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# Formation of DMSO and DMF radicals with minute amounts of base

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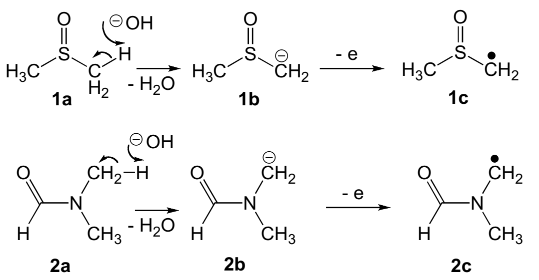
ABSTRACT

So far overlooked DMSO and DMF form long-lived radicals in the presence of small amounts of bases, DMF radicals being less stable than DMSO radicals. In solvent mixtures, the presence of DMSO prolonged the lifetime of DMF radicals. The occurrence of radicals may explain previously reported unexpected outcomes of reactions performed in these solvents. The commonly accepted inertness of these solvents towards minor quantities of alkali seems not to be warranted.

## 1. Introduction

It has been noticed that dimethylsulfoxide (DMSO) can be oxidized, sometimes with devastating consequences,[1] and dimethylformamide (DMF), a simple amide, can easily be hydrolyzed.[2] Explosions have been explained by exothermic polymerization of formaldehyde, formed at the boiling point of DMSO.[3] However, the inertness of these solvents is neither guaranteed under much more temperate conditions in the presence of trace amounts of base. Is there really any doubt about the inertness of alkaline DMSO and DMF? The p$K_a$'s of 1200 compounds have been determined in DMSO, solutions of potassium *tert*-butoxide in DMSO are frequently used in base-catalyzed reactions, the potassium salt of DMSO (dimsyl) acts as superbase in many chemical reactions, the Swern and Kornblum oxidations rely on DMSO with an organic base, the Shonogashira coupling is performed in DMSO with $Cs_2CO_3$, double bonds have been displaced with KOH in DMSO (e.g., eugenol to isoeugenol, lutein to zeaxanthin, α- to β-pinene), and KOH in DMSO is an efficient base for asymmetric cyclization.[4–11] The Suzuki coupling is accomplished in DMF with $Cs_2CO_3$, Claisen rearrangements are best carried out in DMF with MeLi, a one-pot Michael addition was observed in DMF with NaOH, aminoacids racemise in DMF with $K_2CO_3$ and sugar fatty acid esters are synthesized by transesterification involving DMSO or DMF with KOH, $K_2CO_3$ or other alkaline catalysts (Hass–Snell reaction).[12–16] These fragmentarily selected reactions seem beyond doubt to confirm the stability of the solvents in the presence of alkali. Consequently, the fact sheet of a DMSO manufacturer pledges the excellence of DMSO under basic conditions.[17]

On the other hand, explosions have been reported during the preparation of the methylsulfinyl carbanion (dimsyl anion, $DMSO^-$, **1b**, Scheme 1).[18–20] Other peculiar observations have been articulated: DMSO played an ambiguous role in creating radicals during the alkaline degradation of carbohydrates.[21] Unexpected radicals emerged in the Reissert reaction when performed in DMF with NaH,[22] although it was explicitly stated that no radicals are obtained in alkaline DMF.[20] DMSO and DMF radicals have otherwise been generated by rather harsh conditions (photolysis, pulse radiolysis, sonication) and detected at low temperatures.[22–29]



**Scheme 1.** Postulated initiation reaction to radicals of DMSO and DMF with base.

We have found that DMSO and DMF form long-lived radicals at room temperature simply by adding a few drops of potassium

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methylate (MeOK) solution (25% in MeOH) to the solvents, e.g., 10 μL base solution to 10 mL solvent. Besides MeOK, other bases such as BuLi and EtOK react with the solvents, low soluble KOH required longer reaction time. Pyridine and amines do not react. Although we lack the opportunity at the moment to describe the reactions and products in detail we think it advisable to present here the spectra and chemical data verifying radical formation in neat DMSO and DMF and in solvent mixtures after addition of small quantities of base.

