Application of High Pressure and Near-Critical Fluids, NCF's – a Tool for Novel Processes in *Roche*

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Abstract. The development of new processes by means of near-critical fluids, NCF's, has gained increasing importance in the last few years. These processes include physical separation processes for especially thermolabile substances as well as chemical reactions in and with NCF's.
In this contribution, a short phenomenological description of the physical properties of near-critical fluids is given and their influence on the other compounds is discussed. Some general considerations with respect to high-pressure applications of NCF's along with a rough overwiew of *Roche* activities in this field are described.

Meanwhile the application of high pressure in chemical and technical processes has gained old tradition, *e.g.* in the well-known ammonia synthesis process as well as in many processes in the petroleum industry. Many of these processes using elevated pressures are of major importance with respect to output and dimensions (*Table 1*).

In *Roche*, too, processes at elevated pressures, namely catalytic hydrogenations and dehydrogenations, have been carried out frequently since many years [1].

Under the leadership of *K. Steiner* the hydrogenation techniques were substantially improved, new pressure equipment was designed not only for high-pressure applications but also for higher temperatures up to 300° and several special devices were constructed to fulfil all the service assignments coming from the different *Roche*-internal customers. These include
– screening experiments in small-volume vessels (typical: 1–10 ml),
– vessels for batch experiments in the range up to 20 l,
– vessels for special applications (corrosion-resistant).

The remarkable achievements in the field of the hydrogenation technique, the familiarity of the coworkers with the pressure technique or the increasing number of patents and publications, especially from the Japanese in the field of supercritical fluid extraction, all these mentioned reasons may have shared their contribution to the initiative of *Roche* to introduce in 1984 for the first time the extraction techniques, using compressed gases as solvents (so-called supercritical or near-critical fluids) – a pleasure for the author, who was the first to get the order to install high-pressure extraction equipment on a broader basis.

At the same time, a cooperation with external institutions was envisaged. The alliances formed on a friendly and scientific basis remain until today. The first alliance was with the University of Erlangen (Prof. *Peter*), and later the Universities of Hamburg-Harburg (Prof. *Brunner*) and Munich (Prof. *Tiltscher*) as well as the ETH-Zürich (Prof. *Trepp* and Prof. *Baiker*) followed.

Meanwhile the group around *K. Steiner* moved from Basle to Kaiseraugst into a new erected pressure laboratory in order to carry out these techniques on a broader basis. In 1995, this building was further enlarged by additional laboratories and a mini-pilot hall, in which reactor design studies (bubble column, trickle bed *etc.*) and feasibility studies with scale-up factors of 10–100 for high-pressure chemical reactions can be tested.

High-Pressure Equipment – a Versatile Tool

Displacement of common glass equipment should be carried out with respect to both:
– high-pressure *and*
– high-temperature application.

These prerequisites may allow to work in a broad field of applications especially in the field of reaction and reaction engineering techniques as well as in separation processes:
– The normal boiling point of a solvent is no longer a barrier; extractions and reactions can be carried out at much higher temperatures (pressures, resp.).
– Instead of high-boiling solvents, low-boiling ones can be introduced, that means on one hand that higher pressures will be the result at given temperatures. On the other hand, the removal of the low-boiler from the product can be carried out more completely.
– Additionally (for reactions) or as an

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Table 1. *Examples for Common High-Pressure Processes*

Reaction/Starting materials	Product	Catalyst	Conditions	Quantities [mio. t]
Hydroformylation/olefines (oxo-synthesis)	Aldehydes	Co-, Rh-, Ru-compounds	200–450 bar 100–200°	5.1
Indirect oxidation method/ propene	Propenoxide	Hydroperoxides	15–65 bar 90–140°	2.9
Hydrogenation/synthesis gas	Methanol	Cu-Zn-Al-oxides	50–100 bar 240–260°	21.3
Indirect Hydration/ethene	Ethanol	H_2SO_4/ silver sulfate	55–80° 10–35 bar	2.2
Direct Hydration/ethene		acid catalysts	300° 70 bar	

alternative (in extractions), compressed gases (in supercritical or near-critical state) can be introduced [2]. This offers the advantage of complete recovery of these gases after extraction without high-temperature treatment which is extremely useful for the separation of thermolabile substances. Further advantages will be explained in the text.

