s, sp	
508 vw, sp				669 s, sp 536 m, sp 504 w, sp	

Abbreviations: vs = very strong, s = strong, m = medium, w = weak, vw = very weak, sh = shoulder, sp = sharp, br = broad; ν = stretching and δ = bending.

4. Conclusion

Pure gabapentin was separated from the drug Neurontin with high recovery, 85 % based on the quantity of gabapentin in a capsule. Three new solid state molecular complexes; 2:1 gabapentin:adipic acid, 2:1 gabapentin:succinic acid, and gabapentin:benzene-1,2,4,5-tetracarboxylic acid adduct were formed. The product combining gabapentin with salicylic acid shows a lower melting point than the adduct reported in published work. Shifts of infrared bands and lower melting points compared to the individual starting materials indicate adduct formation and the nature of the interactions between the two components in the lattice.

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