## 2. Results

Radicals of DMSO were formed instantaneously, reaching a maximum between 2 and 4 min after base addition (Fig. 1). These primary radicals had disappeared after 25 min being replaced by secondary radicals, detectable after 6 min reaction time. The magnitude of these new DMSO radicals increased slowly until a steady state was reached after about 2 h. The secondary DMSO radicals were stable at room temperature for at least 1 week. The initially formed DMSO radicals showed a hyperfine splitting pattern pointing to a localized radical character at one of the carbon atoms.[25] The splitting further indicates a coupling to two geminal H-atoms. In contrast, the secondary radicals have lost the fine splitting. The obtained EMR spectra, hyperfine splitting constants and g-values were not in resemblance with previously reported data on short-living DMSO-radicals.[26,30]

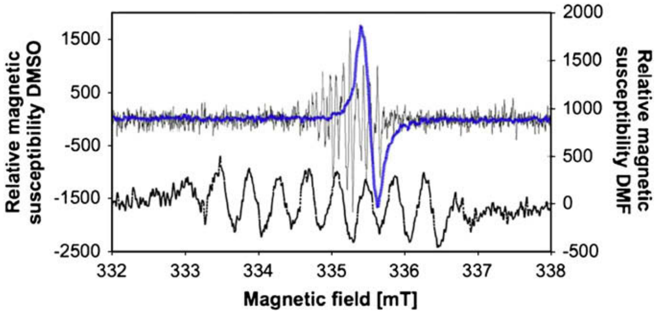


**Figure 1.** Radical formation in DMSO and DMF after adding MeOK. Top lines: DMSO 2 min (—), 4 h (—); bottom line: DMF 2 min.

When radicals were generated from DMSO-$d_6$ the EMR spectra showed immediately the singlet of a free radical (Fig. 2). Three minutes after base addition this singlet was split into a doublet indicating possible DMSO-dimers, allowing the radical center to shift between two different positions. The doublet coalesced then again into a singlet similar to that observed in non-deuterated DMSO. The long-lived final radical species may therefore constitute a radical cluster (radical adducts with solvent molecules) in which the radical position is rapidly delocalized (Fig. 3).

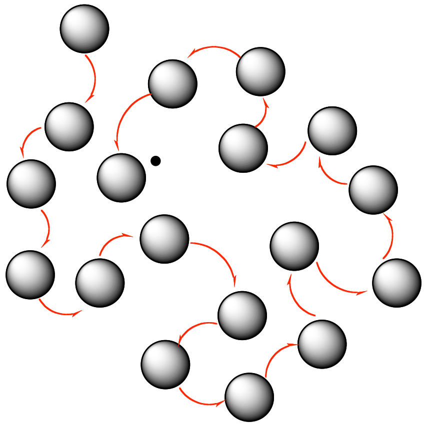


**Figure 3.** Delocalization within radical clusters of radical–solvent molecules.

The NMR spectra, recorded 10 min after addition of base to DMSO, showed signals of many new diamagnetic species. Assessment of the spectra and comparison with data in the literature verified the predominant formation of reduction products such as methane, methanethiol, and dimethylsulfide besides other non-identified compounds in smaller amounts. Earlier works listed oxidation products of DMSO, formed catalytically by residual iron impurities.[20,31–33] However, iron should not interfere in the reaction, since DMSO-$d_6$ can obviously be considered iron-free with regard to NMR and EMR purity requirements.

The appearance of previously detected $O_2^{\cdot-}$ in alkaline DMSO could not be confirmed in our experiments since we were neither able to observe an absorption similar to the published UV spectra nor could we see the characteristic EMR spectra of $O_2^{\cdot-}$ after attempted spin trapping with PNB (α-phenyl-*N*-*tert*-butylnitrone).[34]

Base addition to DMF generated a different radical transient (Fig. 1). The signal intensity reached a maximum after 2–4 min, and then faded away gradually until disappearance after 10–15 min. In the EMR spectra of the DMF-$d_7$ radical low intense, complex signals without fine structure were observed. Interestingly, the presence of 1% DMSO in DMF increased the lifetime of the DMF radicals along with amplified signal intensity in the EMR spectra (Fig. 4). More DMSO had an adverse effect until a concentration of 50% DMSO in DMF was reached, causing again signal enhancement (Fig. 5). The signals from DMF dominated the EMR spectra up to 90% DMSO, demonstrating an efficient radical transfer from DMSO to DMF molecules. The lifetime of DMF radicals (10–15 min) was prolonged