For all mentioned cases, a lot of suitable equipment is meanwhile available in the high-pressure labs in Kaiseraugst.

What is a NCF?

The end point of the vapour-pressure line of a pure compound in the phase diagram (*Fig. 1*) is called the critical point (CP). At this point, liquid and gas phase become indistinguishable.

Properties like the density reveal discontinuous behaviour in the 'normal' regions (gas, liquid and solid), but show continuous behaviour above the critical temperature (Tc). Thus, above Tc it is possible to adjust the density to every value, which is desirable in course of a process.

In the critical region, properties like the density ρ (as well as the viscosity η) vary greatly with only minor changes with respect to temperature and/or pressure. This offers the opportunity for creating very effective phenomena (mass transfer, kinetics), but shows at the same time the need for proper experimental measurements as well as for exact process control in large-scale industrial applications.

The region above Tc and Pc is called the 'supercritical region'. This region can be enlarged to regions, in which the fluids are in the liquid state, but have enough compressibility to accomplish large changes in their density (and therefore solubility behaviour) induced by pressure changes. This is normally the case if the process parameters temperature and pressure lie between $0.85 < Tr < 1$ and $0.9 < Pr < 1$, *i.e.* not far away from Tc. Tr and Pr are the reduced values ($Tr = T/Tc$ and $Pr = P/Pc$). Because of this behaviour, it is common to speak of 'near-critical fluids', and the small shaded area in *Fig. 1* may be additionally considered with respect to optimisation of process parameters.
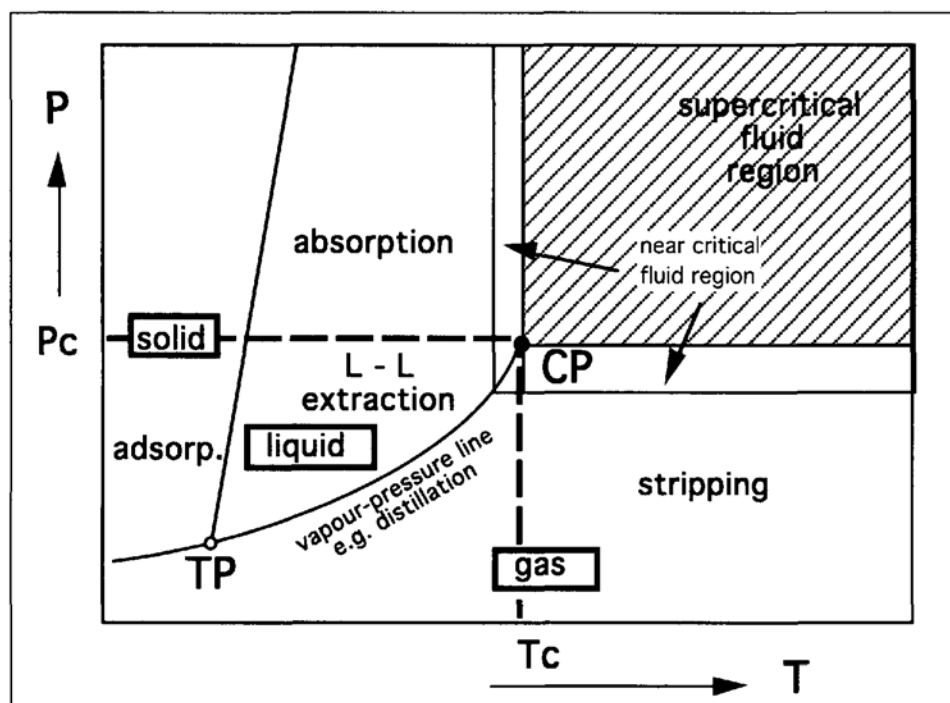

Fig. 1. *Working range for selected unit operations*

Table 2. *Some Gases and Solvents of Interest for Near-Critical Fluid Reactions and Extractions*

