Mechanism of reduction of 1,1-diphenyl-2,2-dinitroethylene by 1-benzyl-1,4-dihydronicotinamide: transition state with partial diradical and partial covalent bonding character

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The mechanism of reduction of 1,1-diphenyl-2,2-dinitroethylene (DPDN) by 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile has been investigated. Based on product analysis, isotopic tracing and electrochemical analysis, the reaction takes place by a hydride transfer mechanism giving 1,1-diphenyl-2,2-dinitroethane (DPDNH). Single crystal X-ray analysis shows that DPDN conforms to idealized C_2 symmetry, but steric repulsions between the bulky substituents result in an appreciable twist about the central bond, such that the phenyl rings make a dihedral angle of 77.7°and the planar C–NO_2 fragments make a dihedral angle of 68.5°. A small kinetic H/D isotope effect was obtained, that we propose is due to steric hindrance. Reaction in oxygen-saturated acetonitrile produced DPDNH and benzophenone in the ratio of 59.2 : 22.0 as the final products with a total yield of 68.6% by GC. Control experiments were performed, by stirring a solution of DPDN or DPDNH alone in oxygen-saturated acetonitrile, or by stirring a solution of DPDN or DPDNH alone in aqueous acetonitrile containing a small amount of hydrochloric acid or in acetonitrile containing triethylamine. These produced no benzophenone. The results clearly indicate the trapping of a radical species by oxygen in the reaction. A curve-crossing model for the reaction projects that the transition state has partial diradical and partial covalent bonding character. As DPDN has a low-lying π* orbital (LUMO), the radical anion $DPDN^{-\bullet}$ is a stabilized radical. It is known that the reaction of alkyl and benzyl radicals with oxygen is exothermic with a rate close to the diffusion-controlled limit. Thus, with use of More O'Ferrall's two-dimensional potential energy diagram, the results are rationalized by a mechanistic change induced by steric hindrance so that the transition state collapses in two directions leading to the formation of DPDNH (polar pathway) and benzophenone (ET pathway), respectively.

The mechanism of reduction of various substrates by co-enzyme NADH model compounds has been extensively studied and continues to be of interest.[1] It is generally recognized that there are two pathways for the formal hydride transfer from NADH model to the substrates: a direct hydride transfer (polar) and an electron transfer (ET) pathway. Pross and Shaik have developed the curve-crossing model and applied the approach to problems of chemical reactivity.[2] The essence of the model is that "a simple description of any reaction profile may be obtained from a schematic energy plot of key electronic configurations that describe reactants, products, and potential intermediates".[3] We[4] have been engaged in studies on the reduction of activated olefinic compounds by NADH models, namely, 1-benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9,10-dihydroacridine ($AcrH_2$), and have found that both polar and ET pathways take place in the reactions. In order to get a better understanding of the structure–reactivity relationship in these reactions, we extend the study to the reduction of 1,1-diphenyl-2,2-dinitroethylene (DPDN) by BNAH and attempt to apply the curve-crossing model with particular reference to the effect of steric interactions on the mechanism. There are several reports[5] on the reduction of nitro compounds by BNAH *via* electron transfer mechanism but to our knowledge the title reaction has never been reported. Herein we present the results.

Results and discussion

Reaction of DPDN with BNAH

DPDN (0.5 mmol) and BNAH (0.5 mmol) were mixed in dry, deoxygenated acetonitrile and the solution was allowed to stand under argon at room temperature in the dark for 4 h. Treatment with 0.1 M hydrochloric acid and conventional work-up gave 1,1-diphenyl-2,2-dinitroethane (DPDNH) in 90% yield. For comparison, the reactions of DPDN with some other nucleophiles were carried out. When DPDN was reduced with $NaBH_4$ in acetonitrile–methanol the same product DPDNH was obtained in 85% yield. When DPDN was reacted with KCN in acetonitrile the Michael addition product 1,1-diphenyl-1-cyano-2,2-dinitroethane was obtained in 80% yield. The reactions are shown in Scheme 1.