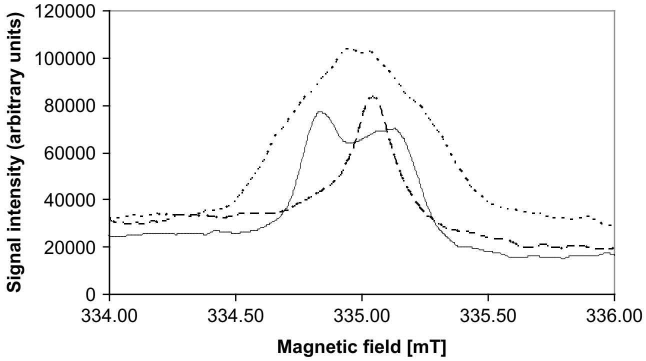


**Figure 2.** Radical formation in DMSO-$d_6$ after adding MeOK: 2 min (——), 9 min (—), 75 min (– – –).

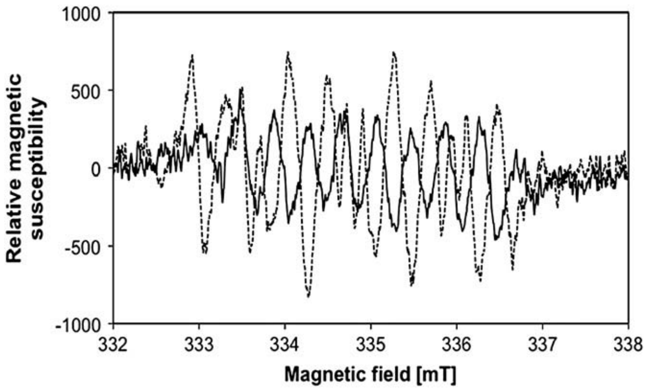


**Figure 4.** EMR spectra of DMF without DMSO (—), with 1% DMSO (- - -).

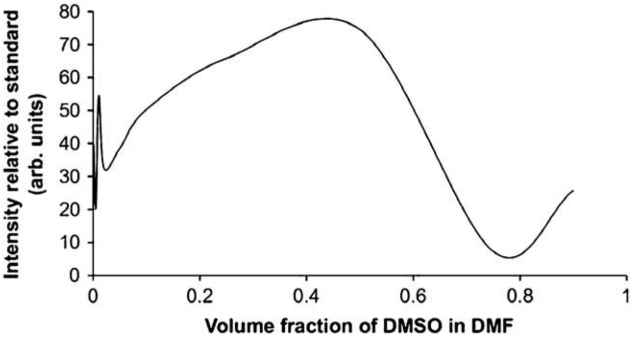


**Figure 5.** Modulation of EMR-signal intensity from the DMF radical in the presence of increasing amounts of DMSO.

in the presence of DMSO to 3–4 h. In addition, the hyperfine splitting of the DMF radicals was greatly improved with DMSO. The now well resolved EMR signals represent three radical species, the first one reaching maximum population at 2 min, the second radical attained its maximum after 6 min (the first radical had then completely disappeared), the maximum of the third radical appeared after 45 min with a subsequent slow decay during 4 h (Figs. 6 and 7). The EMR signals of the third radical could only be observed by 'amplification' with DMSO and was not seen in the neat spectrum of DMF.

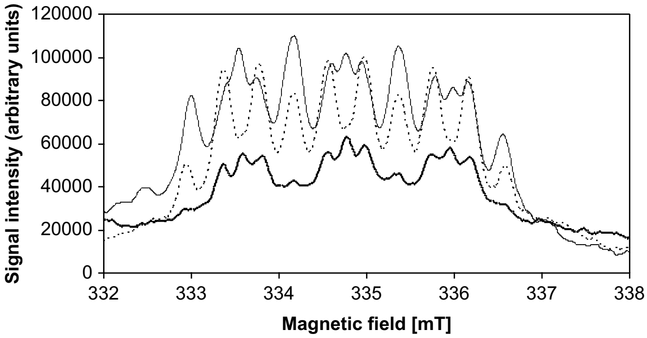


**Figure 6.** EMR spectra of three different DMF radical species in the presence of 1% DMSO, after 2 min (—), 6 min (- - -), 30 min (—).