	Compound	Critical temperature [°]	Critical pressure [MPa]	Critical density [kg/m³]
Gases	CO_2	31	7.36	470
	Ethane	32.2	4.87	203
	Propane	96.7	4.24	220
	Butane	152	3.79	228
	Ethene	9.9	5.1	230
	N_2O	36.5	7.24	460
Solvents	Methanol	240.3	7.79	270
	Ethanol	243.4	6.36	280
	Propan-1-ol	263.5	5.17	275
	Butan-1-ol	289.7	4.96	271
	Water	374	22.02	320

Table 3. *Properties of Compressed Gases vs. Gases and Common Solvents*[a]

	Gases 0.1 MPa, 15–30°	Compressed gases		Solvents 15–30°
		at Tc and Pc	at Tc and 4 Pc	
Density [kg/m³]	0.6 ... 2	200 ... 500	400 ... 900	600 ... 1600
Diff. coeff. in 10⁴ [cm²/s]*	1000 ... 4000	7	2	0.02 ... 0.2
Viscosity [mPa s]	0.01 ... 0.03	0.01 ... 0.03	0.03 ... 0.09	0.2 ... 3

[a]) G. Brunner, *Chem.-Ing.-Tech.* **1987**, *59*, 12.

What Compounds/Gases are Suitable?

In *Table 2*, some of the NCF's of interest in the field of reaction and separation processes are listed. Especially CO_2 is pointed out (in most publications dealing with extractions) because of its benefits with respect to
- inflammability,
- physiological harmlessness,
- cheapness *etc.*

NCF's consisting of hydrocarbons are often banned with a high 'risk factor' with respect to flammability and explosion risks of these gases. In cases, in which CO_2 reveals high solvent power in combination with good selectivity effects, it will actually be the best choice. In contrast to that one can argue, that huge amounts of hydrocarbons are treated all over the world in the petroleum industry and it is only a question of precautions in handling these gases. The use of, *e.g.* compressed propane as a (nearcritical) solvent is known

since several decades [3][4], but was not used extensively for the recovery of high-value substances. In parallel with both, the increasing number of existing commercial high-pressure units and the better understanding of basic thermodynamic behaviour, a renaissance on applications of hydrocarbons as NCF's can be noticed [5][6].

The distinction into 'gases' and 'solvents' in *Table 2* shows roughly the possible applications. The 'gases' are suitable for separation and purification processes in one- or multistep procedures (*e.g.* supercritical fluid extraction, SFE, or supercritical fluid chromatography, SFC) whereas the 'solvents' offer additional opportunities with respect to solubility enhancement for SFE or SFC and particularly for application in reactions under high pressure, near-critical conditions.

It should be pointed out again, that these solvents reveal unusual behaviour in the nearcritical region ($0.9 < Tr < 1$). The polarity of the mentioned alcohols will vanish and they will adopt more and more solvent properties of unpolar ones like benzene, hexane *etc.*, a behaviour which is well-known from the behaviour of water [7][8].

Why are NCF's Suitable?

Referring to compressed gases, the properties are intermediate between gases and common solvents. As can be seen from *Table 3*, the diffusion coefficient of compressed gases is much higher than for common liquids and, additionally, the viscosity is in between gas-like and liquid-like behaviour. This offers special advantages with respect to kinetic effects.

Because of their low boiling points below or in the neighbourhood of ambient temperatures, the mentioned gases reveal high vapour pressures. In this way, a careful removal of the gases only by pressure expansion can be easily achieved. This is of major value for thermolabile substances.

Moreover, in some cases very good solvent capacities for other gases can be noticed. For instance, CO_2 is a marvellous solvent for O_2 or H_2. With O_2 or H_2, CO_2 will reveal its inflammable capabilities. Additionally at higher pressures, O_2 or H_2 are miscible in all portions with especially supercritical CO_2. This gives the following opportunities/advantages:
– the solvent itself is not oxidizable (CO_2),
– explosion limits shift totally to other concentration proportions,

– the solvent is inflammable,
– stirring energy can be minimized (no intense mixing of gases with liquids),
– the rate-limiting step of the reaction may shift to another regime,
– a constant amount of O_2 or H_2 can easily be adjusted in the mixture.