Reaction of DPDN with BNAH-4,4-d_2

In order to ascertain the site of hydride transfer from BNAH to DPDN, tracing experiment with BNAH-4,4-d_2 instead of BNAH was carried out under the same conditions. Deuterium

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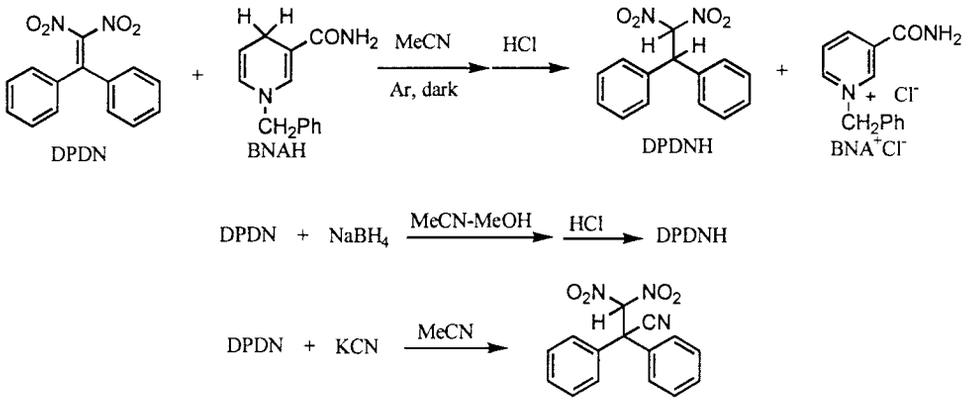


Scheme 1

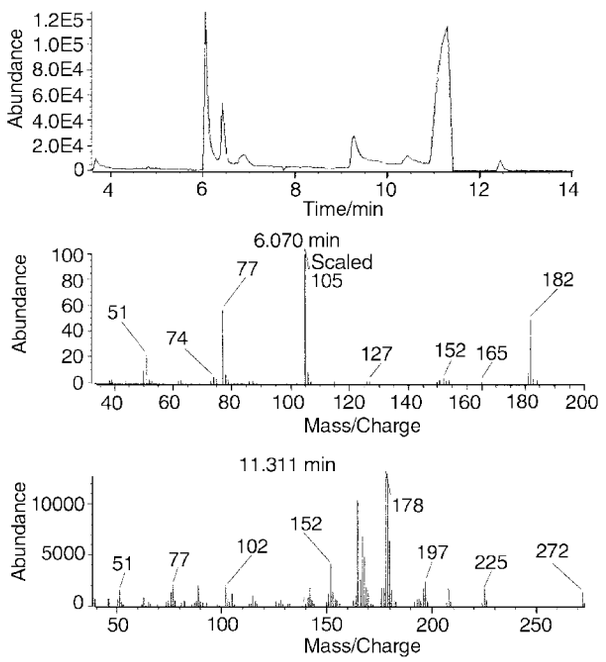


Fig. 1 The GC-MS spectrograph obtained from the reaction of DPDN with BNAH in oxygen-saturated acetonitrile. Column temperature 230 °C, column length 50 m, total yield 68.6%, ratio of DPDNH and benzophenone 59.2 : 22.0.

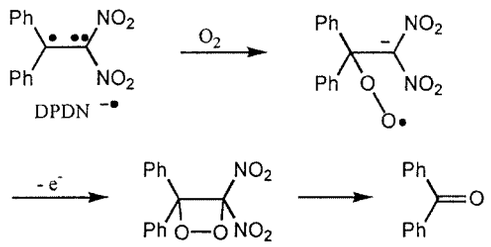
was located at the β-position to the nitro group by ^{1}H NMR and MS. The results are in agreement with the one-step hydride transfer mechanism.

Reaction in the presence of oxygen

When the reaction of DPDN with BNAH was carried out in oxygen-saturated acetonitrile, benzophenone was obtained along with DPDNH. The GC-MS analyses of the reaction mixture showed the formation of DPDNH and benzophenone in the ratio of 59.2 : 22.0 with the total yield of 68.6% (Fig. 1).

Control experiments were performed by stirring a solution of either DPDN or DPDNH alone in oxygen-saturated aqueous acetonitrile for 4 h or by stirring a solution of DPDN or DPDNH in aqueous acetonitrile containing a small amount of 0.1 M hydrochloric acid for 4 h. These produced no benzophenone. Treatment of DPDN or DPDNH with triethylamine in aqueous acetonitrile for 4 h also produced no benzophenone. The results indicated that benzophenone was formed as one of the main products of reaction in oxygen-saturated acetonitrile.

Hoz *et al.*[6] reported that superoxide anion reacted with DPDN to give benzophenone through the intermediacy of a peroxide radical anion (Scheme 2). In the present case, however, no superoxide radical anion could be formed since it has



Scheme 2

been reported[7] that BNAH is inert to molecular oxygen in acetonitrile in the dark. Presumably, the peroxide radical anion could be formed by reaction of oxygen with the radical anion of DPDN, incipiently generated *via* an electron transfer mechanism (*vide infra*).