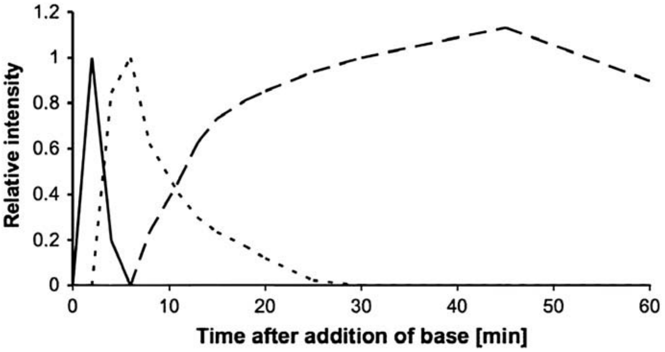
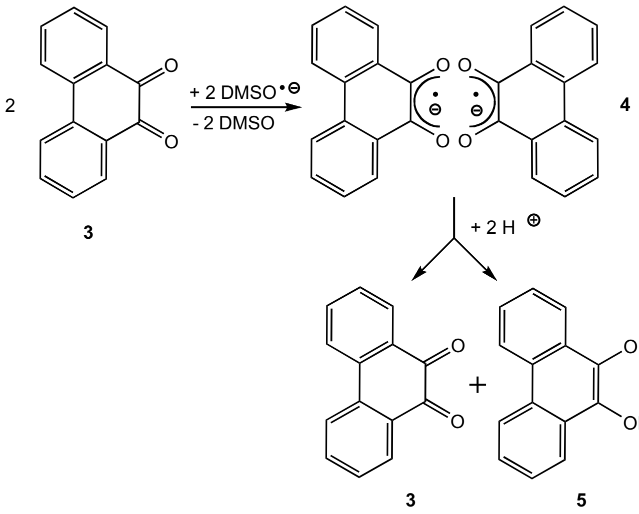


**Figure 7.** Formation and decay of three different DMF radical species in the presence of 1% DMSO. Radical a —, radical b - - -, radical c – – –.



**Scheme 2.**

When the solvent radicals are generated in the presence of conjugated dicarbonyl compounds, consecutive electron transfer results in reduction to dienolates (Scheme 2). The yellow solution of phenanthrenquinone (**3**) in DMSO showed the characteristic signals in the NMR spectra. A small amount of MeOK was then added resulting in a pink solution with complete absence of NMR signals due to the formation of a stabilized paramagnetic radical anion dimer (**4**).[35,36] DMSO radicals could not be observed by EMR, indicating an immediate electron transfer. Addition of $CF_3COOH$ resulted again in NMR-detectable diamagnetic species, which were identified as phenanthrenquinone (**3**) and phenanthrene-9,10-diol (**5**) (Scheme 2). Diol **5** was, however, too sensitive to oxidation in air and could not be isolated. Anthraquinone in basic DMSO reacted in the same manner.

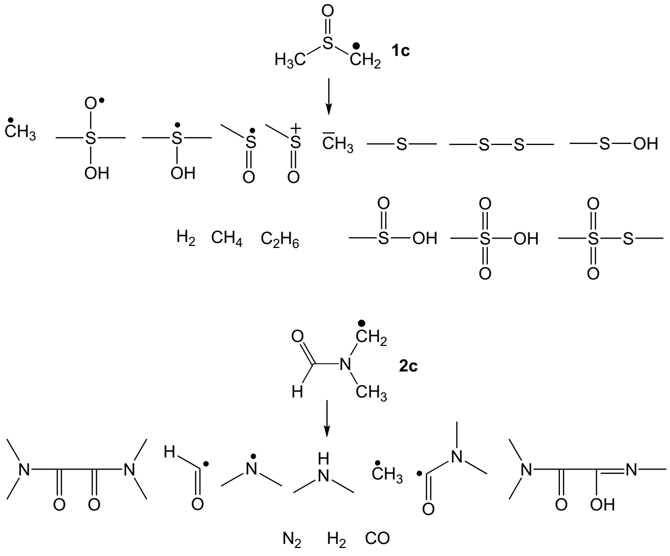
## 3. Discussion

By analogy to a previously proposed reaction mechanism, DMSO radical formation is assumed to occur through an initial fast proton abstraction from DMSO **1a** by the base[37] forming anion **1b** ($DMSO^-$), which loose a single electron resulting in radical **1c** ($DMSO^\bullet$) (Scheme 1).[25] A similar reaction sequence is expected for DMF (**2a**→**2b**→**2c**). Radicals **1c** and **2c** have been identified after pulse radiolysis and photolysis of DMSO and DMF.[28,38–40]

The propagation of radicals has been based on the reaction of $DMSO^-$ (**1b**) with oxygen.[20,31,34,37,41,42] In our experiments the presence or absence of oxygen seems to be of no importance. Dispelling oxygen by passing nitrogen through DMSO during 2 h before adding the base did not change the outcome of the reaction.