Effects of NCF's on Other Compounds

NCF's have not only properties for themselves, as shown in *Table 3*, but reveal very strong effects in combination with, *e.g.* organic substances of higher molecular weight (*Table 4*).

Separation and Reaction Processes with NCF's

In *Fig. 2*, an example for different possibilities of applications for NCF's is given. These processes can be carried out alone but also in combination. The high-

Table 4. *Effects of NCF's on Other Compounds*

| Effects	Benefits
Diminishing of viscosity of liquids can be achieved by dissolved NCF; viscosity can be lowered by factors of 100 and more!	– Stirring energy can be reduced – Very viscous media can be sprayed to form solids or can be mixed with other liquids to form homogeneous precipitates – Mixing can be achieved in short time
Diminishing of interfacial tension	– Strong effects on the hydrodynamic behaviour achievable
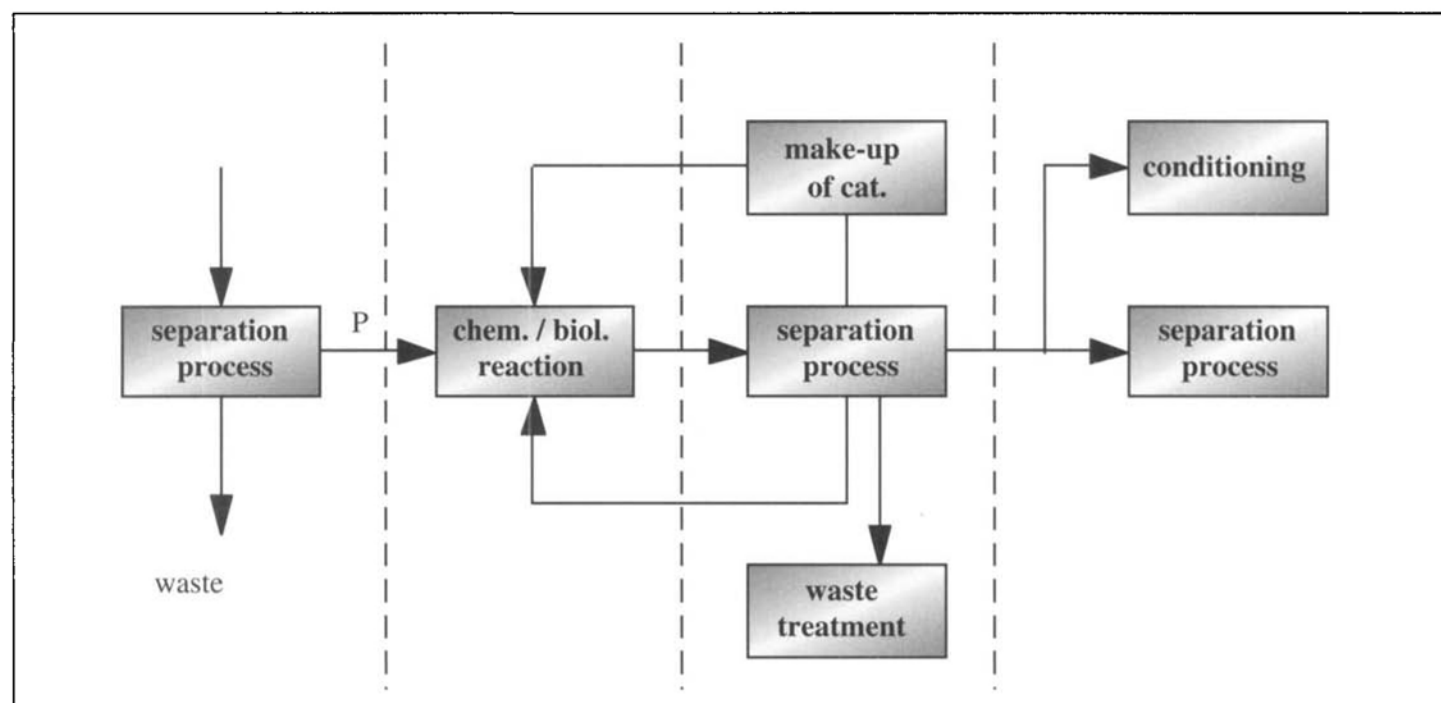
Fig. 2. *Separation- and reaction processes with compressed fluids*

