Pergamon

Tetrahedron, Vol. 53, No. 51, pp. 17407-17416, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10164-8

New Reactions of Furoxans: Formation of Alkynes and Cyclobutaphenanthrenes

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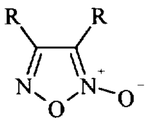
Abstract: Diarylfuroxans were found to give diaryacetylenes upon irradiation at 254 nm. Cyclobutaphenanthrenes were also obtained when reaction was carried out in the presence of alkenes. The acetylenic derivative is supposed to arise by loss of $(NO)_2$ from a diazete-N,N-dioxide. Unimolecular and collision activated dissociation studies by tandem mass spectrometry also support the loss of $(NO)_2$ from diarylfuroxans molecular ions. © 1997 Elsevier Science Ltd.

INTRODUCTION

In the last decade the role of nitric oxide in physiological mechanisms has been deeply studied.[1] Therefore compounds able to release nitric oxide have received a lot of attention, and recently a few papers have been published on the possibility of furoxans as nitric oxide generators.[2-3]

In particular, it was reported that some diarylfuroxans give rise, upon electron-impact ionization, to acetylenic fragments by loss of nitric oxide; the intermediate from which furoxan **1** loses NO, was supposed to be a dinitroso derivative **2** formed by cleavage of the O(1)-N(2) bond.[4]



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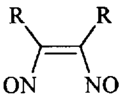

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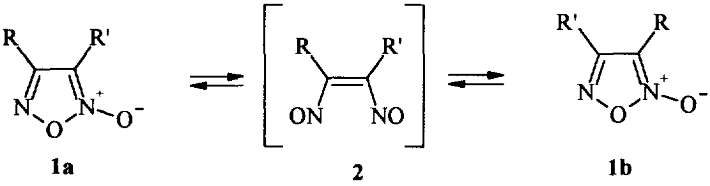
Some years ago we became involved with the photochemical reactions of furoxans;[5] we found that some diarylfuroxans undergo NO loss with formation of the corresponding acetylenic derivatives. As far as we know, only a few studies were made on photochemistry of furoxans, and what is reported is that irradiation of some unsymmetrical furoxans leads exclusively to isomerization.[6-8] The reaction equilibrium, photochemically or thermally induced has been studied and dinitrosoalkenes **2** were proposed early in 1965 as possible intermediates for the **1a** $\rightleftharpoons$ **1b** isomerization (Scheme 1).[9]

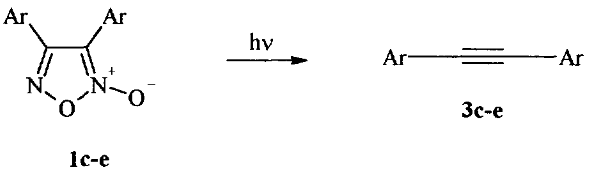


Scheme 1

In the present paper we wish to report the results obtained by photolysis of diarylfuroxans with an attempt to rationalize the different reactivity of these derivatives, upon irradiation in solution and upon electron-impact ionization (EI) mass spectrometry (MS).

RESULTS

Degassed solutions of diarylfuroxans **1c-e** in *n*-hexane were irradiated at 254 nm for 1 hour. Along with the unreacted furoxan, diarylacetylenes **3c-e** were obtained as the only products from the hexane solutions (Scheme 2, Table 1). Also, insoluble tar was always obtained after irradiation, but our attempts in analyzing it failed.