Different authors, irradiating DMSO and DMF with light or ionizing rays, obtain many different radicals and products (Scheme 3).[38–40,43–45] The described reaction of the solvents with alkali is obviously even more complex considering the results obtained in solvent mixtures and, therefore, the exact determination of the reaction sequences (initiation and propagation), of radical species and products have so far escaped investigation. Nonetheless, whatever the reaction mechanisms, the formation of stable radicals, formed from pure solvents and bases under common laboratory conditions, was unequivocally detected by electron magnetic resonance (EMR) spectroscopy, by NMR spectroscopy of products, and chemically by electron-transfer reactions.

It is important to emphasize that some of the reported gaseous products of the solvent radical reactions are potential dangerous, e.g., $H_2$, $CH_4$, $C_2H_6$. They may not only develop from the solvents by high energetic radiation, where risks are expected and appropriately prevented, but could possibly also arise by common manipulations, adding small amount of bases, where no risk is realized. An additional hazardous factor would be the probable dissolution of $H_2$ or other gasses in the solvents.[46,47] Taking into account that only a fraction of the solvent molecules react over a relative long time period the formation of gasses may remain unnoticed.



**Scheme 3.** Reported decay of DMSO radicals (**1c**) and DMF radicals (**2c**) obtained after pulse radiolysis.

## 4. Conclusion

The demonstrated facile generation of long-lived radicals from DMF and DMSO is in variance with the generally accepted inertness of these solvents towards a small amount of base. The presence of radicals may perturb reactions performed in these solvents. Elucidating the progression of the reactions as well as identification of the radicals and secondary products call for future investigations. The presented radical formation in DMSO and DMF at slightly basic conditions invites the solvent producers to update their fact sheets.

## 5. Experimental Section

Dimethylformamide (>99.8%) and dimethylsulfoxide (100%) were purchased from VWR International, Fontenay sous Bois, France, DMF-$d_7$ (NMR grade 99.5% D), DMSO-$d_6$ (NMR grade 99.9% D) were from Sigma–Aldrich, St. Louis, USA and potassium methoxide (25 wt % in MeOH) from Fluka, Switzerland.

EMR spectra were recorded on a JES-FR30 Free Radical Monitor from JEOL, Tokyo, Japan. The microwave frequency was 9.1–9.5 GHz with modulation width 0.05, sweep time 2 min, time constant 0.1 s, and amplifier gain 500. The samples were prepared by adding the appropriate solvent or mixture of solvents into the EMR quartz flat cell (200 μL, 0.4 mm thickness) and then adding the base in a concentration of 0.1%. The lag time from mixing the components until start of the analysis was 1–2 min. The reaction proceeded just as well with analytical grade DMSO from open bottles or with dry DMSO from sealed ampoules.

NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer with a QNP probe. The samples were measured in a glass NMR tube with 5 mm outer diameter. $^{13}C$ NMR spectra were recorded with the inverse gated pulse sequence.