Electrochemical experiment

The electrode potentials of the reactants were determined by cyclic voltammetry at 150 mV s^{-1} in acetonitrile. BNAH gave an irreversible oxidation potential[8] of 0.63 V *vs.* Ag/AgCl. DPDN gave the reduction potential of −0.54 V *vs.* Ag/AgCl.

Kinetic isotope effect

Since the UV-Vis absorptions of BNAH and DPDN overlapped, it was not possible to determine the kinetics of reaction by spectroscopic methods. As an alternative, we reacted DPDN with both BNAH and BNAH-4,4-d_2 in the same experiment and measured the ratio of the non-labelled and labelled products by MS. The average of four separate measurements gave the kinetic isotope effect $k_H/k_D = 1.8$. This value is too low for a primary kinetic H/D isotope effect. For comparison, it was reported[9] that the reduction of benzylidenemalononitrile by BNAH showed a kinetic isotope effect $k_H/k_D = 3.0$ for hydride transfer [reaction (1)].

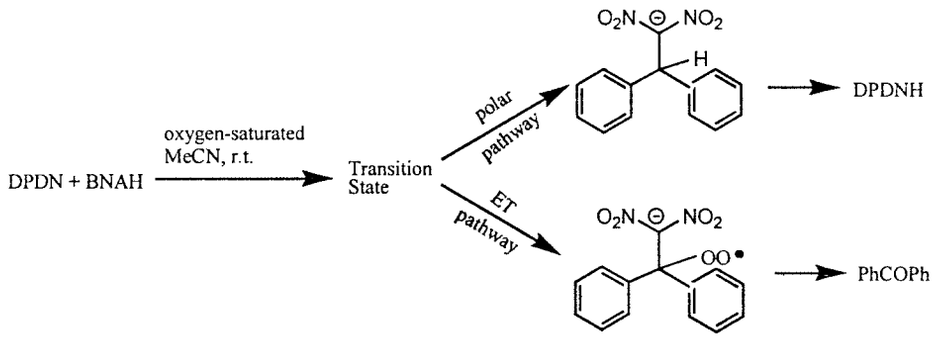
$$\text{Ph–CH=C(CN)}_2 + \text{BNAH} \longrightarrow \text{Ph–CH}_2\text{–CH(CN)}_2 \quad (1)$$

Inhibitor experiment

p-Dinitrobenzene (*p*-DNB) is a strong electron acceptor and an efficient inhibitor for ET reactions.[10] The reduction potential of *p*-DNB[11] is −0.30 V *vs.* NHE, which is slightly higher than that of DPDN (−0.54 V *vs.* Ag/AgCl; −0.32 V *vs.* NHE). When *p*-DNB was added to the reaction mixture of BNAH with DPDN, no inhibiting effect was observed.

Molecular structure of DPDN

X-Ray analysis of DPDN showed that the molecule conforms closely to idealized C_2 symmetry with the two-fold axis aligned



Scheme 3

along the C(1)–C(2) double bond. The phenyl rings and C–NO_2 fragments are each planar, but steric repulsions between them result in an appreciable twist about the central double bond, as reflected by the torsion angles C(3)–C(1)–C(2)–N(1) = 12.1° and C(9)–C(1)–C(2)–N(2) = 13.3°. The phenyl rings make a dihedral angle of 77.7°, and the C–NO_2 fragments make a dihedral angle of 68.5°.

Mechanism

Consider the following electron transfer reaction [reaction (2)].

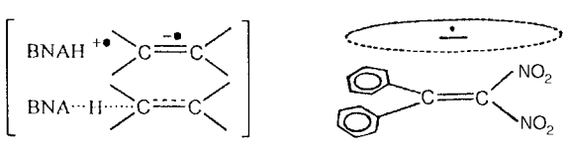
$$\text{BNAH} + \text{DPDN} \longrightarrow \text{BNAH}^{\bullet+} + \text{DPDN}^{\bullet-} \quad (2)$$

Since E_{ox} for BNAH is higher than E_{red} for DPDN, electron transfer from BNAH to DPDN is endergonic and cannot take place. However, when electron transfer is coupled with the formation of a C–H covalent bond resulting in a hydride transfer, the reaction can proceed with efficiency as borne out by experiment.