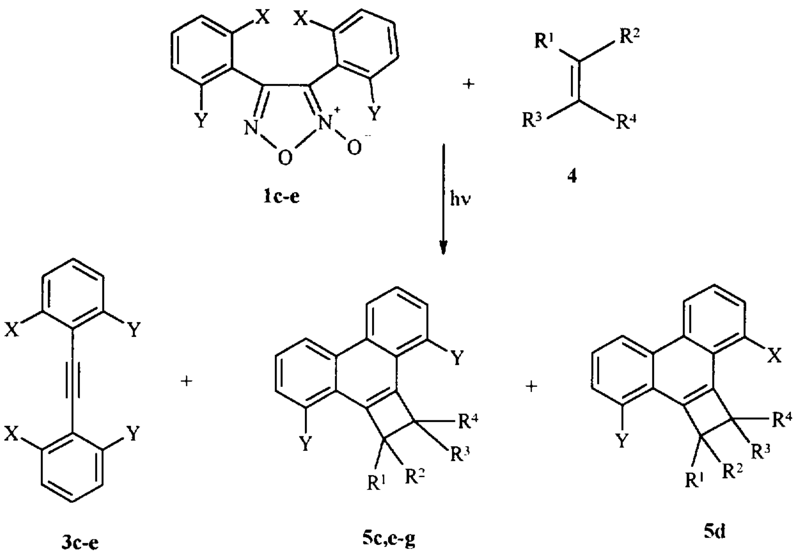
Scheme 2

Table 1. Irradiation of furoxans **1c-e**

Furoxan **1**	Conversion	**3** (Yields)
1c (Ar = C_6H_5)	75%	**3c** (4%)
1d (Ar = ClC_6H_4)	85%	**3d** (12%)
1e (Ar = $Cl_2C_6H_3$)	95%	**3e** (18%)

Conversions and yields are calculated *via* HPLC using an external standard

In order to ascertain if the low yields reported in Table 1 were due to degradation of **3** in the reaction conditions, we tried to trap the alkynes formed from furoxans with various alkenes, through 2+2 cycloadditions (Scheme 3, Table 2).



Scheme 3

Reaction of furoxans **1c-e** with alkenes gave acetylene derivatives **3c-e** and cyclobutaphenanthrene derivatives **5**, in which, formally, the furoxan has lost $(NO)_2$, added the alkene and lost X_2 or XY (H_2, HCl, or Cl_2) to give the phenanthrene derivative.

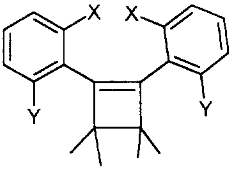
Table 2. Reactions of furoxans **1c-e** with alkenes **4** in *n*-hexane

entry	Furoxan 1	Alkene 4	Conv.	3 (Yields)	5 (Yields)
i	**1c** (X=Y=H)	R^1=R^2=R^3=R^4=Me	80%	**3c** (5%)	**5c** (1%)
ii	**1d** (X=Cl, Y=H)	R^1=R^2=R^3=R^4=Me	79%	**3d** (1%)	**5c** (5%) + **5d** (4%)
iii	**1e** (X=Y=Cl)	R^1=R^2=R^3=R^4=Me	83%	**3e** (1%)	**5e** (10%)
iv	**1e**	R^1=H R^3=Me R^2=R^4=$(CH_2)_4$	83%	**3e** (2%)	**5f** (9%)
v	**1e**	R^1=R^3=H R^2=R^4=$(CH_2)_4$	82%	**3e** (3%)	**5g** (7%)
vi	**1e**	R^1=R^2=R^3=H R^4 =C_4H_9	96%	**3e** (18%)	-

Conversions and yields are calculated *via* HPLC using an external standard

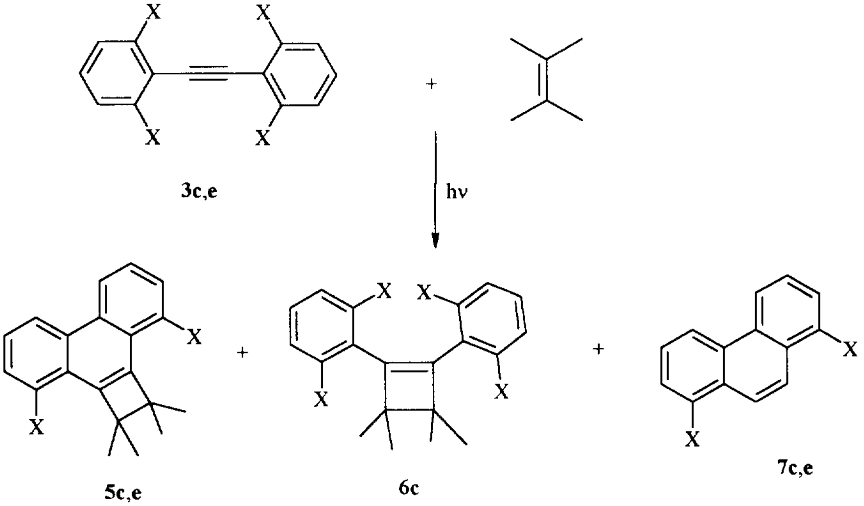
These results show that in these conditions monosubstituted alkenes such as 1-hexene are not able to trap the acetylene formed from furoxan **1e** (entry vi). Tetramethylethylene (**TME**) proved to be the most efficient in trapping the acetylene **3e** formed from furoxan **1e** (entry iii-vi) but still poorly effective in reaction with diphenylfuroxan (**1c**) (entry i). In all cases, anyhow, the amount of adducts **5** and of acetylene **3**, obtained in the presence of the alkenes, did not exceed the amount of acetylene formed in the photolysis without alkenes of furoxans **1c-e**.