pressure labs of *Roche* are involved in all the sketched processes. Beginning from the left hand in *Fig. 2*, the separation process may be an isolated one. Examples for such processes are
- extraction of volatile high-value substances (*e.g.* polyunsaturated fatty acids from oilseed, flavours and aromes from plant material, recovery of spent catalytic material),
- supercritical drying of pharmaceutical products (→ removal of residue solvents).

On the other hand, this process may be useful to purify a liquid raw material, which is submitted to a further chemical or biological reaction. In all cases, in which by-products will hinder the following reaction or will lead to unwanted by-products, a purification with NCF's in one- or multistep procedures (countercurrent extraction) will be useful.

Let's now enter the reaction part in *Fig. 2*. Different reactions with/in NCF's are possible. In one specific reaction at *Roche*, an expensive rhodium catalyst could be exchanged by a cheap rhuthenium one. This was possible because of high-pressure application of hydrogen.

In another *Roche*-relevant synthesis step, a high-boiling solvent was substituted by a low-boiling one. This reaction was carried out at even much higher temperatures and pressures of now 5–15 MPa because of the high vapour pressure of the selected solvent at that temperature. The following effects could be achieved:
- the low-boiling solvent can now be removed much more easily and effective,
- the reaction rates are much higher because of the enhanced process temperatures. This gives the opportunity to carry out the process in a small-volume vessel in continuous instead of batch mode.

Other reactions in NCF's are currently under research. These may include homogeneous catalytic reactions [9] as well as bioreactions [10]. Oxidations and hydro-

genations in CO_2 will be also of big interest in future because of the inflammability of CO_2 and the unlimited mutual solubility of the gases in the critical region of CO_2, which gives the opportunity to change the observed chemistry radically. Additionally, CO_2 is an excellent reaction medium of its own, demonstrated by hydrogenation studies [11].

We leave the reaction part and will come again to a separation process in *Fig. 2*. This separation process could be again a one- or multistep extraction procedure using NCF's as mentioned above. Of special interest in future will be the recovery of high-value products from fermentation broth systems [12].

In many cases, purifications of liquid raw materials with NCF's needs multistep techniques like countercurrent multistep column – or multistep mixer settler type devices. Both types of apparatus are basic equipment in the high-pressure labs in Kaiseraugst and the purification of several synthetic raw materials is of current interest in *Roche*.

In collaboration with the Technical University of Hamburg-Harburg it could be demonstrated, that fatty-acid ethyl esters can be separated by countercurrent extraction with compressed CO_2 [13]. In another contribution together with the ETH-Zürich the suitability of a mixer settler type device was demonstrated [14]. A separation efficiency of 70–95% was achieved depending on the operating conditions.

All work carried out with respect to near-critical fluid extraction is based mainly on three parts:
- extensive measurement of phase equilibria with respect to pressure, temperature, cosolvent-influence, sort of gas and composition of feed,
- experiments with laboratory- and pilot-scale equipment (countercurrent columns, mixer settler, batch extractions),
- correlation of phase-equilibria measurements, simulation and analysis of

separation, scale-up procedures and check of suitable methods.

Upon all three parts, *Roche* is currently involved in experimental as well as theoretical work, again in collaboration with the University of Hamburg-Harburg [15][16] and the ETH-Zürich [17].

Further separation processes may be encountered as scetched in *Fig. 2*, namely the regeneration of spent catalysts [18] or the application of near-critical water for the decomposition of harmful residues in waste streams [19][20]. The latter process, too, is under current research in *Roche*.

If the purity of the yielded products is not sufficient high enough, a further separation process is necessary. In many cases, chromatographic methods are applied to reach the envisaged purities. Along with other companies and universities *Roche* became involved in SFC-techniques. This technique has received meanwhile considerable attention and can be applied to products of the vitamins & fine chemicals production of *Roche* as well as for pharmaceutical and perfumes & flavour specialities [21][22].