As the two phenyl groups and the two nitro groups are bulky substituents and are twisted about the central double bond, the approach of BNAH to the β-carbon of DPDN for hydride transfer meets with steric hindrance. This could result in a transition state with only partial elecron transfer and a lengthening of the C–H covalent bond. A transition state in which the hydrogen is unsymmetrically located between the donor and acceptor molecules should have a smaller kinetic isotope effect than that in a symmetrical transition state in accordance to Melander and Westheimer predictions.[12] The small kinetic isotope effect obtained is in agreement with that prediction.

It should be pointed out that Bethell *et al.*[13] have studied the hydride transfer reaction between polymethylbenzenes and 9-arylfluorenyl cations and concluded that "the overall hydride transfer proceeds through a transition state having considerable electron transfer character and with loosening of the transferred hydrogen". The transition state envisaged in the case investigated here is consistent with that description.

The formation of benzophenone in oxygen-saturated acetonitrile is of particular interest. Although UV-Vis and EPR spectroscopy did not reveal the formation of a charge-transfer complex or radical intermediates, the curve-crossing model projects that the ET and polar mechanisms involve hybrid characters in their corresponding transition states, *i.e.*, both diradical and covalent bond forming character is present as depicted below (A):



Since DPDN has a low-lying π* orbital (LUMO) and the electron it accepts upon electron transfer from BNAH can be delocalized onto the aromatic rings and the substituent groups, the radical anion formed (B) is stabilized.[14] Meanwhile, it is well-documented[15] that the reaction of alkyl and benzyl radicals with oxygen, which is a diradical, is an exothermic reaction and the rate should be close to the diffusion-controlled limit. On the basis of the conditions given above, a mechanistic change from the polar pathway to ET pathway could occur in the reaction in oxygen-saturated acetonitrile according to More O'Ferrall's two-dimensional free energy diagram[16] (More O'Ferrall–Albery–Jencks diagram[17]). Thus the transition state collapses to a carbanion leading to the formation of DPDNH (polar pathway) or dissociates into a peroxide radical anion leading to the formation of benzophenone (ET pathway). Judging from the relative amounts of DPDNH and benzophenone formed, reactions by the two pathways were competitive with the former in preference over the latter (Scheme 3).

In this connection it is noteworthy that Shaik *et al.*[18] recently reported a mechanistic crossover induced by steric hindrance and the bifurcation of potential energy surface near the changeover zone.

Conclusion

In the reduction of DPDN by BNAH, the overall hydride transfer proceeds through a transition state having partial electron transfer and partial covalent bonding character. Supporting evidence includes a small kinetic H/D isotope effect and the results of reaction in oxygen-saturated acetonitrile, wherein benzophenone was obtained along with DPDNH as the final products. The results are rationalized with use of the curve-crossing model and More O'Ferrall's two-dimensional potential energy diagram.

Experimental

General

Melting points were uncorrected. ^{1}H NMR spectra were taken on a Bruker AM-400 NMR spectrometer using $CDCl_3$ as solvent and TMS as internal reference. *J* values are given in Hz. Mass spectra were determined on a VG analytical ZAB-HS mass spectrometer with an ionization potential of 70 eV. Elemental analyses were carried out with an Italian 1106 analyzer. Cyclic voltammetry was performed by means of a CV-27 Voltammograph using Ag/AgCl electrode as reference with tetraethylammonium perchlorate as supporting electrolyte.

BNAH[19] and BNAH-4,4-d_2[20] were prepared according to the literature. DPDN was prepared by nitration of 1,1-diphenylethylene with red fuming nitric acid in HOAc.[21] HPLC grade acetonitrile (BDH) was dried and distilled from CaH_2 before use. Argon and oxygen were dried by passing through a KOH tube and two $CaCl_2$ tubes.

Reaction of DPDN with BNAH

DPDN (0.5 mmol) and BNAH (0.6 mmol) were dissolved in dry acetonitrile (10 ml) and the solution was bubbled with argon for 10 min and then sealed. After stirring under argon in the dark for 4 h the DPDN was completely consumed (TLC). Hydrochloric acid (0.1 M, 1 ml) was added, the mixture was extracted with $CHCl_3$ (3 × 10 ml) and the combined extract was dried with Na_2SO_4. After evaporation of the solvent the residue was subjected to column chromatography on silica with 40–60 petroleum ether–ethyl acetate (40 : 11) as eluent to give DPDNH as a colourless solid (90%), mp 66–67 °C (Found: C, 61.79; H, 4.49; N, 10.25. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29%); δ_H(400 MHz; $CDCl_3$) 7.35 (10H, m), 7.00 (1H, d, *J* 11.7), 5.23 (1H, d, *J* 11.7); *m*/*z* 272 (M^+ 14%), 180 (48), 179 (93), 178 (100), 167 (55), 152 (42), 89 (33), 77 (42), and 51 (46).