It is known that diphenylacetylene (**3c**) and **TME** in diethyl ether afford **6c** when irradiated at 300 nm[10] and **6c**, in turn, yields the phenanthrene derivative **5c** when irradiated at 354 nm.[11] Therefore, we were surprised that in the reactions of furoxans with **TME** the expected cyclobutene derivatives **6c-e** were never found.



6c-e

The absence of **6c-e** in the reaction of furoxans and **TME** could be due to the different conditions used: 254 nm instead that 300 and 354 nm. Reactions between acetylenes **3c,e** and **TME** were therefore performed at 254 nm (Scheme 4).



Scheme 4

The results obtained show that reaction depends upon the nature of the acetylene: acetylene **3e** yields the phenanthrene derivative **5e**, but does not give cyclobutene **6e**, while acetylene **3c** gives a mixture of **5c** and **6c** (Table 3).

Table 3. Reactions of acetylenes **5c,e** with **TME**

Acetylene 3	5 (Yields)	6 (Yields)	7
3c (X= H)	**5c** (4%)	**6c** (16%)	**7c** (traces)
3e (X=Cl)	**5e** (35%)	-	**7e** (traces)

So, the reaction of furoxan **1e** with **TME** and the reaction of acetylene **3e** with **TME** give in both cases the adduct **5e** with no trace of **6e**. On the contrary, while the reaction of acetylene **3c** with **TME** gives a greater amount of **6c** than **5c**, the reaction of furoxan **1c** with **TME** yields **5c** and no traces of **6c**.

DISCUSSION

The present results, compared with literature data, show that the formation of acetylenes from furoxans does not always occur, depending upon the substituents of the furoxan ring: diarylfuroxans lose $(NO)_2$ while other derivatives[6-8] undergo only isomerization.

A different behavior of furoxans that is dependent on their substitution was also observed by EIMS.

EIMS data of variously substituted furoxans have been reported in the literature. Since 1964 the formation of dialkylacetylene fragments were postulated as the charged M-60 fragments arising by the loss of two NO molecules from dialkylfuroxan molecular ions.[12] Later,[13] and also very recently,[4] an analogous proposal was put forward speculatively for diphenyl and some diaryl furoxans, respectively.

Now we provide sound evidence for the acetylenic structure of M-60 fragments by mass-analyzed ion kinetic energy (MIKE) spectroscopy performed in high energy (8 kV) collision activation (CA) conditions, which is an established method for the characterization of ion structures in the gas phase.[14,15] The MIKE CA spectra obtained from the M-60 fragments of diarylfuroxans **1c** and **1e** actually appeared to be perfectly superimposable to those of the molecular ions of the corresponding diarylacetylenes **3c** and **3e**, respectively.

Further, the EI mass spectra reported in the literature[4,12-13] showed also a M-30 peak, due to the loss of NO from molecular ions, which was presumed to represent the first step of the 2NO elimination process taking place within the ion source of the mass spectrometer and leading to acetylene ions.

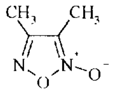
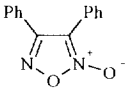
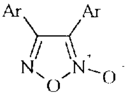
The relative abundances of M-30 and M-60 fragments were substantially dependent upon the furoxan substituents, *i.e.*: the former were more abundant for dialkyl and much less abundant for diaryl and substituted-diaryl furoxans.

