

Explosive properties of 1-hydroxybenzotriazoles

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Abstract

1-Hydroxybenzotriazole and its derivatives are widely used as peptide coupling reagents. However, people are often not aware that such compounds show explosive properties when heated under defined confinement or when subjected to mechanical stimulus. 1-Hydroxybenzotriazole (HOBt) is able to propagate a detonation when a stronger booster is used. Sometimes explosive substances are desensitized to suppress their hazardous properties, yet depending on the amount and nature of desensitizer, the result is often not quite satisfactory.

During the last years, some 1-hydroxybenzotriazoles were tested at BAM. The results are presented in this paper.

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1. Introduction

For many years, 1-hydroxybenzotriazole (HOBt) has been used as a coupling reagent in peptide synthesis, especially in combination with dicyclohexylcarbodiimide (DCC). Later, other benzotriazole derivatives such as 6-chloro-1-hydroxybenzotriazole (6-Cl-HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt) have been introduced. During the last decade, phosphonium and aminium/uronium salts of hydroxybenzotriazoles have been suggested for the synthesis of peptides [1]. The explosive properties of these compounds are often not referenced in literature. Sometimes, material safety data sheets or papers [1] warn that hydroxybenzotriazoles may be unstable with a relatively high sensitivity to friction and sparks. In most cases, however, it is not mentioned how sensitive such substances are to heating under defined confinement and no warning is given with respect to their ability to propagate a deflagration or a detonation. The following note was published in the internet by a company about the explosive properties

of 1-hydroxy-7-azabenzotriazole [2]: “under one of the confinement and high temperature test conditions (exposure of a tube containing HOAt with a small opening to propane burner flames), HOAt exhibited characteristics that may lead to a reclassification under a Class 1 explosive category pursuant to U.S. Department of Transportation (DOT) regulations and UN Guidelines”. BAM received the information [3] that HOAt is sensitive to heating under defined confinement in a steel tube (Koenen test) with a limiting diameter of 12.0 mm (!), which is a relative high value considering the criteria for this test method (see also Section 2.1). However, with regard to the structure, it is not a surprise that this substance shows (violent) explosive properties when tested according to international directives and recommendations [4,5].

BAM is the competent authority in Germany for testing and classification of substances with explosive properties according to the German Explosives Act and according to the regulations concerning the transport of dangerous goods. As such, BAM has carried out tests on HOBt, wetted with 10 and 20% water (m/m), already in 1983 with the result that this substance showed explosive properties according to the Method A.14 [4]. Later on, 6-Cl-HOBt,

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HOBt, dry and wetted with different amounts of water and TBTU were investigated by BAM and Bayer AG. The object of this paper is to give information about the explosive properties of the investigated substances as a basis for safe handling.

2. Test procedure

Although the procedures and criteria of the test methods used are fully described in literature [4,5], some details of the test methods will be given below for a better understanding of the results.

2.1. Koenen test

The Koenen test is used to determine the sensitivity of a substance to the effect of intense heat under defined confinement. The apparatus consists of a non-reusable steel tube (25 mm outer diameter, 24 mm inner diameter, 75 mm length, mass about 25–28 g), which is closed by a plate made from heat-resisting chrome steel. Gases from the decomposition of the sample escape through a hole in the closing plate. The diameter of this hole may vary from 1.0 to 20.0 mm in well-defined increments. The tube is heated by a set of four propane gas burners at a strictly defined heating rate. The tube is filled with 27 cm³ substance, closed with the plate and the closing device and then suspended in a protective box. The burners are lit simultaneously and the time to reaction and its duration are measured. When the tube is split into three or more fragments in at least one out of three experiments with the same diameter hole, the result is evaluated as “explosion”. Substances causing an “explosion” at ≥ 2.0 mm diameter of the hole are considered to present a danger of explosion in the sense of the Commission Directive 92/69/EEC [4] and in the sense of the UN Recommendations on the Transport of Dangerous Goods [5].

2.2. Mechanical sensitivity (impact), BAM Fallhammer

The essential parts of the BAM Fallhammer are described in Refs. [4] and [5]. This test is used to measure the sensitivity of a substance to drop-weight impact. A small sample of a substance is enclosed in an impact device consisting of two co-axial steel cylinders, one above the other in a hollow cylindrical steel guide ring. The filled impact device is placed on the main anvil and the drop weight is released from a defined height. The impact energy is calculated from the mass of the drop weight (1, 5 or 10 kg) and the fall height (e.g. 10 kg \times 0.4 m \approx 40 J). The test result is considered positive when an explosion occurs in at least one out of six trials at 7.5 or/and 40 J [4] (bursting into flame and/or a bang is equivalent to an explosion). According to the UN Manual of Tests and Criteria [5], a substance is considered too dangerous for transport if the lowest impact energy at which an

explosion occurs is 2 J or less in the form in which it was tested.

