COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Polymorphism in butylated hydroxy anisole (BHA)

Jennifer A. McMahon,[a] Michael J. Zaworotko[a] and Julius F. Remenar*[b]

[a] *Department of Chemistry, University of South Florida, 4202 East Fowler Avenue (SCA 400), Tampa, FL, 33620-5205, USA. E-mail: xtal@usf.edu; Tel: 813-974-4129*

[b] *TransForm Pharmaceuticals Inc., 29 Hartwell Avenue, Lexington, MA, 02421-3102, USA. E-mail: jremenar@transformpharma.com; Tel: 781-674-7927*

Received (in Columbia, MO, USA) 19th September 2003, Accepted 14th November 2003
First published as an Advance Article on the web 6th January 2004

Single crystal X-ray analysis of butylated hydroxy anisole (BHA) reveals the existence of two polymorphs with dramatically different crystal packings sustained by OH···ether supramolecular heterosynthons: double helices (Form I) and discrete hexameric assemblies (Form II).

Polymorphism, the ability of a substance to exist in more than one crystalline form,[1] has always been relevant to the pharmaceutical industry since bioavailability and physical properties (solubility, dissolution rate, shelf life, *etc*.) can be critically dependent on crystal packing. It is also particularly topical because of intellectual property issues associated with active pharmaceutical ingredients (APIs),[2] which tend to be predisposed to exhibit polymorphism because they inherently possess exofunctional groups that have multiple avenues for self-assembly. An analysis of polymorphism in organic crystals[3] suggested that it is most common in molecules with more than one functional group that is capable of hydrogen bonding and/or those that contain flexible groups that are able to form strong hydrogen bonds such as OH and NH_2.

Butylated hydroxy anisole (BHA) represents a small molecule that contains flexible groups and hydrogen bond donor and acceptor sites, but it has not been structurally characterized even though its use as an antioxidant in solid dosage forms is ubiquitous throughout the pharmaceutical industry.[4,5] Commercial BHA is a mixture of 90–95% 3-*tert*-butyl-4-hydroxy anisole and 5–10% of the 2-*tert*-butyl isomer, referred to as 3-BHA (Fig. 1) and 2-BHA respectively. Furthermore, the behaviour of BHA is complex and its ability to successfully retard degradation varies depending on concentration, choice of excipients and processing methods, and storage conditions.[4,5] Indeed, in some cases, BHA appears to cause oxidation of the drug in certain formulations/conditions while protecting it in others, even at the same BHA loading.[6] The primary mode of action of BHA is well known;[7,8] it donates a hydrogen atom to a free radical, thus becoming a free radical itself. The BHA radical is stabilized by resonance and interferes with the propagation step of the radical reaction, thereby retarding the degradation.

We report herein single crystal X-ray characterization of both the form of 3-BHA found in commercial BHA (Spectrum Chemical, NJ) and a new polymorph, designated herein as form I and form II, respectively. **Form I** of 3-BHA forms rod-like triclinic crystals (Fig. 2)†. Molecules of 3-BHA self-assemble *via* OH···ether hydrogen bonds. This head-to-tail interaction results in a 4-fold helix, which intertwines with a second helix to form a double helical structure reminiscent of that in DNA. O···O distances of 2.707, 2.710 and 2.740 Å are within expected ranges for such interactions. The t-butyl groups orient outward meaning that the exterior surface of the helix is hydrophobic. The melting point is 61 °C and the calculated density is 1.158 g/cm^3.

Form II (Fig. 3) exists as block-like trigonal crystals.‡ It also consists of supramolecular structures that are the result of head-to-tail OH···ether hydrogen bonds (O···O = 2.778 Å). However, form II is a discrete species that results from the self-assembly of 6 molecules and, unlike form I, all *tert*-butyl groups face inward. The melting point is 64.8 °C and the calculated density, 1.136 g cm^{-3}, is slightly lower than that of form I. The OH···O(ether) supramolecular synthon[9] that occurs in these 3-BHA polymorphs represents an example of a one-point interaction and therefore it should be unsurprising that the angle of interaction between adjacent molecules can vary enough to generate such different supramolecular structures as in forms I and II of 3-BHA. It might appear to be somewhat surprising that it occurs instead of OH···OH supramolecular synthons. However, a CSD[10] survey ($R < 0.075$, 3D coordinates determined) revealed the presence of 3913 crystal structures that contain both a phenol moiety and a methoxy group. Of these structures, 1079 (28%) were found to contain the OH···ether interaction whereas only 937 (24%) exhibited OH···OH hydrogen bonds. The presence of such supramolecular heterosynthons is also of potential relevance in the context of molecular co-crystals that might involve at least one API,[11] the use

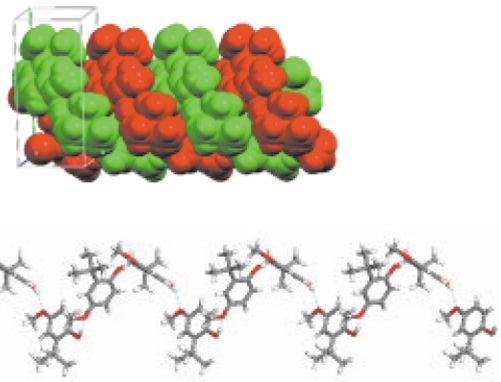

Fig. 2 Top, a space-filling diagram of the double helical structure of Form I. Bottom, a single 4-fold helix of the 3-BHA double helix.