Reaction of DPDN with BNAH in oxygen saturated acetonitrile

Acetonitrile (2 ml) was bubbled with dry oxygen for 5 min. DPDN (0.05 mmol) and BNAH (0.05 mmol) were added and the reaction vessel was sealed. After reaction at room temp. for 2 h in the dark, the reaction mixture was quenched with HCl (1 M, 0.5 ml) and the mixture was analyzed by GC-MS with authentic benzophenone as reference.

Determination of kinetic isotope effect

Acetonitrile (2 ml) was bubbled with dry argon for 10 min. BNAH (0.05 mmol), BNAH-4,4-d_2 (0.05 mmol) and DPDN (0.03 mmol) were added and the reaction vessel was sealed. After reaction at room temp. for 2 h in the dark, the reaction mixture was quenched with HCl (1 M, 0.5 ml) and the mixture was analyzed by MS. The ratio of intensities of *m*/*z* 272/273 was calculated.

Reaction of DPDN with $NaBH_4$

DPDN (0.5 mmol) was added to a suspension of $NaBH_4$ (0.5 mmol) in acetonitrile (10 ml). The mixture was stirred under argon for 2 h. Hydrochloric acid (1 M, 2 ml) was added, the mixture was extracted with $CHCl_3$ (3 × 10 ml) and the combined extract was dried with Na_2SO_4. After removal of the solvent the residue was subjected to column chromatography with 40–60 petroleum ether–ethyl acetate (40 : 1) as eluent to give DPDNH (85%).

Reaction of DPDN with KCN

DPDN (0.5 mmol) and KCN (0.5 mmol) were mixed in acetonitrile (10 ml). The mixture was stirred for 2 h until DPDN was completely consumed (TLC). Hydrochloric acid (1 M, 2 ml) was added, the mixture was extracted with $CHCl_3$ (3 × 10 ml) and the combined extract was dried with Na_2SO_4. After removal of the solvent the residue was subjected to chromatography with 40–60 petroleum ether–ethyl acetate (20 : 1) as eluent to give 1,1-diphenyl-1-cyano-2,2-dinitroethane (85%), oil (Found: C, 60.64; H, 3.71; N, 14.10. $C_{15}H_{11}N_3O_4$ requires C, 60.60; H, 3.73; N, 14.14%); δ_H(400 MHz; $CDCl_3$) 7.40 (10H, m), 7.28 (1H, s); *m*/*z* 297 (M^+, 21%), 204 (25), 192 (100), 190 (51), 165 (76) and 105 (19).

X-Ray structural determination

Crystal data. $C_{14}H_{10}N_2O_4$, $M = 270.24$, monoclinic, space group $P2_1/c$ (no. 14), $a = 9.637(2)$, $b = 15.251(3)$, $c = 9.109(2)$ Å, $\beta = 96.86(3)°$, $U = 1329.1(5)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.101 mm^{-1}; 3385 reflections collected, of which 2041 were independent ($R_{int} = 0.048$). Intensities were measured on a MSC/Rigaku RAXIS IIC imaging-plate diffractometer at 294 K using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å) from a rotating-anode generator operating at 50 kV and 90 mA ($2\theta_{min} = 2.1°$, $2\theta_{max} = 51.1°$, 2–5° oscillation frames in the range of 0–180°, exposure 8 min per frame).[22] A self-consistent semi-empirical absorption correction based on Fourier coefficient fitting of symmetry-equivalent reflections was applied using the ABSCOR program.[23]

The crystal structure was solved by the direct method, and all the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were all generated geometrically (C–H bond lengths fixed at 0.96 Å), assigned appropriate isotropic thermal parameters and allowed to ride on their parent carbon atoms. Full-matrix least-squares refinement on F^2 was performed on an IBM-compatible 486 PC with the *SHELXTL-PC* program package.[24] The final discrepancy indices for 1678 independent observed reflections ($I > 2\sigma(I)$) and 182 variables are $R1 = 0.059$ and $wR2 = 0.144$. CCDC reference number 188/218. See http://www.rsc.org/suppdata/p2/a9/a909716c for crystallographic files in .cif format.