2.3. BAM 50/60 steel tube test [5]

This test is used to measure the ability of a substance to propagate a detonation by subjecting it to a cylindrical detonating booster charge (50 g RDX/wax, 95:5) under confinement in a steel tube (e.g. according to DIN 1629 and DIN 2448, 500 mm length, 60 mm external diameter, 5 mm wall thickness, bottom closed by a welded plate). The tube is filled with the substance and the booster is placed centrally at the upper end of the tube, so that it is surrounded by the substance. When the tube is fragmented completely upon initiation with a commercial detonator, then the substance is able to propagate a detonation (“yes”). The test result “partial” means that the tube is fragmented only at the initiator end and the fragmented length is greater than 1.5 times the fragmentation length found with an appropriate inert material.

2.4. Time/pressure test [5]

This test is used to measure the ability of a substance under confinement to propagate a deflagration. The apparatus consists of a cylindrical steel pressure vessel (total volume is 18 ml) which is 89 mm in length and 60 mm in external diameter. The vessel is equipped with a pressure-measuring device located in a side arm. The pressure transducer must be capable of responding to rates of pressure rise from 690 to 2070 kPa in not more than 5 ms. The specific ignition system, which is mounted onto the firing plug at one end of the vessel, is in contact with up to 5 g substance and consists of a combination of an electrical fusehead wrapped in a piece of primed cambric (chemical ignitor). The other end of the vessel is closed by an aluminium bursting disk. When upon ignition, the time for a pressure rise from 690 to 2070 kPa gauge is less than 30 ms, the result is “yes, rapidly”. “Yes, slowly” means that the time for the pressure rise is ≥ 30 ms.

2.5. TRAUZL test [5]

This test is used to measure the explosive power of a substance. The sample is confined in a hole in a massive cylindrical lead block (200 mm height and 200 mm diameter) and initiated with a commercial detonator. The explosive power is expressed in the form of the increase in volume of the cavity in the lead block per 10 g substance. At a given strength of initiation, the explosive power increases with the volume of expansion. The test criteria for self-reactive substances are as follows:

- “not low”—The expansion of the lead block is 25 cm³ or more;
- “low”—The expansion is less than 25 cm³ but more than or equal to 10 cm³;
- “no”—The expansion is less than 10 cm³.

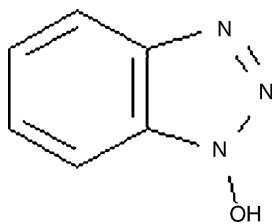


Fig. 1. 1-Hydroxybenzotriazole (HOBt).

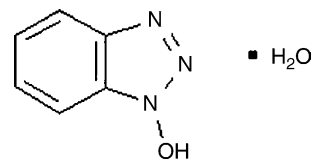


Fig. 2. HOBt monohydrate.

2.6. Differential scanning calorimetry (DSC)

A Perkin-Elmer “Pyris 1” Differential Scanning Calorimeter was operated under nitrogen flow and calibrated against indium. The samples were sealed in closed stainless steel cells, which can withstand an inner pressure of about 15 MPa. The heating rate was 5 K/min.

3. Results and discussion

3.1. 1-Hydroxybenzotriazole, dry and wetted with water

1-Hydroxybenzotriazole (Fig. 1), dry (HOBt anhydrous), $C_6H_5N_3O$, M.W. 135.1, CAS: 2592-95-2, is a white crystalline powder with a melting point of $\geq 155^\circ C$ and usually contains less than 1% water. HOBt monohydrate (Fig. 2) contains about 11.8% water.

Table 1 reports the results of the detonation test, the Koenen test, the impact test, the time/pressure test, the TRAUZL test and the decomposition energy (DSC) of HOBt, dry and wetted with different amounts of water (see also

Figs. 3–6). HOBt, dry and wetted with 10% water, is able to propagate a detonation. The limiting diameter in the Koenen test is 10.0 mm for the dry substance and decreases as the water content increases. It is, however, remarkable that even a water content of about 50% is not sufficient to suppress the sensitivity in the Koenen test below the limiting diameter of 2.0 mm. Up to a water content of about 20%, HOBt is sensitive to drop-weight impact. Another important result with respect to the safe handling of HOBt is the very short time for the pressure rise in the time/pressure test. This result shows that under confinement, dry HOBt is able to propagate a deflagration very rapidly.

3.2. 6-Chloro-1-hydroxybenzotriazole (6-Cl-HOBt)

6-Chloro-1-hydroxybenzotriazole (Fig. 7), $C_6H_5ClN_3O$, M.W. 135.1, CAS: 26198-19-6, is a white crystalline powder with a melting point of $189\text{--}192^\circ C$ (decomposition).

In Table 2, the results of the explosivity tests are given for 6-Cl-HOBt. Unfortunately, we did not obtain sufficient sample material to carry out the detonation test. From our experience, we conclude that dry 6-Cl-HOBt would give also a “yes” in the detonation test since the TRAUZL



Fig. 3. HOBt, dry, Koenen test at 10.0 mm.



Fig. 4. HOBt with 44% water, Koenen test at 2.0 mm.



Fig. 5. HOBt with 50% water, Koenen test at 2.0 mm.