Similar relative abundances of M-30 and M-60 fragment ions were observed by MIKE spectroscopy to be formed upon either CA or unimolecular (metastable) conditions from diaryl (**1c** and **1e**) and dimethyl furoxan molecular ions.

The rather low relative abundance of M-NO fragments generated from diarylfuroxans collisional activated or metastable molecular ions (MIKE spectra), as well as those dissociating into the ion source (normal MS spectra), could suggest that diarylacetylene fragments would mainly originate directly from the molecular ions by loss of neutral $(NO)_2$. This suggestion is in agreement to the B^2/E=constant linked-scan spectra[15], performed either under CA and unimolecular mode, which showed that the molecular ions of **1c** and **1e** are the precursors of the acetylene (M-60) fragments, with only minor contributions from M-30 species.

Eventually, we tried to get further evidence for the mechanism of the fragmentation process(es) leading to acetylene ions by measurements of the kinetic energy released (T) associated to the losses of NO and $(NO)_2$ from the dimethyl and diaryl furoxans (**1c** and **1e**) metastable molecular ions, using MIKE spectroscopy. Following established procedures for correcting the Gaussian-type metastable peak width at half height from the energy spread contribution of the main beam[16], we calculated $T_{1/2}$ values shown in Table 4, using the Beynon's book equation[17] relating T to the metastable peak width.

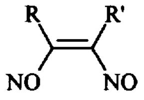
Table 4. Kinetic energy release ($T_{1/2}$) for the M-NO and M-$(NO)_2$ processes of dimethylfuroxan and diarylfuroxans **1c** and **1e**

Kinetic energy release			 Ar=$Cl_2C_6H_3$
$T_{1/2}$ (M-NO)	16 meV	157 meV	89 meV
$T_{1/2}$ (M-$(NO)_2$)	not measurable	32 meV	19 meV

The $T_{1/2}$ experimental values were much larger for M-NO than for M-$(NO)_2$ processes, which further support the possibility that formation of acetylene ions should mostly follow a different reaction path from that involving the M-NO as a precursor ion.

This different behavior could be due to the nature of the intermediate or transition state in the **1**→**3** reaction.

Dinitroso derivatives **2** and **8** were proposed as possible intermediates, respectively, in the thermal isomerization of furoxans and benzofuroxans by Mallory and Cammarata: compound **2** was chosen as possible intermediate only on the basis of thermodynamic considerations, and dioxide **9** was discarded as they calculated it to be at least 20 kcal/mol higher in energy than dinitroso derivative **2**.[9b] The evidence for the existence of a dinitrosobenzene intermediate **8** in the reaction of benzofuroxans is now supported by a lot of literature data.[18-20]



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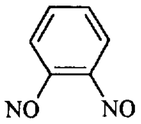

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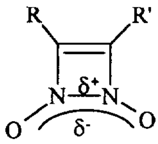
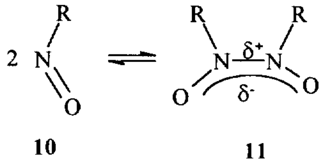


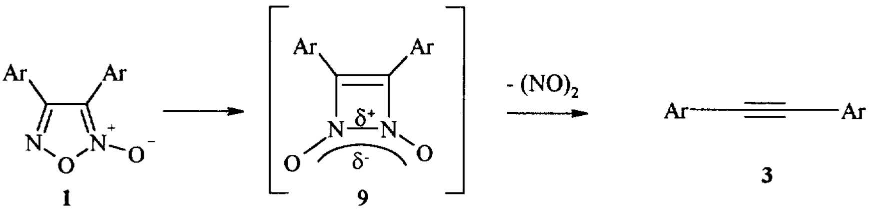
9

It is known that nitroso derivatives **10** are in equilibrium with the corresponding azo-N,N'-dioxides **11** and that the equilibrium lies on one or the other side depending upon the substituents.[21-22] In these equilibria the enthalpy term favors the diazo form, while the entropy term favors the nitroso form.