Acknowledgements

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References

1 For reviews on the reactions and mechanisms of NADH models, see: (*a*) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1; (*b*) D. M. Strout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (*c*) S. Yasuo and A. Ohno, *Bioorg. Chem.*, 1986, **14**, 70; (*d*) D. L. Comins and S. O'Connor, *Adv. Heterocycl. Chem.*, 1998, **44**, 144; (*e*) Y. Murakami, J. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 121.
2 A. Pross and S. S. Shaik, *Acc. Chem. Res.*, 1983, **16**, 363 and references cited therein.
3 A. Pross, *Acc. Chem. Res.*, 1985, **18**, 212.
4 Y. C. Liu, B. Li and Q. X. Guo, *Tetrahedron Lett.*, 1994, **35**, 8429; *Tetrahedron*, 1995, 9671; X. Q. Zhu, Y. C. Liu, J. Li and H. Y. Wang, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 2191.
5 R. J. Kill and D. A. Widdowson, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 755; N. Ono, R. Tamura and A. Kaji, *J. Am. Chem. Soc.*, 1983, **105**, 4107; S. Fukuzumi and M. Chiba, *J. Chem. Soc.*, *Perkin Trans. 2*, 1991, 1393; R. D. Chapman, R. A. O'Brien and P. A. Kondracki, *Tetrahedron*, 1992, **52**, 9655.
6 A. A. Frimer, I. Rosenthal and S. Hoz, *Tetrahedron Lett.*, 1977, 4631.
7 S. Fukuzumi, M. Ishikawa and T. Tanaka, *J. Chem. Soc.*, *Perkin Trans. 2*, 1989, 1037.
8 NAH gave an irreversible oxidation potential at 0.63 V *vs.* Ag/AgCl upon cyclovoltammetry. Verhoeven *et al.* (*Tetrahedron*, 1978, **34**, 443) have extracted the standard electrode potential E^0 ($BNAH^{\bullet+}$/BNAH) = 1.00 V using a photochemical method and employing the Rehm–Weller equation.
9 Y. Wang, Y. C. Liu, X. Q. Zhu and Q. X. Guo, *Chin. J. Chem.*, 1999, **17**, 184.
10 N. Kornblum, *Angew. Chem.*, *Int. Ed. Engl.*, 1975, **14**, 734.
11 J. Q. Chambers and R. N. Adams, *J. Electroanal. Chem.*, 1965, **9**, 400.
12 L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1980, pp. 130–131.
13 D. Bethell, P. N. Clare and G. J. Hare *J. Chem. Soc.*, *Perkin Trans. 2*, 1983, 1889.
14 S. Hoz and D. Speizman, *J. Org. Chem.*, 1983, **48**, 2904.
15 (*a*) D. C. Nonhebel, J. M. Tedder and J. C. Walton, *Radicals*, Cambridge University Press, 1979, ch. 14; (*b*) J. A. Howard, in *Free Radicals*, ed. by J. K. Kochi, vol. 2, Wiley, New York, 1973, ch. 12.
16 R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1970, 274.
17 N. Isaacs, *Physical Organic Chemistry*, Second Edition, Addison Wesley Longman, London, 1995.
18 G. N. Sastry and S. Shaik, *J. Am. Chem. Soc.*, 1998, **120**, 2131.
19 A. G. Anderson, Jr. and G. Berkelhammer, *J. Am. Chem. Soc.*, 1958, **81**, 992.
20 W. S. Caughey and K. A. Schellenberg, *J. Org. Chem.*, 1966, **31**, 1978.
21 E. D. Bergman and E. Mayer, *Chem. Ber.*, 1932, **65**, 446.

22 J. Tanner and K. Krause, *The Rigaku Journal*, 1994, **11**, 4; 1990, **7**, 28; K. Krause and G. N. Phillips, *J. Appl. Crystallogr.*, 1992, **25**, 146; M. Sato, M. Yamamoto, Y. Katsube, N. Tanaka and T. Higashi, *J. Appl. Crystallogr.*, 1992, **25**, 348.
23 T. Higashi, *ABSCOR – An Empirical Absorption Correction Based on Fourier Coefficient Fitting*, Rigaku Corporation, Tokyo, 1995.
24 *SHELXL/PC Version 5.0 Reference Manual*, Siemens Energy & Automation Inc., Madison, WI, 1996; G. M. Sheldrick, in *Computational Crystallography 6: a Window on Modern Crystallography*, eds. H. D. Flack, L. Párkányi and K. Simon, International Union of Crystallography and Oxford University Press, Oxford, 1993, pp. 111 and 112.

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