Table 1
Test data for HOBt

HOBt	Detonation test UN A.1	Koenen test UN E.1 (mm)	Impact test BAM Fallhammer (J)	T/p test UN C.1 (ms)	TRAUZL test UN F.3 (ml)	$-\Delta U$ DSC (5 K/min) (J/g)
Dry	Yes	10.0	10	<0.5	94	2259
With 10% water	Yes	3.5	20		74	1974 (12% water)
With 12.9% water	Partial	3.0	20	From 63 to 424		1693
With 20% water	No	(3.5) ^a Rewetted	20			
With 44% water		2.0	>40	No ignition	6	1363
With 50% water		2.0	>40			

^a Substances rewetted in the laboratory after drying often show a less effective desensitization due to the fact that it is difficult to reintroduce the chemically combined water.



Fig. 6. HOBt: dry, detonation test (UN test A.1).

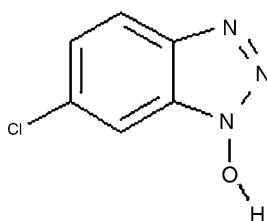


Fig. 7. 6-Chloro-1-hydroxybenzotriazole (6-Cl-HOBt).

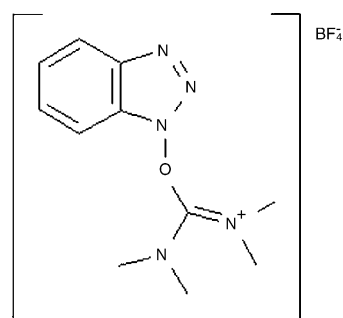


Fig. 9. TBTU.



Fig. 8. 6-Cl-HOBt, Koenen test at 8.0 mm.



Fig. 10. TBTU, Koenen test at 2.0 mm.

test gave a result comparable with that for HOBt and because the limiting diameter in the Koenen test is comparable (see Fig. 8). Thus, a significant difference of the explosive properties between HOBt and 6-Cl-HOBt is not discernible.

3.3. *O*-(1*H*-Benzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

O-(1*H*-Benzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU, Fig. 9), $C_{11}H_{16}N_5O \cdot BF_4$, M.W. 321.1, CAS: 125700-67-6, is a white to off-white microcrystalline powder with a melting point $>200^\circ C$.

TBTU was tested at BAM according to the method A.14 [4] by order of a company. The test was positive with 2 mm as the limiting diameter. The tube was not fragmented completely in three pieces. Two pieces remained connected over a small strip and the pieces were twisted. This may be considered a borderline case (see Fig. 10), but in opinion of BAM, such a fragmentation type should be evaluated as “F” (explosion). TBTU was not sensitive to drop-weight impact or friction. The decomposition

energy measured by DSC was 1250 J/g at a heating rate of 5 K/min.

3.4. Burning test on HOBt with 12.1% water

For the determination of a storage group according to the German Explosives Act, a burning test was carried out on a 100 l fibre drum (UN code 1G) filled with 50 kg HOBt, wetted with 12.1% water. A pallet of wood and wood wool was used to initiate the fire. The test method chosen is comparable to the UN 6c-Test as described in Ref. [5]. Only a slow burning rate of about 29 kg/min was observed in the experiment. The heat radiation intensity was medium. The wetted substance packed in such a “soft” packaging was assigned to storage group Ib according to the German regulations. According to the criteria for the 6c-Test [5], HOBt, wetted with more than 10% water by mass and packed as described, may be excluded from Class 1 and assigned to an other class or division (see also Section 4).

4. Conclusion

Based upon the described test results, the following conclusions were drawn:

- HOBt and 6-Cl-HOBt, dry, are not too insensitive for acceptance into Class 1 [5]. They are thermally stable and not too dangerous for transport (Test Series 3 [5]). HOBt and 6-Cl-HOBt, dry, should be assigned to Class 1.
- HOBt, desensitized with more than 10% water by mass, when packed for transport in a “soft” packaging (fibre

Table 2
Test data for 6-Cl-HOBt

	6-Cl-HOBt, dry
Koenen test UN E.1 (mm)	8.0
Impact test BAM Fallhammer (J)	10
<i>T/p</i> test UN C.1 (ms)	<1.5
TRAUZL test UN F.3 (ml)	96
$-\Delta U$ DSC (5 K/min) (J/g)	1746

board or plastic) is a desensitized explosive of Division 4.1 of the UN Recommendations [6] and should be assigned to UN number 3380, “desensitized explosive, solid, n.o.s.”. The special provision 311 is relevant: “*Substances should not be transported under this entry unless approved by the competent authority on the basis of the results of appropriate tests according to Part I of the Manual of Tests and Criteria. Packaging shall ensure that the percentage of diluent does not fall below that stated in the competent authority approval, at any time during transport*”.

- HOBt, dry and wetted, 6-Cl-HOBt, dry, and TBTU show explosive properties according to the Directive 92/69/EEC [4] and should be classified as substances presenting a danger of explosion. Therefore, they should be labelled with the symbol “E” and the phrase “R2” or “R3” (the R phrase assigned depends on the decision of the European Chemicals Bureau (ECB) under consideration of the criteria listed in the Directive 67/548/EEC [7]).

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