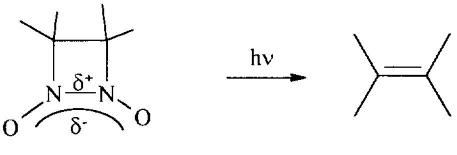
We can therefore consider that dinitroso derivatives **2** are in equilibrium with the dioxides **9**, and that this equilibrium will be shifted towards the most stable compound. In this case, the entropy term should not have a significant influence in the equilibrium. On the contrary the importance of strain energy for the equilibrium azo dioxide-dinitroso form in the four-membered ring azo dioxide should be relevant as postulated by Greene.[22] We found, using MMX[23] calculations that the ΔE_{strain} (E_{strain} (azo dioxide **9**)- E_{strain} (dinitroso **2**)) is actually higher for aliphatic derivatives (ΔE_{strain} = 40 kcal/mol for R= R'= Me; ΔE_{strain} = 25 kcal/mol for R= Me, R'= OEt) than for aromatic derivatives (ΔE_{strain} = 26 kcal/mol for R= R'= C_6H_5;. ΔE_{strain} = 25 kcal/mol for R= R'= $Cl_2C_6H_3$). Therefore the existence of intermediate **9** is more probable for aromatic derivatives than for aliphatic ones.

The tendency of furoxans to give acetylenes could therefore be due to the different intermediates involved: i) for aliphatic furoxans like **1a** (R= Me, R'= OEt) the tendency is low as the stability of the dinitroso form **2** favors the isomerization[7]; ii) for diarylfuroxans the formation of dioxide **9** allows the loss of $(NO)_2$ and the formation of alkynes (Scheme 5).



Scheme 5

This loss of $(NO)_2$ from intermediate **9** is not surprising as it was already observed by Ullman[24] that similar molecules such as 1,2-diazetine-1,2-dioxide **12** can undergo photodecomposition when irradiated with loss of $(NO)_2$ through a cycloreversion (Scheme 6).



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Scheme 6

In conclusion, the mechanism of formation of diarylacetylenes and cyclobutaphenanthrenes by photolysis of diarylfuroxans presents new interesting aspects which will be further investigated.

EXPERIMENTAL

NMR spectra were determined with TMS as internal standard on a Bruker 250 MHz instrument. Mass spectra were performed on a RMU 70. Chromatographic separations were performed using Merck Kieselgel 60. M.p.s are uncorrected. Photolysis samples in quartz tubes were degassed by bubbling nitrogen and irradiated at 254 nm using a Rayonet reactor equipped with a merry-go-round apparatus. The mass spectral measurements were performed with a VG Micromass ZAB-2F instrument, using an EI ion source heated at 150°C, operating with 70eV (0.2 mA) ionizing electron beam and 8kV accelerating potential. The samples were introduced directly into the ion source by the probe inlet system. The spectra were recorded by an UV oscillograph. Collision-activation experiments were made using He as target gas, at a collision cell pressure suitable to reduce the main beam intensity by 1/3.

Photolysis of furoxans 1c-e.

Eight tubes containing a 10^{-3} M solution of furoxans **1c-e** (0.020 mmol) in degassed *n*-hexane (20 mL) were irradiated for 1 hour. The crude was filtered and chromatographed to give acetylene **3c-e**. Diphenylfuroxan[25] (**1c**) gave *diphenylacetylene* (**3c**) in 4% yield. Bis(2-chlorophenyl)furoxan[26] (**1d**) gave *bis(2-chlorophenyl)acetylene* (**3d**)[27] in 12% yield. ^{1}H NMR ($CDCl_3$): 7.58 (2H, m), 7.42 (2H, m); 7.25 (4H, m). Bis(2,6-dichlorophenyl)furoxan[28] (**1e**) gave *bis(2,6-dichlorophenyl)acetylene*[29] (**3e**) in 18% yield; m.p. 153-154 °C. ^{1}H NMR ($CDCl_3$): 7.38 (4H, m), 7.22 (2H, dd, J = 7, 9 Hz); MS: m/z 316 (M+, 100). Anal. Calcd. for $C_{16}H_6Cl_4$: C, 53.40%; H, 1.90%; Cl, 44.90%. Found: C, 52.24%; H, 1.96%; Cl, 43.71%.

*Reactions of furoxans **1c-e** with alkenes **4**.*

Eight tubes containing a 10^{-3} M solution of furoxans **1c-e** (0.020 mmol) and the alkene (1.7 mmol) in 20 mL of degassed *n*-hexane were irradiated for 2 hour. The crude was filtered and chromatographed on silica gel. Yields are given in Table 2.