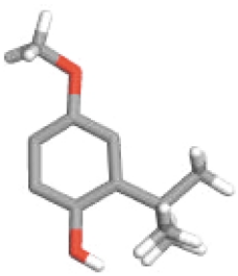

Fig. 1 The molecular structure of 3-BHA.

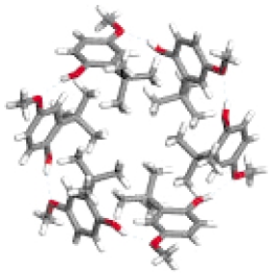

Fig. 3 The supramolecular hexameric structure exhibited by form II of 3-BHA.

DOI: 10.1039/b311606a

of templates for organic synthesis[12] and the generation of organic materials.[13]

The crystal packings of several BHA-related molecules (Fig. 4) were analyzed to compare hydrogen bonding motifs and crystal packing. In simple alcohols such as MeOH, EtOH and *tert*-BuOH, OH···OH···OH interactions afford zigzag chains or helices. Phenol and 2-methylphenol form OH···OH 3-fold helices, whereas 4-methoxyphenol forms an OH···OH zigzag chain. A similar situation was observed in 4-bromophenol, which forms a 4-fold helix *via* OH···OH hydrogen bonds. It is interesting to note that the methoxy group in 4-methoxyphenol does compete with alcohol–alcohol interactions and does not engage in hydrogen bonding. However, for 2,6-di-*tert*-butyl-4-methoxyphenol, an OH···OCH_3 hydrogen bond occurs rather than an OH···OH interaction and in 4-bromo-2,6-di-*tert*-butylphenol there are no hydrogen bond interactions. Therefore, there is precedent for adjacent *tert*-butyl groups to sterically hinder OH···OH interactions and thereby facilitate OH···ether hydrogen bonds, as is the case for both forms of 3-BHA reported herein.

The existence of such dramatically different supramolecular structures, including one that has no precedence in related molecules, underlies the need to gather structural data about polymorphs and opens up opportunities for systematic structure–property studies. It is also closely related to the subject of supramolecular isomerism. Supramolecular isomerism, the existence of more than one network superstructure for the same molecular building blocks, is relatively facile to rationalize in the context of coordination polymers.[14] Indeed, polymorphism can be considered a subset of supramolecular isomerism since polymorphism can be rationalized on the basis of supramolecular interactions and changes in the packing of a polymorph often lead to very different superstructures. Interestingly, as illustrated in Fig. 5, supramolecular isomers of coordination polymers formed from

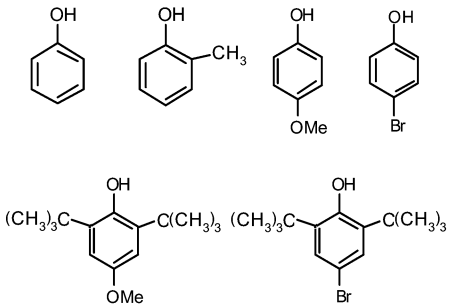

Fig. 4 Molecular structure of BHA-related molecules analyzed for comparison with BHA: Top, phenol, 2-methylphenol, 4-methoxyphenol, 4-bromophenol. Bottom, 2,6-di-*tert*-butyl-4-methoxyphenol, 4-bromo-2,6-di-*tert*-butylphenol.

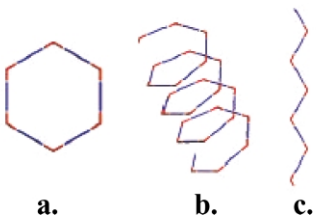

Fig. 5 Schematic representation of possible supramolecular isomers from the assembly of identical angular components; (a) hexagon; (b) helix; (c) zigzag chain.

self-assembly of angular building blocks include discrete (*e.g.* square,[15] hexagon[16]) or infinite structures (*e.g.* helix,[15,17] zigzag[16] chain). Two of these supramolecular isomers are observed in the polymorphs of 3-BHA and it is conceivable that 3-BHA will also be able to form polymorphs that contain zigzag superstructures of the type observed in other alcohols.