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## References and notes

1. Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247–260.
2. Buncel, E.; Symons, E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 164–165.
3. Allan, G. G.; Moks, E.; Nelson, E. N. *Chem. Ind.* **1967**, 1706–1707.
4. Reich, H. J. http://www.chem.wisc.edu/areas/reich/pkatable.
5. Bach, R. D.; Knight, J. W. *Tetrahedron Lett.* **1979**, 3815–3818.
6. Tidwell, T. T. *Synthesis* **1990**, 857–870.
7. Yi, C. Y.; Hua, R. M. *J. Org. Chem.* **2006**, *71*, 2535–2537.
8. Jain, S. M.; Anand, S. M.; Gupta, D. K.; Sama, J. K.; Lal, S.; Dutt, P. IN192967, 2004.
9. Bernhard, K.; Giger, A. US5,780,693, 1998.
10. Webb, R.L. US3,264,362, 1966.
11. Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153–4157.
12. Perissutti, E.; Frecentese, F.; Lavecchia, A.; Fiorino, F.; Severino, B.; De Angelis, F.; Santagada, V.; Caliendo, G. *Tetrahedron* **2007**, *63*, 12779–12785.
13. McIntosh, C. E.; Martinez, I.; Ovaska, T. V. *Synlett* **2004**, 2579–2581.
14. Liang, Y. J.; Dong, D. W.; Lu, Y. M.; Wang, Y.; Pan, W.; Chai, Y. Y.; Liu, Q. *Synthesis* **2006**, 3301–3304.
15. Yokoyama, Y.; Hikawa, H.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1431–1434.
16. Hass, H. B.; Summit, N. J.; Snell, F. D. US2,893,990, 1959.
17. *DMSO Product information Bulletin #123B*; Gaylord Chemical Company: Slidell, LA, USA, 2007.
18. French, F. A. *Chem. Eng. News* **1966**, *11*, 48.
19. Olson, G. A. *Chem. Eng. News* **1966**, *13*, 7.
20. Hyland, K.; Auclair, C. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 531–537.
21. Calle, P.; Sanchez, A.; Sieiro, C. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1181–1185.
22. Melnikov, M. Y.; Belevskii, V. N.; Belopushkin, S. I.; Melnikova, O. L. *Russ. Chem. Bull.* **1997**, *46*, 1245–1247.
23. Misik, V.; Kirschenbaum, L. J.; Riesz, P. *J. Phys. Chem.* **1995**, *99*, 5970–5976.
24. Stein, G.; Stiassny, G. *Nature* **1955**, *176*, 734–735.
25. Symons, M. C. R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 908–915.
26. Földes-Papp, Z.; Gerber, G.; Stosser, R.; Schneider, G. *J. Prakt. Chem.* **1991**, *333*, 293–301.
27. Shishlov, N. M.; Vasilev, Y. V.; Konovalov, V. V.; Korobeynikova, V. N. *Radiat. Phys. Chem.* **1997**, *49*, 451–457.
28. Hayon, E.; Hayashi, N.; Ibata, T.; Lichtin, N. N.; Matsumoto, A. *J. Phys. Chem.* **1971**, *75*, 2267–2272.
29. Kondo, T.; Kirschenbaum, L. J.; Kim, H.; Riesz, P. *J. Phys. Chem.* **1993**, *97*, 522–527.
30. Woodward, J. R.; Lin, T. S.; Sakaguchi, Y.; Hayashi, H. *J. Phys. Chem. A* **2000**, *104*, 557–561.
31. Haseloff, R. F.; Ebert, B.; Damerau, W. *Anal. Chim. Acta* **1989**, *218*, 179–184.
32. Rosenthal, I.; Mossoba, M. M.; Riesz, P. *Can. J. Chem.* **1982**, *60*, 1486–1492.
33. Qiao, X. L.; Chen, S. M.; Tan, L.; Zheng, H.; Ding, Y. D.; Ping, Z. H. *Magn. Reson. Chem.* **2001**, *39*, 207–211.
34. Choi, M. F.; Hawkins, P. *Spectrochim. Acta, Part A* **1995**, *51*, 579–585.
35. Calderazzo, F.; Forte, C.; Marchetti, F.; Pampaloni, G.; Pieretti, L. *Helv. Chim. Acta* **2004**, *87*, 781–789.
36. Taguchi, K.; Fujii, S.; Yamano, S.; Cho, A. K.; Kamisuki, S.; Nakai, Y.; Sugawara, F.; Froines, J. R.; Kumagai, Y. *Free Radical Biol. Med.* **2007**, *43*, 789–799.
37. Corey, E. J.; Chaykovs, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353.
38. Cooper, T. K.; Walker, D. C. *Can. J. Chem.* **1971**, *49*, 2248–2253.
39. Koulkes-Pujo, A.M.; Barat, F.; Mialocq, J.C.; Sutton, J. *J. Photochem.* **1973/74**, *2*, 439–450.
40. Pukhalskaya, G. V.; Kotov, A. G.; Pshezhetskii, S. Y. *Khimiya Vysokikh Energii* **1969**, *3*, 340–345.
41. Stolze, K.; Mason, R. P. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 941–946.
42. Hashimoto, M.; Nakai, Y.; Kohno, M.; Tajima, K.; Kanaori, K.; Endo, N.; Makino, K. *Chem. Lett.* **1997**, 71–72.
43. Kroh, J.; Burzynska, E. *Radiochem. Radioanal. Lett.* **1976**, *27*, 101–108.
44. Kroh, J.; Burzynska, E. *Nukleonika* **1977**, *22*, 453–458.
45. Kroh, J.; Burzynska, E. *Nukleonika* **1977**, *22*, 443–451.
46. Brunner, E. *J. Chem. Eng. Data* **1985**, *30*, 269–273.
47. Dymond, J. H. *J. Phys. Chem.* **1967**, *71*, 1829–1831.