Reaction of furoxan **1c** and **TME** gave **3c** and *1,2-dihydro-1,1,2,2-tetramethylcyclobuta[l]phenanthrene*[10] *(5c)*. Reaction of furoxan **1d** and **TME** gave **3d**, **5c** and *3-chloro-1,2-dihydro-1,1,2,2-tetramethylcyclobuta[l]phenanthrene (5d)*: m.p. 128-132 °C. ^{1}H NMR ($CDCl_3$): 8.72 (2H, m), 7.90-7.40 (5H, m), 1.80-1.10 (12H, m); MS: m/z 294 (M^+, 58), 217 (100). Anal. Calcd. for $C_{20}H_{19}Cl$: C, 81.48%; H, 6.50%; Cl, 12.03%. Found: C, 82.78%; H, 6.65%; Cl, 11.61%. Reaction of furoxan **1e** and **TME** gave **3e** and *3,10-dichloro-1,2-dihydro-1,1,2,2-tetramethylcyclobuta[l]phenanthrene (5e)*: m.p. 161-168 °C. ^{1}H NMR ($CDCl_3$): 8.65 (2H, d, J = 9 Hz), 7.68 (2H, d, J = 9 Hz), 7.48 (2H, t, J = 9 Hz), 1.60 (12H, s); ^{13}C NMR ($CDCl_3$): 146.8, 133.0, 129.0, 128.3, 127.7, 125.8, 123.0, 49.3, 24.9; MS: m/z 328 (M+, 100). Anal. Calcd. for $C_{20}H_{18}Cl_2$: C, 72.96%; H, 5.51%; Cl, 21.53%. Found: C, 74.12%; H, 5.27%; Cl, 20.58%. Reaction of furoxan **1e** and methylcyclohexene gave **3e** and *3,10-dichloro-1,2-dihydro-1-methyl-1,2-tetramethylenecyclobuta[l]-phenanthrene (5f)*: m.p. 102-105 °C. ^{1}H NMR ($CDCl_3$): 8.65 (2H, m), 7.65 (2H, m), 7.50 (2H, m), 3.51 (1H, t, J = 5 Hz), 2.35-1.20 (12H, m); MS: m/z 340 (M+, 70), 83 (100). Anal. Calcd. for $C_{21}H_{18}Cl_2$: C, 75.21%; H, 5.32%; Cl, 20.78%. Found: C, 75.21%; H, 5.47%, Cl, 20.12%. Reaction of furoxan **1e** and cyclohexene gave **3e** and and *3,10-dichloro-1,2-dihydro-1,2-tetramethylenecyclobuta[l]phenanthrene (5g)*: m.p. 122-128 °C. ^{1}H NMR ($CDCl_3$): 8.62 (2H, d, J = 8 Hz), 7.65 (2H, d, J = 8 Hz), 7.50 (2H, t, J = 8 Hz), 3.88 (2H, m), 2.40-1.30 (8H, m); MS: m/z 326 (M+, 100). Anal. Calcd. for $C_{20}H_{16}Cl_2$: C, 73.40%; H, 4.93%; Cl, 21.67%. Found: C, 75.11%; H, 5.14%; Cl, 20.91%. Reaction of furoxan **1e** and 1-hexene gave **3e**.

Reactions of acetylenes 3c,e with tetramethylethylene

Eight tubes containing a 10^{-3} M solution of acetylenes **3c,e** (0.020 mmol) and tetramethylethylene (1.7 mmol) in 20 mL of degassed *n*-hexane were irradiated for 2 hour. The crude was filtered and chromatographed on silica gel. Yields are given in Table 3. Reaction of diphenylacetylene and **TME** gave **5c**, *1,2-Diphenyl-3,3,4,4-tetramethylcyclobutene*[11] *(6c)* and *phenanthrene (7c)*. Reaction of *bis(2,6-dichlorophenyl)acetylene* (**3e**) and **TME** gave **5e**, and *1,8-dichlorophenanthrene*[30] *(7e)*.

ACKNOWLEDGMENTS

We gratefully acknowledge the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for support.

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(*Received in UK* 10 *September* 1997; *revised* 3 *October* 1997; *accepted* 9 *October* 1997)