Again, NCF's play the major role in this technique because of their mentioned low viscosity and their viscosity-lowering effects with respect to introduced liquids, which makes them an ideal carrier for chromatographic processes combined with low pressure drops along the chromatographic column. Additionally, the ease for recovery of the NCF's from the products afterwards can be mentioned here and the recirculation of the NCF reveals neglectable problems in comparison with, *e.g.* the HPLC method.

Further research in the field of high-pressure/high-temperature techniques have been commenced, namely membrane separation processes and crystallisation processes. In this field the applicability of NCF's for *Roche*-specific processes will be tested.

High-pressure techniques are among those, which were forecasted to be introduced on a broad basis in the next years [23]. Looking into the future, the following situation (besides biological processes) seems to emerge (*Table 5*).

Today, research will be considered by results, which are available in short times whereas the gain of basic knowledge plays a minor role. This trend is contraproductive for a sound, long-term development of companies.

With respect to high-pressure techniques, *Roche* invested on long-term basis and for the further future. Until the year 2000 the first high-pressure processes,

Table 5. *Processes Today and in the Future*

Processes today	Future process
Batch mode	Continuous mode
Normal pressure	Elevated pressures, more extreme temperatures
Seldom catalytic	Catalytic
With solvents	With low-boiling solvents, limited to a few allowed species or use of compressed gases

developed in the high-pressure center in Kaiseraugst, will be brought to commercial application and this confirms the rule, that investments into basic research will need about 10–15 years until introduction into commercial scale [24].

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[1] F. Roessler, *Chimia* **1996**, *50*, 106.
[2] G. Brunner, 'Gasextraction', Steinkopff, Darmstadt, 1994.
[3] A.W. Hixson, J.B. Bockelmann, *Trans. Am. Inst. Chem. Engrs.(N.Y.)* **1942**, *38*, 891.
[4] T.P. Zhuze, *Petroleum* **1960**, 298.
[5] S. Peter, E. Weidner, B. Czech, U. Ender, *Fat Sci. Technol.* **1993**, *95*, 475.
[6] E. Weidner, Z. Zhang, B. Czech, S. Peter, *Fat Sci. Technol.* **1993**, *95*, 347.
[7] E.U. Franck, R. Deul, *Discuss. Faraday Soc.* **1978**, *66*, 191.
[8] K. Tödheide, *Ber. Bunsen-Ges. Phys. Chem.* **1982**, *86*, 1005.
[9] P.G. Jessop, T. Ikariya, R. Noyori, *Science* **1995**, *269*, 1065.
[10] D.A. Hammond, M. Karel, A. Klibanov, V.J. Krukonis, *Appl. Biochem. Biotechnol.* **1985**, *11*, 393.
[11] P.G. Jessop, T. Ikariya, R. Noyori, *Nature (London)* **1994**, *368*, 231.
[12] M. Perrut, *Chem. Biochem. Engng.* **1994**, Q8, 25.
[13] C. Tiegs, V. Riha, G. Brunner, K. Steiner, Preprints of the 3rd International Symposium 'High Pressure Chemical Engineering', Zürich (CH), Oct. 7–9, 1996.
[14] W. Pietzonka, C. Trepp, Preprints of the 3rd International Symposium 'High Pressure Chemical Engineering', Zürich (CH), Oct. 7–9, 1996.
[15] J. Stoldt, Dissertation, Hamburg, 1996.
[16] V. Riha, Dissertation, Hamburg, 1996.
[17] W. Pietzonka, Dissertation, in preparation.
[18] H. Tiltscher, U. Siebenhaar, Abstract Handbook of the 2nd International Symposium 'High Pressure Chem. Engng.', Erlangen (FRG), Sept. 24–26, 1990, p. 23.
[19] M. Weber, H.L. La Roche, C. Trepp, Preprints of the 3rd International Symposium 'High Pressure Chemical Engineering', Zürich (CH), Oct. 7–9, 1996.
[20] T. Hirth, E.U. Franck, *Chem.-Ing.-Tech.* **1994**, *66*, 1355.
[21] M. Johannsen, Dissertation, Hamburg, 1995.
[22] F. Reichmann, G. Brunner, 'Proceedings of the International Symposium on Preparative and Industrial Chromatography and Related Techniques', Basel (CH), Sept. 1–4, 1996.
[23] R. Karge, *Chem. Ind.* **1996**, *6*, 26.
[24] A. Bromley, *Phys. Today* **1993**, *46*, 53.