In conclusion, the alcohol–ether interaction found in two polymorphic forms of 3-BHA appears to be facilitated by steric hindrance of the alcohol by the *tert*-butyl group. These interactions sustain head-to-tail self-assembly of 3-BHA molecules in two dramatically different modes that are nonetheless rational based upon structures observed in the field of coordination polymers.

Notes and references

† *Crystal data* for **Form I:** $C_{11}H_{16}O_2$, M = 180.24, triclinic, space group $P\bar{1}$; a = 6.3179(11), b = 14.364(3), c = 17.960(3) Å, α = 74.636(3), β = 80.608(4), γ = 86.767(3)°, V = 1550.5(5) Å^3, T = 100(2) K, Z = 6, μ(Mo–Kα) = 0.078 mm^{-1}, D_c = 1.158 Mg m^{-3}, λ = 0.71073 Å, F(000) = 588, $2\theta_{max}$ = 28.24°, 9728 reflections measured, 6805 unique (R_{int} = 0.0320). Final residuals for 352 parameters were R_1 = 0.0547, wR_2 = 0.1403 for $I > 2\sigma(I)$, and R_1 = 0.0871, wR_2 = 0.1618 for all 6805 data. CCDC 220677. See http://www.rsc.org/suppdata/cc/b3/b311606a/ for crystallographic data in .cif or other electronic format.

‡ *Crystal data* for **Form II:** $C_{11}H_{16}O_2$, M = 180.24, trigonal, space group $R\bar{3}$; a = 24.2612(11), b = 24.2612(11), c = 9.3049(8) Å, γ = 120°, V = 4743.1(5) Å^3, T = 100(2) K, Z = 18, μ(Mo–Kα) = 0.076 mm^{-1}, D_c = 1.136 Mg m^{-3}, λ = 0.71073 Å, F(000) = 1764, $2\theta_{max}$ = 28.30°, 10131 reflections measured, 2504 unique (R_{int} = 0.0600). Final residuals for 130 parameters were R_1 = 0.0435, wR_2 = 0.1185 for $I > 2\sigma(I)$, and R_1 = 0.0552, wR_2 = 0.1269 for all 2504 data. CCDC 220678. See http://www.rsc.org/suppdata/cc/b3/b311606a/ for crystallographic data in .cif or other electronic format.

1 W. C. McCrone, in *Physics and Chemistry of the Organic Solid State*, Eds. D. Fox, M. M. Labes and A. Weisemberg, Interscience, New York, 1965, 726.
2 (*a*) J. Bernstein, *Polymorphism in Molecular Crystals*, Clarendon Press, Oxford, 2002, Chapter 1; (*b*) J.-O. Henck, J. Bernstein, A. Ellern and R. Boese, *J. Am. Chem. Soc.*, 2001, **123**, 1834; (*c*) T. L. Threlfall, *Analyst*, 1995, **120**, 2435; (*d*) G. R. Desiraju, *Science*, 1997, **278**, 404.
3 J. A. R. P. Sarma and G. R. Desiraju, *Crystal Engineering: The Design and Application of Functional Solids*, Eds. M. J. Zaworotko and K. R. Seddon, Kluwer, Dordrecht, 1999, 325.
4 H. Verhagen, P. A. E. L. Schilderman and J. C. S. Kleinjans, *Chem.-Biol. Interact.*, 1991, **80**, 109.
5 J. W. Finley and P. Jr. Given, *Food Chem. Toxicol.*, 1986, **24**, 999.
6 L. Chalmers, *Soap Perfum. Cosmet.*, 1971, **44**, 29.
7 L. R. Mahoney, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 547.
8 T. R. Kommuru, M. Ashraf, M. A. Khan and I. K. Reddy, *Chem. Pharm. Bull.*, 1999, **47**, 1024.
9 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
10 F. H. Allen and O. Kennard, *Chem. Des. Autom. News*, 1993, **8**, 31.
11 S. Fleischman, L. Morales, B. Moulton, N. Rodríguez-Hornedo, R. Bailey Walsh and M. J. Zaworotko, *Chem. Commun.*, 2003, 186–7; S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des.*, 2003, **3**, 909–919.
12 T. Friscic and L. R. MacGillivray, *Chem. Commun.*, 2003, 1306–7.
13 J. C. MacDonald, P. C. Dorrestein and M. M. Pilley, *Cryst. Growth Des.*, 2003, **1**, 29–38.
14 B. Moulton and M. J. Zaworotko, *Chem. Rev.*, 2001, **101**, 1629.
15 F. M. Tabellion, S. R. Seidel, A. M. Arif and P. J. Stang, *J. Am. Chem. Soc.*, 2001, **123**, 7740.
16 H. Abourahma, B. Moulton, V. Kravtsov and M. J. Zaworotko, *J. Am. Chem. Soc.*, 2002, **124**, 9990.
17 K. Biradha, C. Seward and M. J. Zaworotko, *Angew. Chem. Int. Ed.*, 1999, **38**, 492.