Stereoisomers of Tocopherols – Syntheses and Analytics

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Abstract. After an introduction summarizing the relevance of vitamin-E-active compounds, a short overview about the work done at *Roche* (in Basel and Nutley, USA) from the early 1960s to the 1990s is given. Selected research activities of the Basel group during recent years on the synthesis and stereochemical analysis of tocopherols and building blocks are described in more detail.
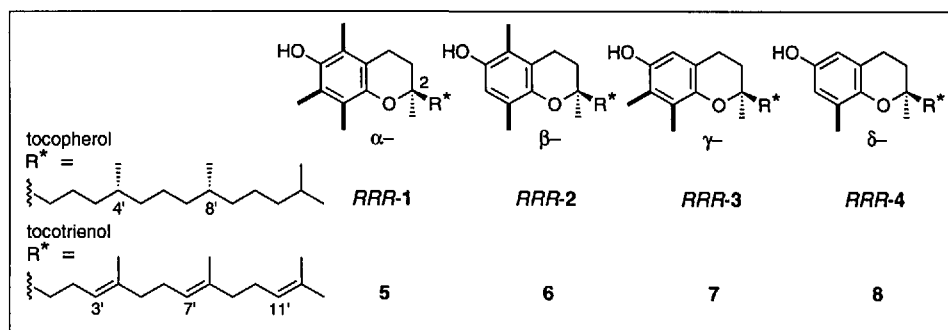
1. Introduction

Vitamin E is the most important fat-soluble antioxidant. The term vitamin E is recommended to be used as the generic descriptor for all tocol and tocotrienol derivatives exhibiting qualitatively the biological activity of α-tocopherol [1]. The naturally occuring components of this group hitherto discovered are single-isomer products. The (2R,4'R,8'R)-configuration is found in α-, β-, γ-, and δ-tocopherol (*RRR-1*–*RRR-4*), and α-, β-, γ-, and δ-tocotrienol (**5–8**) possess (2R,3'E,7'E)-configuration [2][3].

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Rich sources for vitamin-E-active compounds in various proportions are edible oils originating from plants. Typical examples are shown in the *Fig.* Sunflower seeds contain α-tocopherol (**1**) almost exclusively (*Table 1*). A mixture of tocopherol homologues (mainly γ- and δ-tocopherol, **3** and **4**) is contained in oil from soybeans, while palm oil has a high concentration of tocotrienols [4].

The industrial importance of this group of compounds is based on their biological and antioxidant activity [5]. The determination of the vitamin E activity by the fetal resorption-gestation test in rats shows that (*RRR*)-α-tocopherol (*RRR-1*) (from greek: 'τόκος' and 'φέρειν' which means 'to bring forth offspring') has the highest value of the eight naturally occuring compounds *RRR-1*–*RRR-4* and **5–8**) and of the eight stereoisomers of α-tocopherol [6] (see *Table 2*). In addition, all tocopherols and tocotrienols function as antioxidants quenching lipid autoxidation reactions.

Two forms of α-tocopherol (or their acetate derivatives) are produced for application in feed, food, and pharma industry. Currently, the totally synthetic α-tocopherol all-*rac*-**1** ('synthetic vitamin E') is obtained by acid-catalyzed condensation of all-racemic isophytol **9** with trimethylhydroquinone **10** [3][7] (*Scheme 1*) in a 15 000–20 000-t scale per year. Main producers are *BASF* (Germany), *Rhône-Poulenc* (France), *Eisai* (Japan), and *Roche* (Switzerland). (*RRR*)-α-Toco-